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Academia–Pharma Intersect: Lung Cancer

Targeting Angiogenesis with Multitargeted Tyrosine Kinase Inhibitors in the Treatment of Non-Small Cell Lung Cancer

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ABSTRACT

It has been >35 years since the link between angiogenesis and the growth of tumors was first reported. Targeting angiogenesis became feasible with the availability of bevacizumab, an anti–vascular endothelial growth factor monoclonal antibody. Initial studies revealed that the combination of bevacizumab and chemotherapy led to longer overall survival times than with chemotherapy alone in patients with advanced colorectal cancer. Since then, drug development strategies have added small molecule tyrosine kinase inhibitors to the panel of antiangiogenic agents under evaluation; data from numerous trials are now available. The challenge now is to identify the optimal antiangiogenic agent for specific patient groups and to understand not only the mechanistic differences between agents, but also the variability in their antitumor activity across different tumor types and their differing side-effect profiles. As in other solid tumors, angiogenesis contributes to the development of non-small cell lung cancer (NSCLC), and this review summarizes the role of angiogenesis in this disease. We review the current developmental status of antiangiogenic tyrosine kinase inhibitors (including vandetanib, sunitinib, axitinib, sorafenib, vatalanib, and pazopanib) in NSCLC and conclude by briefly discussing the need for optimal patient selection and potential future directions. ***The Oncologist*** 2010;15:436–446

INTRODUCTION

Angiogenesis is a complex process that is essential for the growth of tumors. Judah Folkman first suggested that tumor growth was dependent on angiogenesis in 1971, predicting that tumor size would be limited to 1–2 mm in the absence of angiogenesis and that tumor cells secrete a protein that stimulates angiogenesis [1, 2]. In order for angiogenesis to occur, several signaling pathways must be suppressed or activated [3]. Some of these signaling pathways, such as the vascular endothelial growth factor (VEGF) pathway and platelet-derived growth factor (PDGF) pathway, control the activity of blood vessel–associated cells, including endothelial cells and pericytes.

Whereas the primary stimulus for angiogenesis in the

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Table 1. Factors regulating angiogenesis

Proangiogenic factors	Antiangiogenic factors
Growth factors VEGF, FGF, EGF, TGF-α, PDGF, PIGF, G-CSF, TNF-α	Matrix glycoproteins Thrombospondin-1, thrombospondin-2
Proteases Cathepsin, gelatinase, stromalysin, urokinase-type plasminogen activator	Collagen fragments Angiostatin, endostatin, tumstatin, canstatin
Cytokines IL-1, IL-6, IL-8, MCP-1, ET-1, ET-2	Cytokines IFN-α and IFN-β
Other inducers Angiopoietin-1, integrins, hypoxia, hypoglycemia, NOS, COX-2, lactate	Other inhibitors 2-methoxyestradiol, vasohibin

Abbreviations: COX, cyclo-oxygenase; EGF, endothelial growth factor; ET, endothelin; FGF, fibroblast growth factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; NOS, nitric oxide synthase; PDGF, platelet-derived growth factor; PIGF, placental growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
Adapted from Herbst RS, Onn A, Sandler A. Angiogenesis and lung cancer: Prognostic and therapeutic implications. J Clin Oncol 2005;23:3243–3256.

tumor microenvironment is the hypoxia-driven activation of hypoxia-inducible factor-1α, and the subsequent activation of VEGF, numerous other growth factors and protein products of oncogenes and tumor-suppressor genes are also involved (Table 1) [4]. As tumor-associated blood vessels develop, cytokine-rich plasma is exuded and provides a gradient along which new endothelial cells migrate and new capillary tubes form [5]. Under normal physiologic conditions, blood vessel maturation occurs when endothelial cells secrete PDGF, which in turn stimulates pericyte recruitment. However, tumor-associated vasculature fails to mature completely, typically as a result of the development of hypoxic regions in the tumor that stimulate a perpetual cycle of VEGF production, angiogenesis, and further tumor growth [6]. Because angiogenesis is a complex process mediated by many factors, there are potentially multiple signaling pathways involved that can be targeted by antitumor therapies (Fig. 1). While targeting one signaling pathway may be effective, targeting several interconnected signaling pathways may theoretically result in increased therapeutic benefit, particularly as the tumor may utilize alternative signaling pathways as "escape" mechanisms [7]. This concept is supported by data that suggest an additive effect on tumor response when both the VEGF and PDGF signaling pathways are inhibited [8–10]. Preclinical research has identified several targeted antiangiogenic agents, including monoclonal antibodies and tyrosine kinase inhibitors (TKIs). Monoclonal antibodies prevent receptor activation by binding directly to the ligand, whereas TKIs inhibit kinase activity by competing with ATP in the tyrosine kinase catalytic domain. This review describes the role of angiogenesis in non-small cell lung cancer (NSCLC) and summarizes some of the available data from studies of antiangiogenic agents.

Although multitargeted TKIs are the focus of this review, it is important to consider that numerous antiangiogenic/antivascular agents with alternative mechanisms of action are in preclinical/early clinical development. These include aflibercept, a recombinant fusion protein that binds all isoforms of VEGF, the combretastatins (e.g., CA-4-P), which are tubulin-binding, vascular-disrupting agents, and the bisphosphonates, which may reduce the incidence of bone metastases through antiangiogenic mechanisms.

Tumor Angiogenesis

VEGF is one of the most potent mediators of tumor angiogenesis. There are four homologues within the *VEGF* gene family: VEGF-A, VEGF-B, VEGF-C, and VEGF-D. VEGF-A is a key regulator of blood vessel development in adult tissues, whereas VEGF-B is implicated in embryonic angiogenesis. VEGF-C and VEGF-D are thought to be primarily involved in lymphatic angiogenesis. The VEGF ligands bind to three VEGF receptors (VEGFRs): VEGFR-1 (also known as Flt-1), VEGFR-2 (also known as KDR), and VEGFR-3 (also known as Flt-4). VEGFR-2 is the primary receptor involved in endothelial cell proliferation and migration [11].

Signaling pathways activated by PDGF are integral to the growth and survival of vascular smooth muscle cells and pericytes [12, 13]. There are three active forms of the PDGF protein: PDGF-AA, PDGF-BB, and PDGF-AB (two other forms that require proteolytic cleavage before activation can occur are PDGF-CC and PDGF-DD). These ligands bind with varying affinity to the two receptor subunits (PDGFRα and PDGFRβ), which subsequently dimerize to form PDGFR$\alpha\alpha$, PDGFR$\beta\beta$, or PDGFR$\alpha\beta$. PDGFR expression on pericytes is an essential requirement for the survival of tumor vasculature [14].

Other factors with pro-/antiangiogenic properties include epidermal growth factor (EGF), stem cell factor, fibroblast growth factor (FGF), colony-stimulating factor (CSF)-1, angiopoietin (Ang)-1/Tie-2, placental growth factor, endothelin (ET)-1 and ET-2, thrombospondin, angiostatin, endostatin, and lactate (Table 1). EGF has been linked to cell proliferation, apoptosis, angiogenesis, and metastatic spread in many human carcinomas, whereas overexpression of wild-type EGF receptor (EGFR) has also

been associated with increased angiogenesis and poor prognosis in NSCLC [15, 16].

Although angiogenesis is the primary mechanism by which tumors coopt a blood supply, other methods are also used. These methods include intussusceptive microvascular growth, vasculogenesis via the recruitment of bloodborne endothelial progenitor cells, glomeruloid angiogenesis, and vasculogenic mimicry [3, 7]. Angiogenesis, as measured using microvessel density (MVD), can be a predictor of poor survival in a variety of neoplasms, including NSCLC [17, 18]. Studies have also shown that levels of VEGF (and PDGF) correlate significantly with increased angiogenesis, poor prognosis, and lymph node metastasis in patients with NSCLC [8, 17–20]. Indeed, high levels of VEGF have been linked to shorter survival in patients with NSCLC who received the VEGFR and EGFR inhibitor vandetanib [21, 22]. Furthermore, an immunohistochemical study of NSCLC tumor specimens found that MVD was higher in samples from patients with advanced-stage than those with early-stage NSCLC, and it was also higher in patients with lymph node metastases than in those with no metastases [23]. This same study also hypothesized that high levels of the antiangiogenic factor thrombospondin-1 may delay disease progression [23].

Standards of Care for the Systemic Treatment of Advanced NSCLC

Approximately 219,000 new lung cancer cases and 160,000 deaths were estimated to have occurred in the U.S. in 2009 [24]. Most patients with lung cancer present with advanced disease and, globally, platinum-based doublet chemotherapy remains the standard of care for patients with a good performance status [25]. Although numerous systemic chemotherapy doublets and triplets have been studied, they produce similar outcomes. However, promising data have been reported with the folate antimetabolite, pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis, Indiana), in both a first-line setting [26] and as maintenance therapy [27]. First-line cisplatin plus pemetrexed was noninferior to cisplatin plus gemcitabine, although a significant survival advantage with cisplatin plus pemetrexed was observed in patients with adenocarcinoma or large-cell carcinoma [26]. Based on maintenance data revealing that pemetrexed doubled the time to disease progression, compared with placebo (4.04 months versus 1.97 months), in July 2009 pemetrexed was approved in the U.S. and European Union as maintenance therapy in NSCLC patients with nonsquamous histology [27].

Clinical research efforts with targeted agents have endeavored to improve survival beyond that provided by chemotherapy. Two pivotal phase III trials provide the foundation for using targeted antiangiogenic agents in NSCLC. The Eastern Cooperative Oncology Group (ECOG) 4599 trial randomized patients with advanced nonsquamous NSCLC to receive paclitaxel and carboplatin with or without the anti-VEGF monoclonal antibody bevacizumab (Avastin®; Genentech, San Francisco, CA), or placebo. That study reported a median overall survival (OS) time of 12.3 months with the addition of bevacizumab to chemotherapy, and only 10.3 months with chemotherapy alone [28]. The study established that the VEGF pathway is a valid target for therapy. Subsequently, a second phase III European trial, AVAstin in Lung (AVAiL), assessed bevacizumab (7.5 mg/kg and 15 mg/kg) in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent NSCLC. That study demonstrated a higher objective response rate (ORR) and longer progression-free survival (PFS) time with both doses of bevacizumab; the ORRs were 20.1 months (placebo), 34.1 months (7.5 mg/kg), and 30.4 months (15 mg/kg). The median PFS time was significant for the 7.5 mg/kg dose level (6.5 months versus 6.1 months; $p = .003$). No statistically significant improvement in OS was observed. The reason for a lack of survival benefit is unclear, with proposed reasons including poststudy treatment, a potentially smaller effect size of bevacizumab when combined with more effective chemotherapy, and statistical power [29].

Combination Therapy: Targeting VEGF and EGFR

Combining an antiangiogenic, single-target agent and a chemotherapeutic agent has resulted in proven activity across multiple tumor types; however, the future of cancer treatment may lie with the development of drugs or drug combinations that are directed against multiple tumor targets. Inhibition of multiple targets could be achieved with a single agent or with a combination of agents. In NSCLC, preclinical data in xenograft models have identified the VEGFR and EGFR pathways as rational therapeutic targets; inhibition of tumor growth was most pronounced with the combination of bevacizumab and the anti-EGFR TKI erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA) than with either agent alone [30]. The anti-EGFR monoclonal antibody cetuximab (Erbitux®; Merck Serono, Darmstadt, Germany) has shown promising antitumor activity in NSCLC and was studied in combination with bevacizumab plus chemotherapy in a phase II Southwest Oncology Group (SWOG) trial. The treatment combination was tolerable and evidence of antitumor activity was reported in a presentation at the annual meeting of the American Society for Clinical Oncology (ASCO) in 2009 [31].

A phase I/II study of erlotinib plus bevacizumab en-

Table 2. Antiangiogenic tyrosine kinase receptor inhibitors and their targets

Agent	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR	EGFR	Other targets
Vandetanib		●			●	RET
Sunitinib	●	●	●	●		KIT, FLT3, RET
Axitinib	●	●	●			
Sorafenib	●	●	●	●		KIT, RAF, FLT3
Vatalanib	●	●	●	●		KIT
Cediranib	●	●	●	●		KIT
Motesanib	●	●	●	●		KIT, RET
Pazopanib	●	●	●	●		KIT
BIBF 1120		●		●		FGFR

Abbreviations: FGFR, fibroblast-like growth factor receptor; FLT3, FMS-like tyrosine kinase 3; KIT, stem cell factor receptor; RET, glial cell line-derived neurotrophic factor receptor; VEGFR, vascular endothelial growth factor receptor.

rolled patients with pretreated nonsquamous, advanced NSCLC. The median OS time was 12.6 months and the PFS duration was 6.2 months [32]. Results from another phase II study in pretreated patients again supported further study with this treatment combination; bevacizumab plus erlotinib achieved activity comparable with that of bevacizumab plus chemotherapy (median OS time, 13.7 months for bevacizumab plus erlotinib versus 12.6 months for bevacizumab plus chemotherapy) [33]. Consequently, this combination was studied in the phase III BeTa Lung trial in pretreated patients with advanced NSCLC. Unfortunately, the primary endpoint of a longer OS time than with erlotinib alone was not met (median OS time, 9.3 months versus 9.2 months; $p = .75$; hazard ratio [HR], 0.97) [34].

More recently, other trials have been presented, including the phase III ATLAS trial (investigating bevacizumab and erlotinib versus bevacizumab plus placebo, as maintenance therapy following first-line treatment) [35]. That study was stopped early on the recommendation of an independent data safety monitoring committee after a preplanned interim analysis that showed the combination led to a significantly longer PFS interval than with bevacizumab plus placebo.

Multitargeted Agents

Efforts to identify drugs that inhibit key pathways involved in the pathogenesis of cancer have led to the development of multitargeted agents. Small-molecule TKIs that inhibit receptors such as VEGFR, PDGFR, Raf, and KIT simultaneously may offer advantages over agents with single targets, and therefore a higher likelihood of single-agent activity. In addition, because multitargeted TKIs are often available orally, they may be more convenient for patients. Conversely, a potential disadvantage is the potential for toxicity resulting from off-target kinase inhibition, and the additive toxicity that may be particularly relevant when the agents are combined with chemotherapy.

Several multitargeted, antiangiogenic agents have been studied in clinical trials. Most of these agents inhibit VEGFR, and some also inhibit PDGFR, Raf, and EGFR (Table 2). Clinical experience with these compounds is described below. Those currently being investigated in phase III trials are summarized in Table 3.

Vandetanib

Vandetanib (Zactima®, ZD6474; AstraZeneca Pharmaceuticals, Wilmington, DE) is a VEGFR and EGFR inhibitor, although the difference in the 50% inhibitory concentration for these two targets translates into more potent inhibition of VEGFR than EGFR at pharmacologically achievable doses. In a phase II trial, vandetanib in combination with carboplatin and paclitaxel led to a higher ORR and longer PFS time (primary endpoint) but no difference in OS when compared with vandetanib alone in chemotherapy-naïve patients with NSCLC [36]. Higher incidences of rash, diarrhea, asymptomatic QTc-related events, and hypertension were observed in the vandetanib arm. The study allowed enrollment of patients with central nervous system (CNS) metastases and all NSCLC histologies; patients who entered with CNS metastases or squamous histology did not experience intracranial bleeding or hemoptysis of grade ≥ 2 [36]. The vandetanib-alone arm was stopped early after an interim analysis met the criterion for discontinuation. Vandetanib plus docetaxel was shown to be superior to docetaxel alone in pretreated patients with advanced NSCLC, and vandetanib led to a significantly longer PFS time than with gefitinib, again in a second-line setting [37, 38]. Subsequently, an extensive phase III program has been conducted: ZODIAC (vandetanib plus docetaxel versus

Table 3. Active phase III trials of antiangiogenic multitargeted tyrosine kinase inhibitors in advanced NSCLC

Agent	Design	Target enrollment (*n*)	Primary endpoint
Sunitinib (Sutent®)	Sunitinib + erlotinib versus erlotinib second/third line; NCT00457392 (SUN1087)	956	OS
	Sunitinib as maintenance therapy in nonprogressing patients following platinum-based chemotherapy; NCT00693992 (CALGB30607)	156	PFS
Sorafenib (Nexavar®)	Gemcitabine + cisplatin + sorafenib versus gemcitabine + cisplatin + placebo first-line; NCT00449033 (NEXUS)	350	PFS
	Sorafenib with or without placebo third/fourth line in patients with predominantly nonsquamous histology; NCT00863746	850	OS
Vandetanib (Zactima®)	Vandetanib + BSC versus BSC after therapy with an EGFR TKI; NCT00404924 (ZEPHYR)	930	OS
Motesanib	Motesanib + paclitaxel + carboplatin (MONET1); NCT00460317	1,400	OS
BIBF 1120 (Vargatef®)	BIBF 1120 + pemetrexed versus placebo + pemetrexed second line in patients with nonsquamous histology; NCT00806819 (LUME Lung 2)	1,302	PFS
	BIBF 1120 + docetaxel versus placebo + docetaxel second line; NCT00805194 (LUME Lung 1)	1,306	PFS

Information on ongoing phase III trials was obtained from http://www.clinicaltrials.gov (accessed December 2009) using the name of the TKI and "lung" as search criteria.
Abbreviations: BSC, best supportive care; CALGB, Cancer and Leukemia Group B; EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

docetaxel alone) and ZEAL (vandetanib plus pemetrexed versus pemetrexed alone) are both placebo-controlled, double-blind, randomized studies evaluating the efficacy of vandetanib in second-line advanced NSCLC. Data presented at the 2009 ASCO Annual Meeting revealed acceptable safety profiles and significant improvements in response in both studies versus chemotherapy alone. Similarly, improvements in the primary endpoint (PFS versus chemotherapy alone) were reported but statistical significance was reached only in ZODIAC (PFS for vandetanib plus docetaxel was 4 months versus 3.2 months for docetaxel alone; HR, 0.79; 95% confidence interval [CI], 0.70–0.90, $p < .001$) [39, 40]. However, whether a 3-week improvement in PFS is clinically meaningful remains to be determined. ZEST is a phase III head-to-head comparison of vandetanib versus erlotinib. Again, based on data reported at the 2009 ASCO Annual Meeting, the primary endpoint of PFS was not met (vandetanib, 11.3 weeks versus erlotinib, 8.9 weeks; HR, 0.98; 95% CI, 0.87–1.10; $p = .721$) [41]. Finally, ZEPHYR is a randomized, double-blind phase III study of vandetanib plus best supportive care versus best supportive care alone in patients with advanced NSCLC after failure of prior treatment with an anti-EGFR TKI, and results are expected in 2010. Based on these data, the role of vandetanib in NSCLC remains somewhat uncertain; the initial results are frankly somewhat disappointing.

Sunitinib

Sunitinib (Sutent®, SU11248; Pfizer Inc., New York) is an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFRs, KIT, FLT3, RET, and CSF-1R, and is approved multinationally for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumor. The antitumor activity of sunitinib in NSCLC is supported by preclinical data derived from in vivo models. Combination treatment with sunitinib plus docetaxel, pemetrexed, gemcitabine, or platinum agents resulted in significantly greater tumor growth inhibition than with sunitinib alone [42]. In a phase II trial, in which sunitinib was administered on a continuous daily dosing (CDD) schedule in patients with previously treated NSCLC, the median PFS time was 11.9 weeks (95% CI, 8.6–14.1 weeks), the median OS time was 37.1 weeks (95% CI, 24.2–52.5), and treatment was generally well tolerated; most adverse events were grade 1 or 2 [43]. An earlier pa-

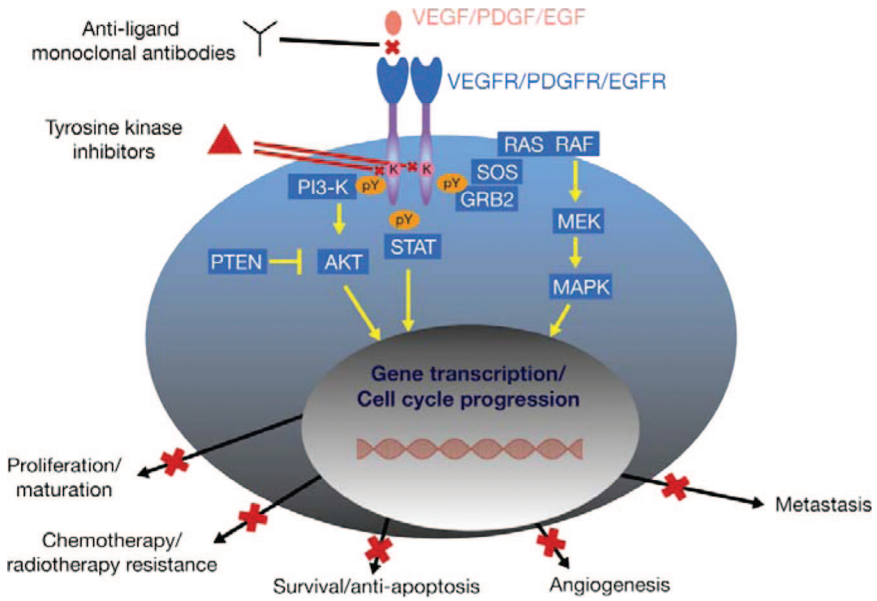

Figure 1. Pathways blocked by tyrosine kinase inhibitors and monoclonal antibodies.

Abbreviations: EGF, endothelial growth factor; EGFR, endothelial growth factor receptor; GRB2, growth factor receptor-bound protein-2; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; PI3K, phosphoinositide 3-kinase; PDGF, platelet-derived growth factor; PTEN, phosphatase and tensin homologue deleted on chromosome ten; SOS, son of sevenless; STAT, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

tient cohort in that trial received sunitinib, 50 mg/day, on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment); again, treatment appeared active with a median PFS duration of 12.0 weeks (95% CI, 10.0–16.1 weeks) and a median OS time of 23.4 weeks [44]. Sunitinib was well tolerated, with most adverse events being grade 1 or 2. Responses were also observed in a phase I study of sunitinib plus gemcitabine and cisplatin [45]. Ongoing trials of sunitinib in advanced, platinum-refractory NSCLC include SUN1058 and SUN1087 (Table 3). SUN1058 is a phase II trial investigating sunitinib (37.5 mg) plus erlotinib (150 mg) on a CDD schedule; patients are stratified based on smoking history and EGFR status. SUN1087 is a phase III trial of sunitinib (37.5 mg) and erlotinib (150 mg), again on a CDD schedule, and employs the same stratification criteria in addition to stratification based on prior treatment with bevacizumab. By targeting EGFR as well as VEGFR and PDGFR, this combination may increase the potential for activity.

Axitinib

Axitinib (AG-013736; Pfizer Inc., New York) is a TKI with activity against all three VEGFRs (VEGFR-1, VEGFR-2, and VEGFR-3) at clinical doses and is currently being studied in multiple solid tumor settings [46]. In a phase II study of patients with advanced NSCLC treated with single-agent axitinib (in the first-line, second-line, or third-line setting), the median PFS interval was 4.9 months overall (95% CI, 3.6–7.0 months), and the median OS time of 14.6 months was greater than expected in such a mixed patient population [47]. Treatment was also well tolerated. Ongoing trials of this agent in nonsquamous NSCLC patients include the phase II AGILE 1030 trial (axitinib plus paclitaxel plus carboplatin versus bevacizumab plus paclitaxel plus carboplatin), the phase II AGILE 1039 trial (axitinib plus cisplatin and pemetrexed versus cisplatin and pemetrexed), and the phase II AGILE 1038 trial in squamous cell carcinoma (axitinib plus cisplatin and gemcitabine).

Sorafenib

Sorafenib (Nexavar®, BAY 43–9006; Bayer Pharmaceuticals Corporation, West Haven, CT) is a Raf and VEGFR inhibitor (VEGFR-2 and VEGFR-3) with activity against PDGFR and KIT. It is licensed in many countries for the treatment of advanced RCC and hepatocellular carcinoma [48]. In xenograft models, sorafenib plus vinorelbine, cisplatin, or gefitinib resulted in tumor growth delay at least comparable with that observed with each agent alone [49]. In the phase III ESCAPE trial (carboplatin plus paclitaxel, with and without sorafenib in first-line, advanced NSCLC), the primary endpoint of OS was not met and the study was terminated early as a result of the detrimental effect of sorafenib on patients with squamous cell carcinoma and the lack of effect in the population with nonsquamous cell car-

cinoma. Further investigation of sorafenib in the third- or fourth-line treatment setting is currently under consideration [50]. Data from a phase II trial of heavily pretreated patients with advanced NSCLC revealed a statistically significant higher number of patients with stable disease at 2 months with sorafenib (sorafenib, 47% versus placebo, 19%; $p = .01$), and toxicities were manageable [51]. Single-agent sorafenib showed disease stabilization in 59% of 51 NSCLC patients in a phase II trial, with an OS time of 6.8 months and a median PFS time of 2.8 months [52].

Vatalanib

Vatalanib (PTK787; Novartis/Schering AG, Berlin, Germany) is a VEGFR, PDGFR, and KIT inhibitor that is currently being studied in phase II/III trials. Data from a phase II trial examining vatalanib monotherapy administered once or twice daily in previously treated patients with NSCLC have been reported [53]. Single-agent treatment appeared active, with a trend toward greater efficacy with twice-daily treatment (11% of evaluable patients had a partial response in this cohort). Additionally, treatment was well tolerated, with no apparent differences between once- and twice-daily dosing.

Cediranib

Cediranib (Recentin®, AZD2171; AstraZeneca Pharmaceuticals, Wilmington, DE) is a potent VEGFR-2 inhibitor that also inhibits VEGFR-1, VEGFR-3, and PDGFR [54]. Initial phase I data with cediranib (30 mg) in combination with cisplatin and gemcitabine was promising in patients with previously untreated NSCLC [55]. Toxicities, including hypertension, fatigue, and diarrhea, were manageable and predictable, with the maximum-tolerated dose not reached. Given that the 30-mg dose was better tolerated than the 45-mg dose in the phase I trial, the 30-mg dose of cediranib was selected for combination with carboplatin and paclitaxel in the first-line BR24 phase II/III study in patients with NSCLC. In early 2008, AstraZeneca reported that the study would not continue into phase III following the planned end of phase II efficacy and tolerability analyses. According to the study's data safety monitoring committee, although evidence of clinical activity was observed, there appeared to be an imbalance in toxicity between the treatment and control arms, and therefore the study was considered not to have met the predefined criteria for continuation into phase III [56]. A retrospective analysis revealed a higher risk for weight loss, hypoalbuminemia, and grade 5 adverse events in patients receiving cediranib (30 mg) plus chemotherapy than in those receiving chemotherapy alone. However, despite these safety data, cediranib (30 mg) plus chemotherapy led to a higher response rate and longer PFS time than with chemotherapy alone [56]. Consequently, a reduced dose of cediranib (20 mg) plus carboplatin and paclitaxel will be investigated in a randomized trial in patients with a good performance status, no significant weight loss, and no hypoalbuminemia.

Motesanib

Motesanib (AMG 706; Amgen, Thousand Oaks, CA) is a VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, KIT, and RET inhibitor that is currently in clinical development in multiple tumor types, including NSCLC. Phase I data have shown that motesanib can be combined safely with paclitaxel plus carboplatin and/or panitumumab, an anti-EGFR monoclonal antibody, in patients with advanced NSCLC [57]. Treatment-related adverse events in that study were generally mild to moderate, with fatigue and hypertension being the most common grade 3 adverse events [57]. A phase III trial investigating motesanib (125 mg daily) in combination with paclitaxel and carboplatin was temporarily suspended in November 2008 because of a higher risk for hemoptysis in patients with squamous cell histology. These patients were discontinued and the study was restarted; patients with nonsquamous cell histology (approximately two thirds of the original study population) are continuing on treatment, and patients with this histology are continuing to be enrolled (Table 3).

Pazopanib

Pazopanib (GW786034; GlaxoSmithKline, Philadelphia) is a VEGFR, PDGFR, and KIT inhibitor currently in phase III development for advanced RCC and in phase II development in advanced NSCLC. Initial data from a phase II trial in early (stage I/II) NSCLC have been presented; 87% of patients ($n = 20$) had a reduction in tumor volume, and the tolerability profile in this setting was favorable [58]. Numerous phase II studies of pazopanib in patients with advanced NSCLC have either been completed or are ongoing, and data are keenly awaited. These include pazopanib as monotherapy, as well as combination studies with paclitaxel and pemetrexed. In addition, a phase II study of erlotinib plus pazopanib versus erlotinib plus placebo is planned [59]. Antitumor activity in the first-line setting was observed in patients with malignant pleural mesothelioma. A phase II study revealed a PFS duration of 5.9 months (95% CI, 3.1–8.4 months) and OS time of 14.4 months (95% CI, 7.2 to not achieved) [60].

BIBF 1120

BIBF 1120 (Vargatef™; Boehringer-Ingelheim, Ingelheim, Germany) is an oral indolinone derivative that inhibits VEGFR-2, FGFR, and PDGFR. Phase I data in

patients with advanced solid tumors established the phase II dose to be 200 mg twice daily and revealed that the observed toxicities at this dose were manageable. Adverse events judged to be related to treatment were most often gastrointestinal, and there were responses in patients (three of 23) with RCC and colorectal cancer [61]. Results from a phase II trial of BIBF 1120 involving patients with advanced NSCLC were reported at the 13th World Conference on Lung Cancer [62]. This double-blind multicenter trial included patients with an ECOG performance status score of 0–2 who had relapsed following the failure of first- or second-line chemotherapy. Again, adverse events were most often gastrointestinal; the most common grade 1–3 toxicities were vomiting, nausea, diarrhea, anorexia, and abdominal pain [62]. The median OS time was 264 days [63]. Phase III trials of BIBF 1120 in advanced NSCLC are under way—LUME Lung 1 and LUME Lung 2 (Table 3).

Challenges Facing the Effective Treatment of NSCLC

Toxicity

The TKIs described above all inhibit multiple receptors, therefore influencing multiple signaling pathways and their respective downstream signaling molecules. Consequently, the antitumor activity of these agents may be superior to that of agents with single targets; however, this must be balanced against the potential for additive toxicity. For example, inhibition of KIT has been associated with changes in skin and hair pigmentation, whereas inhibition of VEGFRs can lead to hypertension, hemorrhage, skin toxicity, fatigue, hand–foot syndrome, and hypothyroidism (also linked to inhibition of RET) [64–66]. Interestingly, some studies have suggested that hypertension may actually be a predictor of response in a variety of tumor types following treatment with multitargeted TKIs [67]. Furthermore, inhibition of PDGFR has been linked to cardiotoxicity (possibly as a result of the expression of PDGFR on cardiomyocytes), skin reactions, and edema.

Treatment with multitargeted TKIs may be associated with off-target kinase activities resulting in possibly unexpected side effects, for example, cardiac-related events [68]. Toxicities associated with the pharmacological action of antiangiogenic TKIs, so called "class-effect" toxicities, have also been reported, such as hypertension, hand–foot syndrome, and impaired wound healing [69, 70]. It is becoming increasingly clear that a comprehensive understanding of the spectrum of effects exerted by all anticancer agents, including multitargeted TKIs, is fundamental for understanding the efficacy and safety profiles of targeted agents. While most toxicities associated with TKIs are manageable, patients should continue to be monitored carefully for evidence of toxicity, particularly because prolonged periods of therapy may be required and side effects may impact treatment compliance.

Combining Targeted Agents

As discussed earlier, combining targeted agents is a valid strategy and is one that is being pursued in numerous trials (e.g., the SUN1087 trial). It is conceivable that such regimens may avoid the adverse effects commonly associated with chemotherapy, while providing comparable and possibly superior antitumor activity. The safety and efficacy data from the ATLAS study were recently presented. Although no unexpected safety signals were observed, grade 3 or 4 rash and diarrhea were more common in the erlotinib plus bevacizumab arm than in the bevacizumab plus placebo arm (10.4% versus 0.5% and 9.3% versus 0.8%, respectively) [35]. Based on the statistically significant longer median PFS time (the primary endpoint) of 4.8 months for the erlotinib plus bevacizumab arm, versus 3.7 months for the bevacizumab plus placebo arm (HR, 0.72; 95% CI, 0.59–0.88; $p = .0012$), that trial met its primary endpoint and was terminated early.

Biomarkers of Response

The effective use of VEGFR TKIs will depend on identifying patients who are most likely to benefit from therapy. A number of translational medicine biomarkers are being explored to identify predictors of response and/or toxicity based on a variety of parameters, such as tumor histology and pretreatment levels of angiogenic molecules such as VEGF and PDGF, levels of tumor-associated blood vessels (MVD), *KRAS* mutations, and levels of circulating endothelial cells (CECs). An in vitro profiling study reported at the ASCO–National Cancer Institute–European Organization for Research and Treatment of Cancer meeting demonstrated distinct patterns of protein secretion in response to certain treatment regimens [71]. Furthermore, evidence suggests a correlation between levels of some VEGF isoforms and survival in NSCLC patients [72, 73], with a particularly high correlation between levels of soluble VEGFR-2 and tumor shrinkage in response to pazopanib [74]. However, there are conflicting reports regarding the effectiveness of using pretreatment VEGF levels as a predictive biomarker, and it is possible that it is actually bioavailable, rather than circulating, VEGF that is the most effective predictor [75]. Similarly, high expression of PDGF-B and PDGFRα have been linked to poor outcome in tumor cells derived from patients with stage I–III NSCLC [76]. High MVD has been linked to poor survival and tumor progression in NSCLC patients, and it has a par-

ticularly strong correlation with the development of distant metastases [77]. In addition, it is hypothesized that treating patients with antiangiogenic agents may dissociate endothelial cells from the tumor vasculature, therefore increasing the number of CECs in patients' blood. High levels of CECs may indicate that a patient is responding to treatment with an antiangiogenic agent, a theory with some preclinical support [78]. In summary, while efforts are under way to identify biomarkers predictive of response to antiangiogenic therapy, so far no single marker or set of markers seems ready for routine clinical use.

SUMMARY

Angiogenesis is a complex process that is essential for the growth of tumors. Initial clinical data have shown modest efficacy when single-target agents are combined with chemotherapy. Multitargeted antiangiogenic agents may provide advantages over agents with single targets; however, the use of one strategy over another will rely on optimizing the benefit–risk ratio of targeted agents, using clinical and translational medicine biomarker characteristics of individual patients. Further exploration of multitargeted angiogenesis inhibitors may offer additional clinical benefits and may pave the way toward the development of rational combinations of targeted agents for NSCLC. Because similar efficacy outcomes are being achieved with conventional chemotherapy agents, it is conceivable that chemotherapy regimens have reached a plateau in terms of efficacy, possibly because of the development of resistance [72, 79]. In addition, there is continuing debate over the efficacy and safety profiles of platinum- versus nonplatinum-based chemotherapy regimens, particularly when considering the potential toxicity concerns with platinum-based agents. As with all treatments, the advantages obtained in terms of activity must be weighed against the potential for greater treatment-related toxicity.

Ultimately, personalizing anticancer therapy through the use of biomarkers may improve the response to treatment. In addition, identifying the most effective treatment combinations, doses, and schedules may also help to improve response rates. It is conceivable that inhibiting angiogenesis may become a cornerstone of NSCLC treatment in the future.

AUTHOR CONTRIBUTIONS

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