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Adding to the Mix: Fibroblast Growth Factor and Platelet-derived Growth Factor Receptor Pathways as Targets in Non–small Cell Lung Cancer

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Abstract

The treatment of advanced non–small cell lung cancer (NSCLC) increasingly involves the use of molecularly targeted therapy with activity against either the tumor directly, or indirectly, through activity against host-derived mechanisms of tumor support such as angiogenesis. The most well studied signaling pathway associated with angiogenesis is the vascular endothelial growth factor (VEGF) pathway, and the only antiangiogenic agent currently approved for the treatment of NSCLC is bevacizumab, an antibody targeted against VEGF. More recently, preclinical data supporting the role of fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) signaling in angiogenesis have been reported. The platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) pathways may also stimulate tumor growth directly through activation of downstream mitogenic signaling cascades. In addition, 1 or both of these pathways have been associated with resistance to agents targeting the epidermal growth factor receptor (EGFR) and VEGF. A number of agents that target FGF and/or PDGF signaling are now in development for the treatment of NSCLC. This review will summarize the potential molecular roles of PDGFR and FGFR in tumor growth and angiogenesis, as well as discuss the current clinical status of PDGFR and FGFR inhibitors in clinical development.

Keywords

angiogenesis; fibroblast growth factor (FGF); fibroblast growth factor receptor (FGFR); non–small cell lung cancer (NSCLC); platelet-derived growth factor (PDGF); platelet-derived growth factor receptor (PDGFR)

INTRODUCTION

In the United States, 222,520 new diagnoses and 157,300 deaths due to lung cancer (approximately 85% non-small cell lung cancer [NSCLC]) were anticipated in 2010 [1]. Of the two-thirds presenting with advanced disease [2], the 5-year survival rate is only 4% [1]. New therapeutic approaches for addressing NSCLC are urgently needed.

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Many therapeutic advances will likely arise through the recognition that the term “NSCLC” indicates a molecularly heterogeneous set of diseases. The first step for therapeutic advance may be the identification of molecular targets that drive tumor proliferation directly and/or indirectly via host-derived tumor support mechanisms such as angiogenesis. This article focuses on 2 such targets, reviewing the overlapping influences of the fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) pathways on tumor angiogenesis and on the tumor directly. The potential of these pathways to drive both de novo (primary) and/or acquired (secondary) resistance to therapies that target epidermal growth factor receptor (EGFR)- or vascular endothelial growth factor (VEGF)-related pathways is explored. Many new drugs with activity against either or both of these pathways are being developed and may eventually be “added to the mix” of relevant and effective NSCLC treatment strategies.

EGFR

Most NSCLC tumors express the EGFR protein. Almost half exhibit increased *EGFR* gene-copy number, but only approximately 10% of patients will possess an *EGFR*-activating mutation in unselected non-Asian populations [3]. Without an *EGFR*-activating mutation, most patients will not exhibit a dramatic response to EGFR-inhibitor monotherapy [4], either because the EGFR pathway does not drive tumor growth [5], or because other molecular co-drivers attenuate the efficacy of targeting EGFR [6]. Even among patients with *EGFR*-activating mutations, a small proportion will exhibit de novo resistance to reversible EGFR-tyrosine kinase inhibitor (TKI) therapy, and a majority of initial responders will likely eventually exhibit acquired resistance to reversible EGFR-TKI treatment through the selection of clones with additional resistance characteristics [7]. Although some of these acquired resistance mechanisms in *EGFR*-mutant cells/tumors have been identified, including c-Met amplification and the *EGFR* T790M mutation, the mechanism(s) remains currently unknown in at least 30% of cases [8].

OVERVIEW OF ANGIOGENESIS

Sustained angiogenesis is one of the “hallmarks of cancer” and is established in NSCLC pathogenesis [9], as tumors require a blood supply to maintain viability and metastatic potential [10]. Elevated lung tumor microvessel density correlates with metastatic potential and reduced survival [11–14]. Of the known angiogenic factors, VEGF is the best characterized and mediates angiogenesis through activation of endothelial cells, predominantly through ligand activation of VEGF receptor-2 (VEGFR-2) [15]. Endogenously produced VEGF from platelets, muscle cells, or the tumor stroma contribute to signaling [16–19]. Autocrine, paracrine, and intracrine signaling have also been described [20–23]. Because of its dominant role in angiogenesis, the VEGF/VEGFR pathway is an attractive therapeutic target. Targeting blood vessel formation with either monoclonal antibodies directed against the VEGF ligand or small-molecule TKIs directed against VEGFRs have validated VEGF pathway-directed therapy in a number of different tumors [24–27]. Bevacizumab (Avastin®, Genentech; South San Francisco, CA), a humanized VEGF-specific monoclonal antibody, initially gained approval by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer [28]; however, a license for NSCLC followed the results of Eastern Cooperative Oncology Group (ECOG) 4599, which showed improved median overall survival (OS; 12.3 vs 10.3 months) with the addition of bevacizumab to carboplatin/paclitaxel in the first-line treatment of advanced nonsquamous NSCLC. In ECOG 4599, 878 patients with advanced NSCLC (excluding those with squamous tumors, brain metastases, clinically significant hemoptysis, or poor performance status) were randomized to receive 6 cycles of carboplatin/paclitaxel alone or with bevacizumab, with bevacizumab continued every 3 weeks in the absence of progression

or intolerance. In addition to prolonging the primary endpoint of OS, the bevacizumab arm had significant improvement in both progression-free survival (PFS; 6.2 vs 4.5 months) and response rate (RR; 35% vs 15%). Rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were significantly (P 0.05) higher among patients who received bevacizumab, including 15 treatment-related deaths [24]. Dowlati and colleagues evaluated correlative biomarkers in the ECOG 4599 trial via baseline plasma VEGF sampling, as well as baseline and Week 7 measurement of basic fibroblast growth factor (bFGF), soluble intercellular adhesion molecule (ICAM), and E-selectin [29]. High baseline VEGF levels were associated with an increased probability of response to bevacizumab-containing chemotherapy, but only baseline ICAM levels were both predictive of response and prognostic for survival for all patients irrespective of treatment assignment. Zhang and colleagues analyzed the sera of 133 patients enrolled in ECOG 4599 and found germline single nucleotide polymorphisms (SNPs) for VEGF G-634C, ICAM1 T469C, and WNK1-rs11064560 to be associated with improved OS (P 0.05), and SNPs for ICAM1 T469C, EGF A-61G, and CXCR2 C785T to be associated with better PFS (P 0.05)[1]. Prospective data are needed to further our understanding of potential prognostic and predictive markers in antiangiogenic therapy.

Factors beyond VEGF, including the angiopoietin/TIE-2 interaction, interleukins, Notch/delta-like ligand 4, PDGFs, and fibroblast growth factors (FGFs), influence angiogenesis [30–33]. These factors may drive angiogenesis directly in tumors refractory to prior VEGF/VEGFR-directed therapies or they may contribute to acquired resistance via selection pressures following VEGF/VEGFR-directed therapy. The FGF and PDGF pathways are increasingly being targeted therapeutically both alone and in combination with VEGFRs due to the spectrum of activity displayed by specific multitargeted kinase inhibitors (Figure 1).

THE FGF/FGFR PATHWAY

The mammalian FGF family plays a critical role in embryogenesis and adult tissue repair/maintenance [34] through binding FGF receptors (FGFR-1 through -4), inducing dimerization and downstream signaling [35]. Activation of FGF signaling has been reported in a number of human malignancies, including myeloproliferative disorders, lymphomas, prostate cancer, breast cancer, lung cancer, and others via activating mutations, overexpression, or gene amplification [34–39]. The ligand FGF-2 is directly associated with neovascularization [40]. Schweigerer and colleagues [41] showed that adrenal-cortex-derived capillary endothelial cells produced FGF-2, inducing proliferation of capillary endothelial cells—a mark of angiogenesis.

In addition to its role in angiogenesis, the FGF/FGFR pathway is a primary driver of tumor proliferation. Activating mutations in *FGFR-2* have been described in urothelial, ovarian, gastric, and colorectal cancer cell lines [39,42]. Selective inhibition of FGFR activity caused G1 growth arrest in breast cancer cell lines [38]. Kunii and colleagues [43] identified *FGFR-2* amplification as promoting cell proliferation and survival in gastric cancer cell lines, and FGFR-2 knockdown inhibited growth. Similarly, Takeda and colleagues [39] demonstrated anti-FGFR pharmacologic growth inhibition of human gastric cancer cell lines expressing FGFR-2 in vitro and in vivo.

Autocrine and paracrine signaling independent of somatic mutations have also been implicated in FGF-related tumorigenesis [44–47]. Marek and colleagues [48] noted frequent

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coexpression of distinct FGFs (FGF-2 and FGF-9) and FGFRs, suggesting a potential autocrine loop in NSCLC cell lines; moreover, they found cellular proliferation was inhibited by the multikinase TKI R04383596 (anti-FGFR, -PDGFR, and -VEGFR) in FGF/FGFR-expressing cell lines that lacked VEGFR and PDGFR [49]. Similar findings have been observed in NSCLC cell lines via inhibition of FGF signaling by antisense RNA, neutralizing FGF-2 antibodies, or anti-FGFR pharmacologic inhibition [48,50–52].

An emerging role of the FGFR pathway lies in its potential to mediate de novo or acquired resistance in EGFR-driven cells via upregulation of an alternative autocrine loop. Acquired resistance to EGFR TKIs in cells initially driven by *EGFR*-activating mutations, via the selection of alternate molecular pathway co-drivers that permit ongoing proliferation, survival, and angiogenic signaling is well documented [5,53]. Engelman and colleagues [54] described a NSCLC cell line with a known *EGFR*-activating mutation that was initially gefitinib-sensitive and then developed gefitinib-resistance via *MET* amplification; furthermore, inhibition of MET signaling restored gefitinib sensitivity.

In NSCLC, the FGF/FGFR signaling pathway may be another example of co-driver selection, but primarily through transcriptional upregulation of co-driver expression, rather than selection of hard-wired changes as with *MET* amplification. This pathway appears to generate an alternative autocrine loop leading to EGFR-TKI resistance in otherwise sensitive cells [48,52]. Recently, in both *EGFR* wild type and mutant NSCLC cell lines, FGFR-2 and FGFR-3 expression was induced at both the mRNA and protein level following gefitinib treatment [55]. Exogenous FGF-2 or FGF-7 or coculture in the presence of FGF-producing fibroblasts caused upregulation of these receptors that mediated phenotypic resistance to gefitinib in cells that were otherwise sensitive to the EGFR TKI. Pharmacologic FGFR inhibition in combination with gefitinib abrogated this effect.

The FGF/FGFR pathway is dominant among mesenchymal NSCLC histologies, typically thought of as less sensitive to EGFR TKIs [52]. The diminished sensitivity may result from a lower prevalence of *EGFR* mutations, or, conceivably, from the higher prevalence of FGFR signaling associated with the mesenchymal phenotype, where it may act as a primary driver or co-driver in concert with EGFR [52,56].

THE PDGF/PDGFR PATHWAY

PDGF functions in embryonal development, mesenchymal cell proliferation, connective tissue development, and wound healing [57–59]. In tumors, PDGF promotes cell proliferation, invasion, migration, and angiogenesis [57]. Four PDGF polypeptide chains (PDGF-A, -B, -C, and -D) dimerize into PDGF-AA, -BB, -CC, -DD, or -AB, and interact with receptors (PDGFR-α/β) to signal through PI3K, src, phospholipase C-γ, and Ras pathways [57,60].

The PDGF/PDGFR pathway appears to be involved in a number of distinct aspects of tumorigenesis and angiogenesis, including recruitment and activation of cancer-associated fibroblasts (CAFs) as a consequence of PDGF-CC-associated paracrine signaling [61] and the recruitment of pericytes critical to blood vessel maturation [62] and VEGF-producing stromal fibroblasts critical to both tumorigenesis and angiogenesis [63]. In fibroblastic NIH3T3 cells, Li and colleagues demonstrated PDGF-D to be involved in tumorigenesis via reorganization of the actin cytoskeleton, induction of anchorage-independent growth, and increased cell proliferation [64]. In a NSCLC model (A549 cells transfected with the PDGF-A mutant PDGF-0), inhibiting both PDGFR-α and PDGFR-β was shown to impede tumor growth by impairing periendothelial cell recruitment [65]. The underlying biologic activity of the PDGF/PDGFR pathway may also vary in NSCLC based on histologic subtype. For example, in a recent series by Tsao and colleagues [66], PDGFR-β expression by

immunohistochemistry (IHC) was found to be significantly higher in rare sarcomatoid NSCLC versus non-sarcomatoid NSCLC controls, and this higher tumor cell expression was significantly associated with gene copy number gain and a higher gene copy ratio.

Direct PDGF pathway activation has also been shown in multiple tumor types. Coexpression of PDGFR and its ligands suggest a role for both autocrine and paracrine PDGF signaling [67]. Tejada and colleagues showed fibroblastic tumor infiltration to correlate with PDGF-A and -C paracrine signaling in a NSCLC cell line. Donnem and colleagues [68] analyzed NSCLC tumor specimens (stage I–IIIA) and found tumor cell coexpression by IHC of FGFR-1 and PDGF-B to be a negative prognostic factor. Similarly, they correlated IHC tumor cell expression of PDGF-A with the presence of lymph node metastasis, and coexpression of PDGF-B and VEGFR-3 with poor survival in NSCLC patients [69].

VEGF/VEGFR, FGF/FGFR, AND PDGF/PDGFR PATHWAY INTERACTIONS

In addition to their separate roles described above, the VEGF/VEGFR, FGF/FGFR, and/or PDGF/PDGFR pathways may interact, with this crosstalk believed to promote angiogenesis in malignant and non-malignant settings. For example, Casanovas and colleagues [70] used a pancreatic islet cell mouse model to demonstrate that blocking VEGFR-2 initially inhibited angiogenesis with eventual progression and that this acquired resistance could be overcome with an adenovirus-delivered soluble FGFR-2 (serving as a FGF trap), decreasing tumor burden and angiogenesis. Crawford et al [71] examined tumor-associated fibroblasts from anti–VEGF-A-sensitive and -resistant tumors in a mouse model. Anti–VEGF-A-sensitive tumors maintained growth when stimulated by tumor-associated fibroblasts obtained from anti–VEGF-A-resistant tumors, even in the presence of VEGF inhibitors. PDGF-C was upregulated in the tumor-associated fibroblasts from refractory tumors, and inhibition of PDGF-C by neutralizing antibodies blocked angiogenesis and slowed tumor growth in mice. In a preclinical series involving a mouse model of pancreatic neuroendocrine carcinoma, PDGFR inhibition led to detachment of pericytes from tumor vessels, resulting in increased sensitivity of endothelial cells to VEGFR inhibition [72].

Whereas VEGF, PDGF-BB and FGF-2 were unable to establish stable vasculature on their own in animal models of hind-limb ischemia, PDGF-BB and FGF-2 (but not VEGF plus either PDGF-BB or FGF-2) acted in a synergistic manner to induce angiogenesis and maintain functional vessels [73]. It was speculated that this interaction may have been the consequence of FGF-2-induced upregulation of PDGFR-α and PDGFR-β expression in new vasculature. Nissen and colleagues [74] later showed that FGF-2 and PDGF-BB act synergistically in both tumor angiogenesis and metastasis. Mechanistically, both FGF-2-induced upregulation of endothelial cell PDGFR expression and PDGF-BB-induced upregulation of vascular smooth muscle cell FGFR1 expression were implicated in this synergistic interaction. Consequently, while some tumors may be sensitive to only 1 or the other approach, a therapeutic advantage may be gained by targeting both pathways, offering the potential to affect both tumor and vasculature independently.

INVESTIGATIONAL TARGETED THERAPIES WITH ACTIVITY AGAINST THE FGF/FGFR AND/OR PDGF/PDGFR PATHWAYS IN CLINICAL DEVELOPMENT

Many TKIs developed as VEGFR inhibitors also inhibit PDGFR and FGFR isoforms, potentially due to homology among these receptors [75,76] (Table 1). These investigational multitargeted agents differ with respect to their specific targets, as summarized in Figure 2, and are discussed below in relation to NSCLC.

Sorafenib

Sorafenib (Nexavar®, Bayer; Leverkusen, Germany) is a multitargeted kinase inhibitor with activity against VEGFR-2 and -3, PDGFR-β, stem cell factor receptor (c-kit), v-raf 1 murine leukemia viral oncogene homolog 1 (Raf), and fms-like tyrosine kinase 3 (FLT-3) [77,87,88]. Wilhelm et al [77] noted that sorafenib inhibited wild-type BRAF, VEGFR-2 and -3, and PDGFR-β in breast, colon, and NSCLC cell lines; additionally, human colon, lung, and breast xenograft tumor growth was inhibited. Sorafenib is FDA approved in unresectable hepatocellular carcinoma and advanced renal cell carcinoma (RCC) [89]. In a phase II study of single-agent sorafenib in refractory advanced NSCLC (Table 2), activity was reported and grade 3 or 4 toxicities included hand-foot skin reaction, hypertension, fatigue, and diarrhea [90]. An interim analysis of a phase III trial evaluating carboplatin/paclitaxel with or without sorafenib in patients with advanced NSCLC showed no clinical benefit and a higher mortality in the subset of patients with squamous histology who received sorafenib, prompting early termination [91]. The phase III NEXUS trial [92] did not show an OS benefit with the addition of sorafenib to gemcitabine/cisplatin in advanced nonsquamous NSCLC; however, PFS was significantly improved. Sorafenib is currently being evaluated in the third/fourth-line setting in the placebo-controlled MISSION trial (NCT00863746).

Sunitinib

Sunitinib (Sutent®, Pfizer; New London, CT), a TKI with activity against PDGFR-α/β, c-kit, FLT-3, VEGFR-1 through -3, colony stimulating factor 1 receptor (CSF-1R), and rearranged during transfection (RET), is FDA approved in advanced RCC and imatinib-resistant gastrointestinal stromal tumors [100]. In phase II trials of sunitinib in patients with refractory NSCLC, RR was 2.1% with 37.5 mg/day [94] and 11.1% with 50 mg/day [95] (Table 2). The most common grade 3 or 4 toxicities observed with the 50 mg/day dosing schedule (4 weeks on and 2 off) were fatigue/asthenia, lymphopenia, pain/myalgia, dyspnea, and nausea/vomiting [95]. Scagliotti and colleagues recently published data from the SUN 1087 trial in patients with previously treated NSCLC, which showed an improvement in PFS with the combination of sunitinib plus erlotinib compared with placebo plus erlotinib (15.5 vs 8.7 weeks, respectively; $P = 0.0023$), but no difference in OS (9.0 vs 8.5 months)[2]. Ongoing studies are evaluating the role of combination therapy with sunitinib and cytotoxic chemotherapy in NSCLC.

Cediranib

Cediranib (Recentin™, AstraZeneca; Wilmington, DE), is a TKI targeting VEGFR-1 through -3, PDGFRα/β, FGFR-1, and c-kit [79]. In addition to multikinase inhibition, preclinical data from Wedge and colleagues [79] revealed significant inhibition of angiogenesis in a fibroblast/endothelial cell co-culture model, as well as inhibited growth of human tumor xenografts (colon, lung, prostate, breast, ovary). Goss and colleagues [101] reported cediranib 30 mg dosing in combination with cisplatin/gemcitabine in patients with advanced NSCLC to be tolerable, with responses in 4 of 12 evaluable patients (33.3%). However, in 2010, a phase II/III trial evaluating carboplatin/paclitaxel with or without cediranib 30 mg in advanced NSCLC was placed on hold to review imbalances in assigned causes of death [96]. The 30 mg dose was poorly tolerated due to hypertension, hand-foot syndrome, gastrointestinal toxicity, fatigue, neutropenia, and hypothyroidism; a trial of carboplatin/paclitaxel with or without 20 mg cediranib was subsequently initiated but closed early [102]. Further information is awaited.

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Motesanib

Motesanib (Amgen; Thousand Oaks, CA) is a TKI targeting VEGFR-1 through -3, PDGFR, RET, and c-kit [80]. In a phase Ib study, motesanib was tolerable in conjunction with carboplatin/paclitaxel and/or panitumumab (anti-EGFR monoclonal antibody; Vectibex®, Amgen; Thousand Oaks, CA) in patients with advanced NSCLC [103]. In a randomized, open-label phase II trial of motesanib versus bevacizumab combined with paclitaxel/carboplatin, motesanib 125 mg/day continuous dosing resulted in an objective RR of 30% and a median PFS and OS of 7.7 and 14.0 months, respectively [97]. Grade ≥3 adverse events—gastrointestinal (nausea, vomiting, diarrhea) and hypertension—were more common with motesanib than with bevacizumab. The phase III MONET1 trial evaluating the combination of carboplatin, paclitaxel, and motesanib was halted after an interim safety analysis revealed unacceptable rates of hemoptysis; however, the trial had been approved to restart with accrual limited to those with nonsquamous histology (NCT00460317). Recently reported results revealed no improvement in the primary endpoint of OS with motesanib plus chemotherapy versus chemotherapy alone (13.0 vs 11.0 months) despite significant improvement in the secondary endpoints of PFS (5.6 vs 5.4 months) and RR (40% vs 26%); grade ≥3 adverse events that occurred more frequently with motesanib compared with placebo included neutropenia, diarrhea, hypertension, and cholecystitis[3].

Axitinib

Axitinib (Pfizer; New London, CT) targets VEGFR-1 through -3, PDGFR-β, and c-kit [81,98]. Hu-Lowe and colleagues found that axitinib primarily inhibits VEGFR, with in vitro inhibitory effects on endothelial cell proliferation, survival, and tube formation [104]. Additionally, axitinib reduced retinal vascular VEGFR-2 phosphorylation in rats, inhibited tumor growth and angiogenesis in human xenograft tumors (colon, lung, melanoma, renal cell) in mice, and enhanced the antitumor efficacy of chemotherapy in multiple human tumor models. Schiller and colleagues [98] noted single-agent activity in patients with advanced NSCLC, with an acceptable toxicity profile (Table 2). Grade 3 adverse events included fatigue, hypertension, hyponatremia, diarrhea, and vomiting. Ongoing studies include a randomized phase II trial of axitinib in combination with cisplatin/gemcitabine (NCT00735904).

Linifanib

Linifanib (ABT-869; Abbott; Abbott Park, IL) inhibits VEGFR-1 through -3, PDGFR-β, CSF-1R, c-kit, and FLT-3 [82,105]. In addition to inhibition of VEGF and PDGF at the cellular level, Albert and colleagues showed a dose-dependent growth inhibition in human tumor xenograft models, including small cell lung, breast, and colon carcinomas [105]. In a phase I trial, stable disease for >12 weeks was seen in 16 of 29 patients with refractory solid malignancies; 2 patients with NSCLC had a partial response (PR), with toxicity rates comparable with similar drugs [106]. Dose-limiting toxicities observed included fatigue, proteinuria, and hypertension. A phase II trial is currently investigating ABT-869 (low vs high dose) in patients with advanced NSCLC (NCT00517790).

Brivanib

Brivanib (Bristol-Myers Squibb; New York, NY) inhibits VEGFR-1 through 3 and FGFR-1 through -3 [83]. Brivanib suppressed tumor growth of human hepatocellular (HCC)

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xenografts in mice, decreased phosphorylated VEGFR-2, microvessel density and cell proliferation, and increased apoptosis [83]. The expression of FGFR-1 and -2 in tumors was correlated with growth inhibition, suggesting a potential predictive biomarker [83]. Platero and colleagues[4] correlated positive tumor FGF-2 expression by IHC (n = 24) with a trend for improved PFS ($P = 0.075$) and improved RR ($P = 0.03$) in patients treated with brivanib versus those whose tumors did not express FGF-2 (n = 19) in a phase I trial of advanced solid malignancies. In another phase I trial of brivanib in solid tumors, 1 of 4 patients enrolled had NSCLC and achieved stable disease, and no serious adverse treatment-related events were reported. Single grade 2 events including fatigue, abdominal pain, dysphagia, back pain, cognitive disorder, and cachexia were observed [107]. A randomized phase II discontinuation study evaluating the efficacy of brivanib in multiple tumor types, including lung cancer, is accruing patients (NCT00633789). Preliminary results included a 12-week stable disease rate of 24% for 42 patients with NSCLC, considered insufficient for expanding accrual to this tumor-specific cohort (as was also the case for the pancreatic, gastric, and bladder cohorts); however, early evidence of activity led to an expanded cohort of patients with soft tissue sarcoma[5].

BIBF 1120

BIBF 1120 (Boehringer Ingelheim; Ingelheim, Germany) is an angiokinase inhibitor targeted against VEGFR-1 through -3, FGFR-1 through -3, PDGFR-α/β, FLT-3, and src [85]. Hilberg and colleagues [85] found that BIBF 1120 inhibited MAP kinase and Akt signaling, diminished proliferation, and induced apoptosis in endothelial cells, pericytes, and smooth muscle cells. In a phase II study of BIBF 1120 monotherapy in 73 patients (ECOG performance status 0–2) with relapsed advanced NSCLC (Table 2), the most common grade 3 or 4 toxicities were alanine aminotransferase (ALT) increase, diarrhea, and nausea [99]. Tumor stabilization (SD, complete response [CR], or PR) was achieved in 46% of all patients (ECOG 0–2) and 59% for ECOG 0–1 patients. For all patients (ECOG 0–2), median PFS was 6.9 weeks and median OS was 21.9 weeks. Median PFS and OS for ECOG 0–1 patients (n = 57) were 11.6 and 37.7 weeks, respectively. Two randomized 2-arm, placebo-controlled phase III trials of BIBF 1120 as second-line therapy in combination with either docetaxel (NCT00805194; LUME-Lung 1) or pemetrexed (NCT00806819; LUME-Lung 2) in NSCLC patients have been initiated; BIBF 1120 will be continued as maintenance therapy after cessation of combination therapy in both trials.

Pazopanib

Pazopanib (GlaxoSmithKline; London, UK) is a TKI with activity against VEGFR-1 through -3, PDGFR-α/β, FGFR-1 and -3, and c-kit [86]. In preclinical models, Kumar and colleagues found that pazopanib inhibited VEGF- and bFGF-mediated angiogenesis (mouse corneal assay); in a NSCLC mouse xenograft model, pazopanib produced an almost complete inhibition of human tumor growth [86]. Phase III data have shown efficacy of pazopanib in RCC [108]. A study of preoperative pazopanib monotherapy in 35 patients with stage I/II (94% stage I) NSCLC has completed accrual and shown a manageable safety profile [109]. Thirty (86%) patients had a post-treatment reduction in tumor volume (range, 1%–86%), 3 of whom had a PR. Grade 2 hypertension, diarrhea, and fatigue were the most

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common adverse events observed. Currently enrolling studies in NSCLC include pazopanib plus paclitaxel and pazopanib as third-line treatment. In an analysis of pazopanib in early-stage NSCLC, elevated baseline plasma levels of hepatocyte growth factor and IL-12 levels correlated with response, suggesting potential predictive biomarkers [110].

PDGFR-SPECIFIC THERAPIES IN CLINICAL DEVELOPMENT

In addition to trials evaluating the aforementioned multitargeted agents (Table 3), therapies specifically targeting PDGFR or FGFR are currently in development in various advanced malignancies (Table 4; Figure 2), with limited NSCLC-specific information currently available.

IMC-3G3

IMC-3G3 (ImClone Systems; New York, NY) is a fully human IgG_1 monoclonal antibody with high affinity for PDGFR-α but does not cross-react with PDGFR-β. Loizos and colleagues found that IMC-3G3 inhibited signaling as well as cell proliferation through PDGFR-α, in normal, glioblastoma and leiomyosarcoma cell lines [111]. Growth inhibition was seen in glioblastoma and leiomyosarcoma human xenografts. IMC-3G3 has also been shown to inhibit proliferation in ovarian and hepatoma cell lines [112,113] and to enhance the antitumor effects of docetaxel in ovarian cancer cell lines and mouse xenograft models[6]. Russell and colleagues injected PC3-ML human prostate cancer cells (highly bone-metastatic) directly into the bloodstream of mice and noted that treatment with IMC-3G3 delayed progression of skeletal metastases and decreased the size of existing metastases [114]. A phase I trial evaluating IMC-3G3 in patients with advanced solid malignancies showed preliminary safety, with no dose-limiting toxicities in the first cycle; one patient had prostate-specific antigen (PSA) decrease >50%[7]. An ongoing phase II study (NCT00918203) is evaluating paclitaxel/carboplatin alone or in combination with IMC-3G3 as first-line treatment of advanced NSCLC[8].

MEDI-575

MEDI-575 (MedImmune LLC; Gaithersburg, MD) is a fully humanized IgG_2 monoclonal antibody that targets the PDGFR-α receptor without blocking PDGFR-β. Mouse tumor models showed antitumor efficacy with MEDI-575 in glioblastoma multiforme xenografts[9]. Another mouse xenograft model found that MEDI-575 enhanced the activity of carboplatin and paclitaxel in NSCLC, possibly related to a MEDI-575-associated reduction in phosphorylated PDGFR-α expression in tumor stroma[10]. In a phase I study of MEDI-575 in patients with advanced solid tumors, most treatment-related adverse events were grade 1/2 and reversible[11]. MEDI-575 is currently being evaluated in phase I and phase II clinical

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trials, including a recently initiated phase I/II study of carboplatin/paclitaxel with or without MEDI-575 in previously-untreated advanced NSCLC (NCT01268059).

SU101

SU101 (leflunomide, Arava®, Sanofi Aventis; Bridgewater, NJ) is FDA approved for the treatment of rheumatoid arthritis. In preclinical studies by Xu and colleagues, the active metabolite of SU101, A77 1776, more effectively inhibited PDGFR than EGFR and had no effect on FGFR [115]. A77 1776 demonstrated anti-proliferative activity against the C6 glioma cells both in vitro and in nude mice. In vivo, the anti-proliferative effects were independent of pyrimidine nucleotide synthesis inhibition and potentially due to tyrosine phosphorylation inhibition. In a phase I trial of 26 patients with advanced solid malignancies, SU101 was tolerable, with the most common toxicities being mild to moderate nausea, vomiting, and fever; 2 patients experienced grade 3 neutropenia [116].

FGFR-SPECIFIC THERAPIES IN CLINICAL DEVELOPMENT

BGJ398

BGJ398 (Novartis; Basel, Switzerland) is a small molecule TKI that selectively targets FGFRs (data on file, Novartis) and is currently being investigated in a phase I dose-escalation trial in patients with advanced solid malignancies (NCT01004224).

AZD4547

AZD4547 (AstraZeneca; Wilmington, DE) is a pan-FGFR inhibitor currently being evaluated in phase I trials of patients with advanced solid malignancies (NCT00979134; NCT01213160), as well as in a phase I/II breast cancer trial in combination with exemestane (NCT01202591). Preclinical data have not yet been published on this compound.

CONCLUDING REMARKS

NSCLC represents a molecularly heterogeneous set of diseases. Preclinical and clinical data suggest that the PDGFR and FGFR pathways are viable targets in NSCLC; both pathways may have a role in angiogenesis and, in some cases, stimulating tumor growth directly. Potential predictive biomarkers for these pathways, such as serum PDGF-α, -β, and tumor expression of FGF ligand or receptor, are being investigated, but none have been validated for clinical use.

Adding FGFR and/or PDGFR inhibition to the mix of antiangiogenic agents for NSCLC may have broad applicability given that these reflect host-derived angiogenic mechanisms. Mutations and gene-copy number increases in tumor cells relating to both pathways have been reported, although their clinical significance in NSCLC remains unknown. Consequently, direct antitumor activity from anti-FGFR/PDGFR therapeutic approaches is likely to be more restricted as not all NSCLC tumors will directly utilize these pathways. Recent preclinical studies have suggested targeting FGFR as a strategy for treating de novo or acquired resistance to EGFR-TKI therapy. Demonstrating the presence of FGFR pathway upregulation in the clinical setting of erlotinib/gefitinib resistance in patients with or without an activating *EGFR* mutation will be the next step and may suggest a population that could most benefit from dual EGFR/FGFR inhibition.

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
bFGF	basic fibroblast growth factor
bid	twice per day
CAF	cancer-associated fibroblast
c-kit	stem cell factor receptor
CR	complete response
CSF-1R	colony stimulating factor 1 receptor
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FLT-3	fms-like tyrosine kinase 3
HCC	human hepatocellular
IC_{50}	half maximal inhibitory concentration
ICAM	intercellular adhesion molecule
ICMJE	International Committee of Medical Journal Editors
IHC	immunohistochemistry
NR	not reported
NSCLC	non–small cell lung cancer
OS	overall survival
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PS	performance status
qd	once per day
Raf	v-raf 1 murine leukemia viral oncogene homolog 1

RCC	renal cell carcinoma
RET	rearranged during transfection
RR	response rate
SD	stable disease
SNP	single nucleotide polymorphism
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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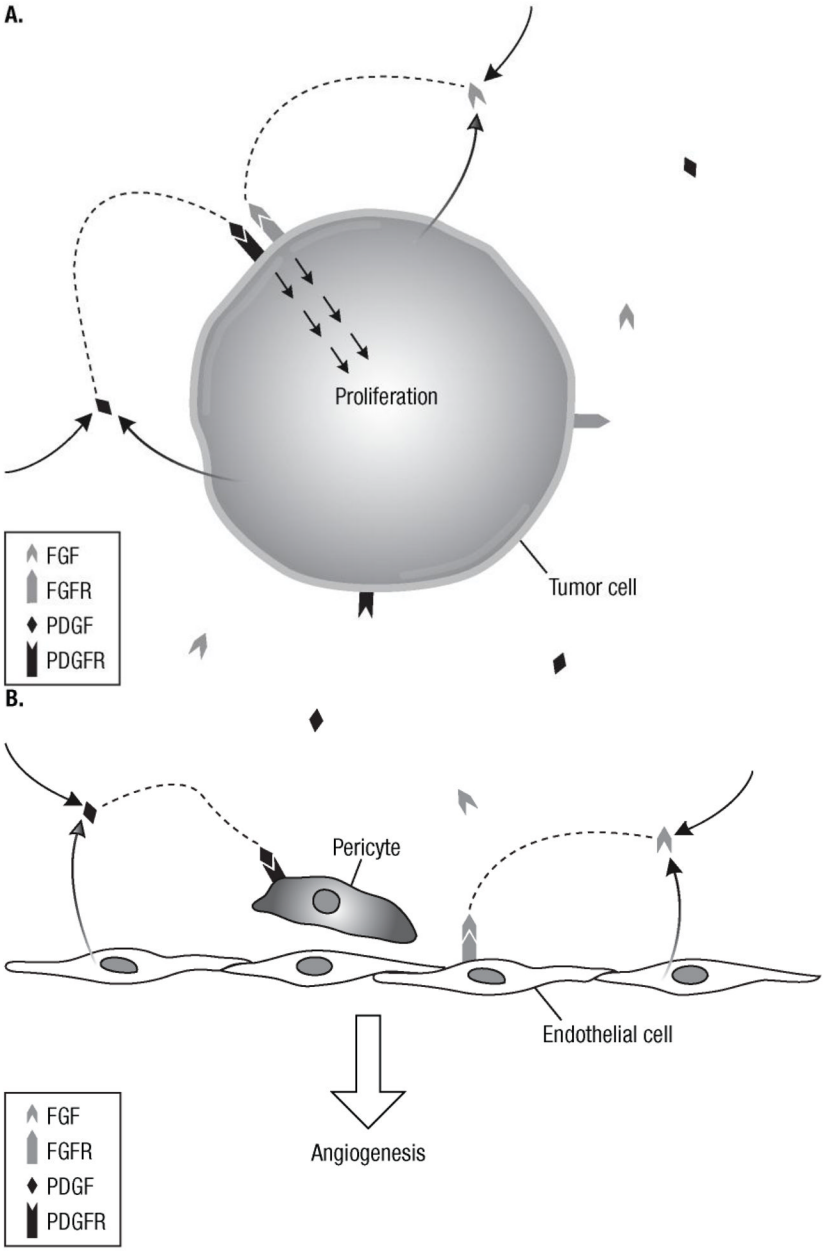

Figure 1. Schematic of the potential roles of the FGFR and PDGFR pathways in tumor proliferation and angiogenesis

Autocrine and paracrine signaling of the FGF and PDGF pathways may contribute to tumor proliferation (A) and angiogenesis (B). (A) Activation of FGFR and PDGFR from ligands expressed by tumor cells or other tissues results in stimulation of mitogenic downstream cascades. (B) Similarly, PDGF secreted from endothelial cells may recruit pericytes necessary for angiogenesis through paracrine signaling. In addition, activation of FGFR on endothelial cells results in cellular proliferation and increased angiogenesis.

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor.

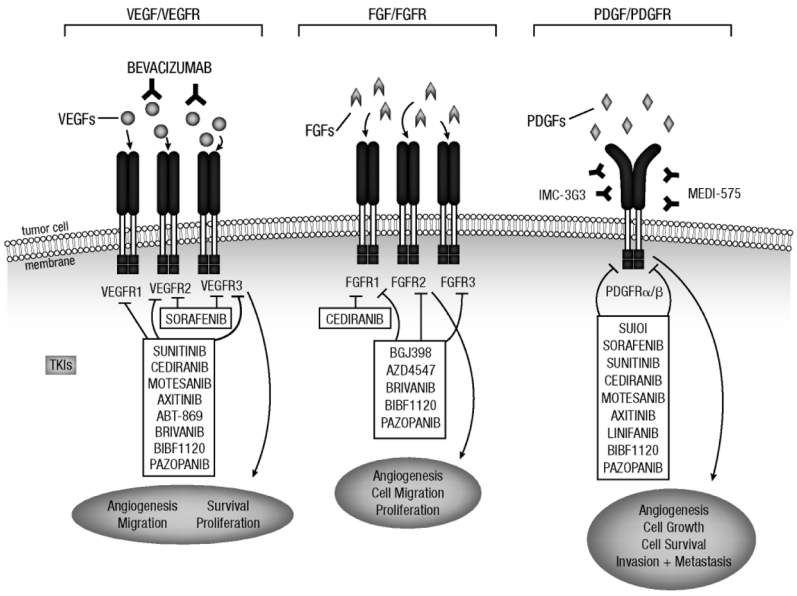

Figure 2. Molecular targets of the investigational multitargeted TKIs being studied in NSCLC and PDGFR- and FGFR-specific agents in earlier clinical development

Illustration depicting targeted inhibition of the VEGF, PDGF, and FGF pathways by monoclonal antibodies and TKIs.

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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Table 1

In vitro VEGFR, PDGFR, and FGFR kinase activity of multitargeted TKIs in clinical development for NSCLC.

Agent	IC_{50}, nM			Other targets	Clinical phase
	VEGFR-1, -2, -3	**PDGFR-α, -β**	**FGFR-1, -2, -3**		
Sorafenib [77]	NR, 90, 20[a]	NR, 57[a]	580, NR, NR	c-kit, FLT-3, Raf	III
Sunitinib [78]	NR, 80, NR	NR, 2	2,900, NR, NR	c-kit, FLT-3, CSF-1R, RET	III
Cediranib [79]	5, 1, 3	36, 5	26, NR, NR	c-kit	III
Motesanib [80]	2, 3, 6	NR, 84	>2,800, NR, NR	c-kit, RET	III
Axitinib [81]	NR[b]	NR[b]	NR	c-kit	II
Linifanib [82]	3, 4, 190	NR, 66	>12,500, NR, NR	FLT-3, CSF-1R, c-kit	II
Brivanib [83,84][c]	380, 25, 10	NR, >6,000	148, 125, 68	NR	II
BIBF 1120 [85]	34, 21, 13	59, 65	69, 37, 108	FLT-3, src	III
Pazopanib [86]	10, 30, 47	71, 84	140, NR, 130	c-kit	II/III

[a] IC_{50} values of sorafenib against murine VEGFR-3 and PDGFR-β.

[b] Axitinib reportedly inhibits VEGFRs at subnanomolar concentrations and PDGFR-β at low-nanomolar concentrations [81].

[c] IC_{50} values for brivanib (BMS-582664) are reported for BMS-540215, the active moiety hydrolyzed in vivo.

c-kit, stem cell factor receptor; CSF-1R, colony stimulating factor 1 receptor; FGFR, fibroblast growth factor receptor; FLT-3, fms-like tyrosine kinase 3; IC_{50}, half maximal inhibitory concentration; NR, not reported; PDGFR, platelet-derived growth factor receptor; Raf, v-raf 1 murine leukemia viral oncogene homolog 1; RET, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.

Table 2

Data from published phase II trials of investigational multitargeted antiangiogenic TKIs in patients with advanced NSCLC.

Trial description	Prior therapy/performance status	RR, %	SD, %	PFS	OS	Most common (≥25%) treatment-related AEs[a] (%)
Sorafenib 400 mg bid (N = 54); phase II [93]	1 or 2 chemotherapy regimens ECOG PS 0–2	0	59	2.7 mo	6.7 mo	Diarrhea, 40 Hand-foot skin reaction, 37 Fatigue, 27 Nausea, 25
Sunitinib 37.5 mg qd (N = 47); phase II [94]	1 or 2 chemotherapy regimens ECOG PS 0 or 1[b]	2.1	23.4	11.9 wks	37.1 wks	Diarrhea, 27.7 Fatigue, 27.7
Sunitinib 50 mg qd (N = 63); phase II [95]	≥ 1 chemotherapy regimens ECOG PS 0 or 1	11.1	28.6	12 wks	23.4 wks	Fatigue/asthenia, 70[c] Lymphopenia, 69 Leukopenia, 68 Pain/myalgia, 60 Anemia, 58 Thrombocytopenia, 52 Nausea/vomiting, 52 Neutropenia, 49 Stomatitis/mucosal inflammation, 43 Anorexia/weight loss, 35 Dyspnea, 35 Diarrhea, 33 Dysgeusia, 27 Cough, 25
Cediranib 30 mg[d] qd versus placebo in combination with carboplatin/paclitaxel (N = 296[e]); phase II/III[f] [96]	Adjuvant chemotherapy ≥1 yr prior, radiation, EGFR-targeted therapy ECOG PS 0 or 1[g]	38 vs 16; *P* <0.001	NR	5.6 vs 5.0 mo; *P* = 0.13	10.5 vs 10.1 mo; *P* = 0.11	Fatigue; 88 (all grades), 29 (grade ≥3)[c] Diarrhea; 79 (all grades), 15 (grade ≥3) Dyspnea; 75 (all grades), 10 (grade ≥3) Neutropenia; 65 (all grades), 49 (grade ≥3) Sensory neuropathy; 63 (all grades), 3 (grade ≥3) Anorexia; 61 (all grades), 6 (grade ≥3) Increased TSH; 45 (all grades), 27 (grade ≥3) Stomatitis; 41 (all grades), 6 (grade ≥3) Bleeding; 25 (all grades), 3 (grade ≥3)
Motesanib 125 mg qd versus motesanib 75 mg bid versus bevacizumab in combination with carboplatin/paclitaxel (N = 186); phase II [97]	Chemotherapy-naive ECOG PS ≤ 1	30 vs 23 vs 37	35 vs 50 vs 42	7.7 vs 5.8 vs 8.3 mo	14.0 vs 12.8 vs 14.0 mo	Fatigue; 63 vs 52 vs 60 (all grades), 17 vs 5 vs 8 (grade 3/4)[c] Diarrhea; 51 vs 47 vs 28 (all grades), 19 vs 11 vs 3 (grade 3/4) Hypertension; 47 vs 27 vs 15 (all grades), 5 vs 8 vs 2 (grade 3/4) Nausea; 47 vs 47 vs 38 (all grades), 8 vs 2 vs 2 (grade 3/4) Vomiting; 47 vs 35 vs 23 (all grades), 5 vs 5 vs 3 (grade 3/4) Alopecia; 41 vs 34 vs 38 (all grades), 0 vs 0 vs 3 (grade 3/4) Constipation; 34 vs 32 vs 33 (all grades), 3 vs 2 vs 2 (grade 3/4) Dehydration; 32 vs 21 vs 10 (all grades), 17 vs 11 vs 3 (grade 3/4)

Trial description	Prior therapy/performance status	RR, %	SD, %	PFS	OS	Most common (≥25%) treatment-related AEs[a] (%)
						Anorexia; 32 vs 24 vs 28 (all grades), 12 vs 2 vs 3 (grade 3/4) Weight decreased; 31 vs 19 vs 13 (all grades), 3 vs 0 vs 2 (grade 3/4) Peripheral neuropathy; 27 vs 26 vs 45 (all grades), 3 vs 2 vs 7 (grade 3/4) Dyspnea; 25 vs 21 vs 23 (all grades), 5 vs 0 vs 3 (grade 3/4)
Axitinib 5 mg bid (N = 32); phase II [98]	Chemotherapy- naive and previously treated ECOG PS 0 or 1[h]	9	31	4.9 mo	14.8 mo	Fatigue; 50 (grade 1/2), 22 (grade 3) Anorexia, 50 (grade 1/2) Diarrhea; 41 (grade 1/2), 3 (grade 3) Nausea, 34 (grade 1/2) Anemia, 31 (grade 1/2) Hoarseness, 28 (grade 1/2)
BIBF 1120 250 mg bid or 150 mg bid (N = 73 [ECOG PS 0–2]; n = 56 [ECOG PS 0–1]); phase II [99]	1 or 2 chemotherapy regimens ECOG PS 0–2	PS 0–2, 1.4	PS 0–2, 47.9	PS 0–2, 6.9 wks PS 0–1, 11.6 wks	PS 0–2, 21.9 wks PS 0–1, 37.7 wks	Nausea; 57.5 (all grades), 6.8 (grade 3/4) Diarrhea; 47.9 (all grades), 8.2 (grade 3/4) Vomiting; 42.5 (all grades), 2.7 (grade 3/4) Anorexia, 28.8 (all grades), 1.4 (grade 3/4)

[a] AEs reported at all grades unless otherwise indicated.

[b] One enrolled patient had a performance status of 2.

[c] Only all-cause AEs were reported.

[d] The first 45 patients received cediranib 45 mg qd.

[e] Thirty patients were not evaluable for response.

[f] Trial did not proceed to phase III.

[g] Performance status was originally 0–2 but was revised per protocol amendment (in response to increased treatment-related deaths in the cediranib arm [45-mg/day cohort]).

[h] Three enrolled patients had an unknown performance status.

AE, adverse event; bid, twice per day; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NR, not reported; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; qd, once per day; RR, response rate; SD, stable disease; TKI, tyrosine kinase receptor; TSH, thyroid-stimulating hormone.

Table 3

Overview of ongoing trials of investigational multitargeted antiangiogenic TKIs in NSCLC.[a]

Agent (type; target)	Trial description	Identifier number (status)[b]
BIBF 1120 (TKI: VEGFR-1 through -3, FGFR-1 through -3, PDGFR-α/β, FLT-3, src)	Phase I trial of BIBF 1120 in combination with pemetrexed in Japanese patients with advanced NSCLC	NCT00979576 (Recruiting)
	Phase I trial of BIBF 1120 in combination with docetaxel in Japanese patients with advanced NSCLC	NCT00876460 (Recruiting)
	Phase III trial of docetaxel in combination with BIBF 1120 or placebo as second-line therapy in patients with advanced NSCLC (LUME-Lung 1)	NCT00805194 (Active, no longer recruiting)
	Phase III trial of pemetrexed in combination with BIBF 1120 or placebo as second-line therapy in patients with advanced NSCLC (LUME-Lung 2)	NCT00806819 (Active, no longer recruiting)
Cediranib/AZD2171 (TKI: VEGFR-1 through -3, PDGFR-α/β, FGFR-1, c-kit)	Phase I trial of cediranib in combination with chemotherapy as first-line treatment in patients with lung cancer	NCT00621361 (Active, no longer recruiting)
	Phase II trial of gemcitabine/carboplatin with or without cediranib as first-line therapy in patients with NSCLC	NCT00326599 (Unknown)
	Phase II trial of cediranib and pemetrexed in patients with relapsed NSCLC	NCT00410904 (Recruiting)
	Phase II/III trial of paclitaxel/carboplatin with or without cediranib in patients with NSCLC	NCT00245154 (Active, no longer recruiting)
	Phase III trial of cediranib in combination with paclitaxel/carboplatin in patients with advanced NSCLC	NCT00795340 (Active, no longer recruiting)
Pazopanib/GW786034 (TKI: VEGFR-1 through -3, PDGFR-α/β, FGFR-1 and -3, and c-kit)	Phase I trial of pazopanib and vinorelbine in patients with NSCLC and breast cancer	NCT01060514 (Recruiting)
	Phase II trial of pazopanib as third-line therapy in patients with NSCLC	NCT01049776 (Recruiting)
	Phase II trial of erlotinib and pazopanib in patients with previously treated advanced NSCLC	NCT01027598 (Active, no longer recruiting)
	Phase II trial of pazopanib and paclitaxel in patients with advanced NSCLC	NCT00866528 (Active, no longer recruiting)
	Phase II/III trial of pazopanib as adjuvant treatment after surgery in patients with stage I NSCLC	NCT00775307 (Recruiting)
	Phase II trial of pazopanib versus pemetrexed as maintenance therapy in patients with advanced NSCLC not progressing after carboplatin or cisplatin plus pemetrexed induction	NCT01313663 (Recruiting)
	Phase II/III trial of pazopanib or placebo in NSCLC patients not progressing after first-line chemotherapy	NCT01208064 (Recruiting)
	Phase II trial of pazopanib in advanced NSCLC after progression on first-line bevacizumab- containing therapy	NCT01262820 (Recruiting)
	Phase II trial of pazopanib with or without pemetrexed in advanced NSCLC previously treated with bevacizumab	NCT01107652 (Recruiting)
Brivanib/BMS-582664 (TKI: VEGFR-1 through -3 and FGFR-1 through -3)	Phase II trial of brivanib in patients with multiple tumor types (including advanced NSCLC)	NCT00633789 (Active, no longer recruiting)

Agent (type; target)	Trial description	Identifier number (status)[b]
Motesanib/AMG 706 (TKI: VEGFR-1 through -3, PDGFR, c-kit, RET)	Phase II trial of motesanib or bevacizumab in combination with paclitaxel/carboplatin in patients with advanced NSCLC	NCT00369070 (Active, no longer recruiting)
	Phase III trial of motesanib or placebo in combination with paclitaxel/carboplatin in patients with advanced nonsquamous NSCLC	NCT00460317 (Active, no longer recruiting)
Sorafenib (TKI: VEGFR-2 and -3, PDGFR-β, FLT-3, c-kit, Raf)	Phase I trial of sorafenib in previously untreated patients with NSCLC	NCT00533585 (Active, no longer recruiting)
	Phase I trial of panobinostat and sorafenib in patients with renal cancer or NSCLC	NCT01005797 (Recruiting)
	Phase I trial of sorafenib in combination with metronomic vinorelbine in patients with advanced NSCLC	NCT00870532 (Unknown)
	Phase I trial of sorafenib with carboplatin, paclitaxel, and bevacizumab in patients with untreated stage IIIb NSCLC	NCT01069328 (Active, no longer recruiting)
	Phase II trial of sorafenib after failure of an EGFR-TKI in patients with NSCLC	NCT00922584 (Unknown)
	Phase II trial of sorafenib in patients with NSCLC (BATTLE)	NCT00411671 (Active, no longer recruiting)
	Phase II trial of sorafenib/erlotinib or erlotinib alone in patients with previously treated advanced NSCLC	NCT00600015 (Active, no longer recruiting)
	Phase II trial of sorafenib and erlotinib in patients with NSCLC that has not responded to chemotherapy	NCT00801385 (Unknown)
	Phase II trial of sorafenib/erlotinib or sorafenib alone in patients with advanced NSCLC progressing on erlotinib	NCT00609804 (Active, no longer recruiting)
	Phase II study of metronomic docetaxel and sorafenib as first-line therapy in patients with advanced nonsquamous NSCLC	NCT00801801 (Active, no longer recruiting)
	Phase II trial of erlotinib and sorafenib in chemonaive patients with locally advanced or metastatic NSCLC	NCT00722969 (Unknown)
	Phase II trial of sorafenib in non-smokers or former light smokers with relapsed or refractory NSCLC	NCT00754923 (Unknown)
	Phase II trial of sorafenib in combination with pemetrexed as second-line therapy in patients with NSCLC	NCT00454194 (Active, no longer recruiting)
	Phase II trial of sorafenib in patients with refractory NSCLC	NCT00064350 (Unknown)
	Phase III trial of sorafenib as third- or fourth-line therapy in patients with predominantly nonsquamous NSCLC	NCT00863746 (Active, no longer recruiting)
Sunitinib (TKI: VEGFR-1 through -3, PDGFR-α/β, c- kit, FLT-3, CSF-1R, RET)	Phase I trial of sunitinib and rapamycin in patients with advanced NSCLC	NCT00555256 (Active, no longer recruiting)
	Phase I trial of sunitinib and erlotinib in patients with NSCLC	NCT00581789 (Active, no longer recruiting)
	Phase II trial of salvage therapy with sunitinib, docetaxel, and a platinum agent in patients with NSCLC	NCT01019798 (Recruiting)
	Phase II trial of pemetrexed and/or sunitinib as second-line therapy in patients with NSCLC	NCT00698815 (Recruiting)
	Phase II trial of sunitinib in patients over 70 years of age with NSCLC	NCT00864721 (Active, no longer recruiting)

Agent (type; target)	Trial description	Identifier number (status)[b]
	Phase II trial of sunitinib/erlotinib or erlotinib alone in patients with NSCLC	NCT00265317 (Active, no longer recruiting)
	Phase II trial of sunitinib as maintenance therapy in patients with advanced NSCLC	NCT01210053 (Recruiting)
	Phase III trial of sunitinib/erlotinib or erlotinib alone in patients with NSCLC	NCT00457392 (Active, no longer recruiting)
	Phase III trial of sunitinib as maintenance therapy in patients with advanced NSCLC previously treated with combination chemotherapy	NCT00693992 (Recruiting)
Linifanib (TKI: VEGFR-1 through -3, PDGFR-β, c-kit, and FLT-3)	Phase II trial of ABT-869 in patients with advanced NSCLC	NCT00517790 (Active, no longer recruiting)
	Phase II trial of paclitaxel/carboplatin in combination with ABT-869 in patients with advanced or metastatic NSCLC	NCT00716534 (Recruiting)
	Phase I trial of ABT-869 in combination with paclitaxel/carboplatin in Japanese patients with NSCLC	NCT01225302 (Active, no longer recruiting)
Axitinib/AG-013736 (TKI: VEGFR-1 through -3, PDGFR-β, c-kit)	Phase II trial of axitinib, cisplatin, and gemcitabine in patients with squamous NSCLC	NCT00735904 (Active, no longer recruiting)
	Phase II trial of axitinib or bevacizumab in combination with carboplatin/paclitaxel in patients with advanced lung cancer	NCT00600821 (Active, no longer recruiting)

[a] Based on ClinicalTrials.gov accessed on March 22, 2011, with updates based on status as of November 15, 2011.

[b] Active status indicates the trial is ongoing, but no longer recruiting patients.

c-kit, stem cell factor receptor; BAC, bronchioloalveolar carcinoma; CSF-1R, colony stimulating factor-1 receptor; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; FLT-3, fms-like tyrosine kinase 3; FGFR, fibroblast growth factor receptor; NSCLC, non–small cell lung cancer; PDGFR, platelet-derived growth factor receptor; RET, rearranged in transformation; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Table 4

Overview of ongoing oncology trials of agents targeting PDGFR or FGFR signaling.[a]

Agent (type; target)	Trial description	Identifier number (status)[b]
PDGFR-targeted agents		
IMC-3G3 (Ab: PDGFR-α)	Phase II trial of IMC-3G3 in combination with paclitaxel/ carboplatin in previously untreated patients with advanced NSCLC	NCT00918203 (Recruiting)
	Phase II trial of liposomal doxorubicin with or without IMC-3G3 in platinum-refractory or platinum-resistant advanced ovarian cancer	NCT00913835 (Active, no longer recruiting)
	Phase II trial of ramucirumab or IMC-3G3 in patients with glioblastoma multiforme	NCT00895180 (Recruiting)
	Phase II trial of IMC-3G3 in prostate cancer	NCT01204710 (Recruiting)
	Phase I/II trial of IMC-3G3 in soft tissue sarcomas	NCT01185964 (Recruiting)
	Phase I trial of safety and pharmacokinetics of IMC-3G3 in Japanese patients with solid tumors	NCT01199822 (Active, no longer recruiting)
MEDI-575 (Ab: PDGFR-α)	Phase I trial evaluating dose escalation and dose expansion of MEDI-575 in patients with advanced cancer	NCT00816400 (Active, no longer recruiting)
	Phase I trial of MEDI-575 in patients with advanced solid malignancies	NCT01102400 (Recruiting)
	Phase I/II trial of MEDI-575 in combination with paclitaxel/ carboplatin in previously untreated patients with advanced NSCLC	NCT01268059 (Recruiting)
	Phase II trial of MEDI-575 in patients with recurrent glioblastoma multiforme	NCT01268566 (Recruiting)
SU101 (small molecule: PDGFR)	Phase II trial of leflunomide (SU101) in patients with relapsed anaplastic astrocytoma	NCT00003775 (Unknown)
FGFR-targeted agents		
BGJ398 (TKI: FGFRs)	Phase I dose escalation study in patients with advanced solid malignancies	NCT01004224 (Recruiting)
AZD4547 (TKI: FGFR)	Phase I dose escalation study in patients with advanced tumors	NCT00979134 (Recruiting)
	Phase I/II trial of AZD4547 in combination with exemestane in estrogen receptor-positive breast cancer	NCT01202591 (Recruiting)
	Phase I trial of AZD4547 in Japanese patients with advanced solid malignancies	NCT01213160 (Recruiting)

[a]Based on ClinicalTrials.gov accessed on March 22, 2011, with updates based on status as of November 15, 2011.

[b]Active status indicates the trial is ongoing, but no longer recruiting patients.

Ab, antibody; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor.