Angiogenesis inhibitors in the treatment of non-small cell lung cancer

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***Abstract*:** A therapeutic plateau seems to have been reached with the standard treatment of cytotoxic chemotherapy alone for advanced stage non-small cell lung cancer (NSCLC) and new treatment options are urgently needed. Recent insight into the molecular biology of cancer has identified angiogenesis as one of the key biological processes. The major player in tumor angiogenesis is the vascular endothelial growth factor (VEGF) pathway. VEGF is expressed in the majority of NSCLC and overexpression is associated with a poor prognosis. The VEGF pathway can be inhibited in two main ways: targeting VEGF directly or inhibiting the VEGF receptors. The development of angiogenesis inhibitors has shown great promise in the treatment of NSCLC. Bevacizumab, an anti-VEGF antibody, has been approved for the treatment of advanced NSCLC and other drugs are undergoing phase III investigation. However, a number of unresolved issues remain. In this review, we discuss the main angiogenesis inhibitors in development for the treatment of NSCLC focusing on the VEGF pathway.

***Keywords*:** angiogenesis inhibitors, non-small cell lung cancer, vascular endothelial growth factor, bevacizumab

Introduction

Lung cancer is the leading cause of cancer related deaths worldwide [Jemal *et al.* 2008]. The majority of patients present with locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC). The standard first-line treatment for these patients is at present a platinum-based doublet chemotherapy regimen with a third generation cytotoxic agent. Despite multiple studies to evaluate different schedules, doses and combinations the results remain poor with a median survival of 8 to 12 months and 1-year survival rate of 33 to 46% [Scagliotti *et al.* 2008; Le Chevalier *et al.* 2005; Fossella *et al.* 2003; Scagliotti *et al.* 2002; Schiller *et al.* 2002; Kelly *et al.* 2001]. A therapeutic plateau seems to have been reached with cytotoxic chemotherapy alone and new treatment options are urgently needed.

In recent years, increasing insight into the molecular biology of cancer has identified key biological processes [Hanahan and Weinberg, 2000]. Of considerable interest and amenable to therapy is angiogenesis: the formation of new blood vessels from the existing vasculature. Solid tumors depend in part on angiogenesis for growth and metastasis. The development of angiogenesis inhibitors has shown great promise in the treatment of cancer.

Angiogenesis is a multi-step process involving numerous pro- and anti-angiogenic factors [Carmeliet, 2000]. The key player in tumor angiogenesis is the vascular endothelial growth factor (VEGF) pathway. Tumor cells secrete VEGF in response to hypoxia. VEGF binds to transmembrane cell surface tyrosine kinase receptors VEGFR-1 (Flt-1), 2 (KDR/Flk-1), and 3 (Flt-4). These receptors are found on host vascular endothelial cells, monocytes and hematopoetic precursors. Ligand binding activates the intracellular tyrosine kinase domain of the receptor, resulting in a downstream signalling cascade. This stimulates endothelial cell proliferation, differentiation, migration and survival and thereby the formation of new blood vessels [Ferrara, 2004].

VEGF is expressed in the majority of NSCLC and overexpression is associated with a poor prognosis [Han *et al.* 2001; Yuan *et al.* 2001; O'Byrne *et al.* 2000; Fontanini *et al.* 1997]. In addition, elevated serum levels of circulating VEGF are frequently found in patients with NSCLC. Whether this is of prognostic value remains unclear [Kaya *et al.*

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2004; Nieder *et al.* 2003]. VEGF also appears to play a role in developing malignant pleural effusions, enhancing the rate of pleural dissemination, and in lymph node metastasis [Ishii *et al.* 2004; Zebrowski *et al.* 1999]

The VEGF pathway can be inhibited in two main ways: targeting VEGF directly or inhibiting the VEGF receptors. In this review, we discuss the main angiogenesis inhibitors in development for the treatment of NSCLC (Table 1). VEGF inhibition affects only the newly formed, immature and developing blood vessels. Another new class of anticancer drug targeting the established, mature tumor vasculature is in development. These vascular disrupting agents (VDAs) will not be discussed in this review.

Direct VEGF inhibitors

Bevacizumab

Bevacizumab (Avastin), a recombinant, humanized anti-VEGF antibody, has established efficacy in NSCLC. A randomized phase II trial compared carboplatin (area under the curve (AUC) 6) plus paclitaxel (200 mg/m^2) alone or with bevacizumab (7.5 mg/kg or 15 mg/kg) every 3 weeks in 99 patients with previously untreated locally advanced or metastatic NSCLC [Johnson *et al.* 2004]. The addition of bevacizumab at 15 mg/kg led to improved tumor response rates (31.5 *versus* 18.8%) and median time to progression (17.7 *versus* 14.9 months, $p = 0.63$) compared to chemotherapy alone. The treatment was generally well tolerated. However, there was a higher incidence of bleeding including major life-threatening pulmonary hemorrhage, which was fatal in 4 out of 6 cases. This appeared to be associated with squamous cell histology, tumor necrosis, cavitation and location close to major blood vessels. The subsequent randomized phase III trial (ECOG 4599) therefore excluded patients with squamous cell carcinoma and central lesions. This trial compared carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) with and without bevacizumab (15 mg/kg) [Sandler *et al.* 2006]. Patients in the bevacizumab arm ($n = 434$) had higher response rates (35 *versus* 15%, $p < 0.001$) and longer overall and progression free survival (PFS) (6.2 *versus* 4.5 months and 12.3 *versus* 10.3 months, $p = 0.003$ respectively). Treatment was well tolerated although there was a higher incidence of bleeding (4.5 *versus* 0.7%, $p < 0.001$) and treatment-related deaths (15 *versus* 2, $p = 0.001$) including five cases of fatal pulmonary hemorrhage. Based on the ECOG 4599 trial, the Food and Drug Administration (FDA) approved bevacizumab plus carboplatin and paclitaxel as first-line treatment of advanced and metastatic non-squamous NSCLC in October 2006 [Cohen *et al.* 2007]. A recent subgroup analysis found the addition of bevacizumab

Table 1. Angiogenesis inhibitors in development for non-small cell lung cancer.

Drug class	Agent	Mechanism of action	Molecular Targets	Phase of development
VEGF inhibitor	Aflibercept	Soluble fusion protein	VEGF-A, PlGF	III
	Bevacizumab	Inhibitory Ab	VEGF	approved
VEGFR inhibitor	Axitinib	TKI	VEGFR-1, VEGFR-2, PDGFR-β, c-Kit	II
	Cediranib	TKI	VEGFR-1, VEGFR-2, VEGFR-3	III
	CP-547, 632	TKI	VEGFR-2, PDGF	I/II
	Motesanib	TKI	VEGFR-1, VEGFR-2, PDGFR-β, c-Kit, c-Ret	III
	Pazopanib	TKI	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-Kit	II
	Sorafenib	TKI	VEGFR-2, VEGFR-3, PDGFR-β, B-RAF, C-RAF, c-Kit	III
	Sunitinib	TKI	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α PDGFR-β, c-Kit, Flt-3	III
	Vandetanib	TKI	VEGFR-2, VEGFR-3, Ret, EGFR	III
	Vatalanib		VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-Kit	II
	XL 647	TKI	EGFR, Her2, VEGFR-2, EphB4	II
	Thalidomide		bFGF, VEGF, TNF-α	III

EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis factor.

to specifically benefit patients with adenocarcinoma histology. The PFS and overall survival in this subgroup increased from 5 to 6.6 months (hazard ratio (HR) 0.65; 95% CI 0.54–0.78) and 10.3 to 14.2 months (HR 0.69, 95% CI 0.58–0.83) respectively [Sandler *et al.* 2008].

Another phase III trial (AVAIL) combining bevacizumab with chemotherapy as first-line treatment for non-squamous NSCLC has recently completed enrolment. Patients were randomized to receive cisplatin (80 mg/m^2) plus gemcitabine (1.250 mg/m^2) with or without bevacizumab (7.5 mg/kg or 15 mg/kg) every 3 weeks. The results showed that patients receiving chemotherapy alone ($n = 347$) had significantly lower response rates compared to those receiving bevacizumab (20 *versus* 34% (low dose, $n = 345$), $p < 0.0001$, and 30% (high dose, $n = 351$), $p = 0.0023$) [Reck *et al.* 2009]. The median PFS was 6.1 months in the placebo arm, 6.7 in the low-dose arm and 6.5 in the high-dose arm. The treatment was well tolerated although there was an increased incidence of grade 3 bleeding and hypertension in the bevacizumab arms. The incidence of grade 3 pulmonary hemorrhage was low across the 3 groups (0.6% in placebo arm, 1.5% in low dose arm and 0.9% in high-dose arm). The smaller difference in PFS compared with the ECOG 4599 trial may be explained by the slight superiority of gemcitabine–platinum regimens compared to other platinum-containing regimens [Le Chevalier *et al.* 2005]. An alternative explanation is offered by the preclinical study of Shaked *et al.* which showed that antiangiogenic agents enhance the antitumor effect of chemotherapy drugs that induce acute endothelial progenitor cell mobilization, such as paclitaxel, and do not potentiate the efficacy of chemotherapy drugs that do not do so, such as gemcitabine [Shaked *et al.* 2008].

Based on the results of the abovementioned phase III trials the European Medicines Agency (EMEA) approved bevacizumab in combination with platinum-based chemotherapy as first-line treatment for advanced non-squamous NSCLC in August 2007. However, although the exact overall survival data has yet to be published, at the European Society for Medical Oncology (ESMO) 2008 conference in Stokholm it was announced that there was no significant prolongation of overall survival with addition of either doses of bevacizumab to cisplatin and gemcitabine in the AVAIL trial [Manegold *et al.* 2008].

Two phase II trials show promising results when bevacizumab is combined with pemetrexed in patients with advanced NSCLC in the first-line setting. In one trial bevacizumab (15 mg/kg) was added to pemetrexed (500 mg/m^2) and carboplatin (AUC 6) followed by maintenance bevacizumab and pemetrexed [Patel *et al.* 2008]. Out of 49 evaluable patients the objective response rate was 49% (1 complete response and 23 partial responses (PRs)). Time to progression was 7.2 months and median survival 14.0 months. In the other trial bevacizumab (15 mg/kg), pemetrexed (500 mg/m^2) and oxaliplatin (120 mg/m^2) led to a PFS of 7.8 months and overall survival of 16.7 months [Waples *et al.* 2008]. Phase II studies combining bevacizumab with pemetrexed in the second-line setting similarly demonstrate encouraging results. This combination achieved a 50% disease control rate at 3 months with a median PFS of 4.1 months and overall survival of 8.6 months in one trial [Adjei *et al.* 2008]. In another trial bevacizumab, pemetrexed and oxaliplatin led to a PFS of 5.8 months and overall survival of 12.5 months [Heist *et al.* 2008]. These results compare favorably with those achieved with current standard first- and second-line treatment in this patient group and justify further development of these combinations.

There is also encouraging data on the combination of bevacizumab with erlotinib. Erlotinib is a highly selective tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). EGFR is expressed in 50 to 90% of NSCLC. Activation of the EGFR pathway plays a role in cell migration, proliferation, adhesion, invasion, angiogenesis and inhibition of apoptosis [Woodburn, 1999]. Following the randomized phase III BR.21 trial, which showed a 2-month survival benefit *versus* placebo, erlotinib was approved by the FDA and EMEA for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen [Shepherd *et al.* 2005].

Preclinical studies show an interplay between the VEGF and EGFR pathways. Upregulation of EGFR signalling results in the production of pro-angiogenic factors including VEGF. In turn, upregulation of VEGF and other angiogenic factors may result in resistance to EGFR inhibitors [Camp *et al.* 2005]. Preclinical and clinical studies have shown at least an additive antitumor activity when EGFR and VEGF

pathways are inhibited simultaneously. A phase II study evaluated the efficacy and safety of bevacizumab (B) with either chemotherapy (pemetrexed or docetaxel) or erlotinib (E) compared to chemotherapy (C) alone for recurrent or metastatic non-squamous NSCLC after failure of one prior platinum-containing regimen [Herbst *et al.* 2007]. No unexpected adverse events were observed and the toxicity profile of the B + E arm was favorable compared with the chemotherapy arm. Relative to chemotherapy the adjusted hazard ratio for PFS was 0.66 (95% CI, 0.38–1.16) for B + C and 0.72 (95% CI, 0.42–1.23) for B + E. Overall survival was also longer in these arms: 12.6 months B + C and 13.7 months B + E *versus* 8.6 months for chemotherapy alone. Another phase II study of erlotinib (150 mg) and bevacizumab (15 mg/kg) as first-line treatment for patients with stage IIIB/IV non-squamous NSCLC found a rate of nonprogression at 6 weeks of 75% (24/32) and median time to progression of 5.5 months with low rates of grade 3 adverse events [Groen *et al.* 2007]. However, disappointingly a subsequent randomized, placebo-controlled phase III trial (BeTa) failed to show a survival difference when bevacizumab was added to erlotinib (9.3 months ($n = 319$)) compared to erlotinb alone (9.2 months ($n = 319$)) as second-line treatment [Hainsworth *et al.* 2008]. This was despite a doubling of both PFS (3.4 *versus* 1.7 months, $p < 0.0001$) and response rate (12.6 *versus* 6.2%, $p = 0.006$).The reason why prolonged PFS did not translate into prolonged survival is unclear. A large proportion of subjects in both arms received subsequent therapies, of which 13.2% in the erlotinib arm compared to 8.9% in the bevacizumab arm received a bevacizumab-containing post-study treatment regime. These factors may, in part, have confounded the primary endpoint of overall survival.

There are a number of ongoing phase III trials assessing bevacizumab combined with chemotherapy regimens and/or targeted therapies such as erlotinib in the first and second-line setting. The results of these will further determine the role of bevacizumab in the treatment of NSCLC.

Aflibercept

Aflibercept (VEGF Trap) is a recombinant soluble receptor that combines the extracellular domains of VEGFR-1 and VEGFR-2 with the Fc region of human immunoglobulin IgG. It binds with high affinity to all isoforms of VEGF and placental growth factor (PlGF). An interim analysis of a single arm phase II trial of aflibercept (4 mg/kg every 2 weeks) in platinum- and erlotinib-resistant lung adenocarcinoma reported 2 (3.7%) partial responses [Massarelli *et al.* 2007]. The treatment was well tolerated with no grade 3 pulmonary hemorrhage. A randomized phase III study (VITAL) combining aflibercept (6 mg/kg) with docetaxel (75 mg/m^2) every 3 weeks as second-line treatment for advanced NSCLC is ongoing.

VEGF receptor tyrosine kinase inhibitors

Sorafenib

Sorafenib (Nexavar) is an oral multityrosine kinase inhibitor targeting B-RAF, C-RAF, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-β and c-Kit [Wilhelm *et al.*, 2004]. It improves survival and has been approved for the treatment of advanced renal cell carcinoma and advanced hepatocellular carcinoma [Llovet *et al.* 2008; Kane *et al.* 2006]. Two phase II trials have studied sorafenib monotherapy (400 mg bid) in patients with relapsed or refractory NSCLC [Gatzemeier *et al.* 2006; Liu *et al.* 2006]. In the first trial the most common adverse events were diarrhea, hand-foot skin reaction (HFS), fatigue and nausea. Grade 3 toxicity included hypertension (4%) and HFS (10%). Out of 51 evaluable patients stable disease (SD) was achieved in 30 (59%), with tumor shrinkage in 15 (29%) and unconfirmed PR in four. Sorafenib did not adversely impact on patient reported health-related quality of life measures [Gondek *et al.* 2006]. The second trial similarly found sorafenib (400 mg bid) to be well tolerated with tumor responses in two out of five patients. In addition, an interim analysis of a randomised phase II discontinuation trial in heavily pretreated patients (at least two prior chemotherapy regimens) found a longer median PFS with sorafenib monotherpay *versus* placebo (3.6 *versus* 1.9 months, $p = 0.01$) [Schiller *et al.* 2008]. This study will form the basis of a phase III study in third-line treatment for NSCLC. There are also a number of ongoing phase II trials further evaluating sorafenib monotherapy in chemotherapy naïve patients with advanced NSCLC.

Three ongoing phase III trials are assessing sorafenib in combination with chemotherapy as first-line treatment in patients with stage IIIB/IV NSCLC: two in combination with carboplatin

and paclitaxel and one with gemcitabine and cisplatin (NExUS). However, the ESCAPE trial (Evaluation of Sorafenib, Carboplatin And Paclitaxel Efficacy) was stopped early after a planned interim analysis concluded that the study would not meet its primary endpoint of improved overall survival [Bayer and Onyx Provide Update on Phase III Trial of Nexavar® in Patients with Non-Small Cell Lung Cancer. http://www.press.bayer.com/baynews/baynews.nsf/id/en_home]. In fact, similarly to bevacizumab a higher mortality was observed in patients with squamous cell carcinoma receiving sorafenib compared to those in the placebo arm. As a consequence the NExUS trial is now excluding patients with squamous cell histology. Whether the combination of sorafenib with chemotherapy will continue being developed depends largely on the results of the two ongoing trials.

A phase 1 dose-escalating trial of sorafenib plus bevacizumab in solid tumors found enhanced intensity, rapidity and frequency of adverse events, including hypertension, HFS, diarrhea, transaminitis and fatigue, in addition to promising clinical activity. This occurred at doses lower than the single-agent doses. There is also phase I evidence that sorafenib (400 mg bid) can be safely combined with the EGRF inhibitors erlotinib (150 mg) and gefitinib (250 mg) with promising antitumor activity [Adjei *et al*. 2007; Duran *et al*. 2007]. Four phase II trials are evaluating the efficacy of sorafenib with erlotinib in patients with advanced NSCLC in the first-line setting.

Sunitinib

Sunitinib (Sutent) is an oral, multitargeted tyrosine kinase inhibitor of VEGFR-1 to 3, PDGFR-α and β, c-Kit and Flt-3. It has been approved for the treatment of imatinib-refractory or intolerant gastrointestinal stromal tumors (GIST) and advanced renal cell carcinoma [Goodman *et al*. 2007]. For these diseases, it is administered as a 4-weeks on and 2-weeks off treatment regime (4/2 schedule). Two open-label phase II studies have assessed sunitinib monotherapy (50 mg/day continuously ($n = 63$) and 37.5 mg/day 4/2 schedule ($n = 47$)) in previously treated patients with stage IIIB/IV NSCLC [Socinski *et al*. 2008; Brahmer *et al*. 2007]. Both found single-agent sunitinib to be generally well tolerated although there was less grade 3 fatigue with the 4/2 schedule. Antitumor activity was encouraging. In the first trial, confirmed partial responses were observed in 7 patients (11%) (95% CI: 4.6–21.6%) with stable disease achieved for at least 8 weeks in 18 patients. PFS was 12 weeks (95% CI: 10.0–16.1 weeks) and median overall survival 23.4 weeks (95% CI: 17.0–28.3 weeks). In the second trial, one patient (2%) had a confirmed PR and eight (17%) had stable disease for longer than 3 months. PFS was 12.1 weeks (95% CI: 8.6–13.7 weeks). Currently, a randomized, double-blind, placebo-controlled phase III trial is evaluating sunitinib as maintenance therapy in patients with stage IIII/IV NSCLC after 4 cycles of platinum-based chemotherapy.

Sunitinib in combination with chemotherapy (pemetrexed; pemetrexed and cisplatin; premetrexed and carboplatin; docetaxel) is undergoing phase I and II investigation. However, a phase II trial combining sunitinib with bevacizumab, carboplatin and paclitaxel (SABRE-L) in patients with advanced NSCLC was terminated early in July 2008 after Genentech reported the occurrence of several cases of microangiopathic haemolytic anaemia (MAHA) in a dose-escalation phase I study combining sunitinib and bevacizumab [Genentech Warns Against Use of Avastin in Combination With Pfizer's Sutent. http://www.fdanews.com/DID071508]. Five out of 12 patients had laboratory evidence of MAHA, two of which were severe. Other trials with this combination have also been closed.

Sunitinib (37.5 mg continuously) combined with erlotinib (150 mg) is being tested in a randomized, double-blind, placebo-controlled phase III trial in previously treated patients with advanced NSCLC.

Cediranib

Cediranib (Recentin) is an orally active tyrosine kinase inhibitor of all VEGFR isoforms. Two phase I trials established the safety and tolerabilty of cediranib in combination with chemotherapy in advanced NSCLC with associated antitumor activity. In one study, cediranib (30 or 45 mg) was combined with gemcitabine (1250 mg/m^2) and cisplatin (80 mg/m^2) [Goss *et al*. 2007]. In the other, cediranib (30 or 45 mg) was combined with paclitaxel (200 mg/m^2) and carboblatin (AUC 6) [Laurie *et al*. 2008]. Common adverse events included hypertension, fatigue and diarrhea. PRs were seen in five out of nine and nine out of 20 patients, respectively. In both studies, the lower dose was better tolerated without compromising efficacy. The authors,

therefore, recommended, at that time, a dose of 30 mg for future studies. However, the subsequent randomized, double-blind, placebo-controlled phase II/III trial (BR.24) evaluating the addition of cediranib 30 mg to paclitaxel and carboplatin in patients with stage IIIB/IV NSCLC was recently closed due to excessive toxicities. Greatest toxicity was observed in patients with a history of weight loss or low albumin. Despite the increase in early potentially toxic deaths a significantly higher response rate was seen in the cediranib arm, and the PFS met its endpoint. A new trial (BR.29) has therefore opened with cediranib 20 mg daily plus paclitaxel and carboplatin in which patients with a history of weight loss or low albumin are excluded.

A phase II trial will also assess gemcitabine and carboplatin with or without cediranib as first-line treatment in patients with advanced NSCLC.

Motesanib

Motesanib (AMG 706) is an oral inhibitor of all VEGFR subtypes, PDGFR and c-Kit. A phase Ib study established the safety of motesanib combined with carboplatin and paclitaxel or panitumumab, a humanized anti-EGFR antibody, in patients with stage IIIB/IV NSCLC [Blumenschein *et al.* 2006]. It is currently undergoing phase III evaluation as first-line treatment in combination with paclitaxel and carboplatin and in combination with gemcitabine and cisplatin. In addition, a randomised phase II trial is comparing the efficacy of motesanib plus paclitaxel and carboplatin versus bevacizumab plus paclitaxel and carboplatin in advanced non-squamous NSCLC.

Pazopanib

Pazopanib (GW786034) inhibits VEGFRs 1–3, PDGFR-α and β and c-Kit. A phase II study of preoperative pazopanib in patients with stages I–II NSCLC demonstrated clear single-agent activity with a reduction in tumor volume in 20 (87%) patients [Altorki *et al.* 2008]. Monotherapy pazopanib is being evaluated as second- or third-line treatment for advanced NSCLC in a phase II trial and a randomized phase II/III trial is assessing pazopanib postresection of stage I NSCLC.

Vandetanib

Vandetanib (Zactima) is an oral anilinoquinazoline, tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, EGFR and Ret. Results of vandetanib in previously treated NSCLC patients are promising. A randomized, double-blind phase IIa study of vandetanib monotherapy (100–300 mg) in 53 Japanese patients with advanced NSCLC demonstrated an objective response rate of 13.2% (all PRs) with an acceptable safety and tolerability profile [Kiura *et al.* 2008]. The commonest grade three or four adverse events were hypertension and asymptomatic QTc prolongation. A crossover phase II trial found vandetanib (300 mg) to significantly prolong median PFS compared to gefitinib (250 mg) (11 *versus* 8.1 weeks; HR 0.632; $p = 0.025$) [Natale *et al.* 2006]. Adverse events included diarrhea, rash and asyptomatic QTc prolongation. Two phase III trials are assessing vandetanib monotherapy in advanced or metastatic NSCLC. The ZEST (Zactima Efficacy when Studied versus Tarceva) trial, a randomized, 2-arm study, compares vandetanib (300 mg/day) with erlotinib after failure of at least one prior chemotherapy regimen. The ZEPHYR (Zactima Efficacy trial for NSCLC Patients with History of EGFR-TKI chemo-Resistance) trial is comparing vandetanib monotherapy (300 mg/day) with placebo after failure of both chemotherapy and an EGFR tyrosine kinase inhibitor. AstraZeneca recently announced that ZEST did not meet the primary objective of demonstrating a statistically significant prolongation of PFS for vandetanib [Phase III Studies Show That Vandetanib (ZACTIMA) Brings Clinical Benefits to Patients With Lung Cancer. http://www.astrazeneca.com/media/latest-press-releases/2008/4215815?itemId=4215815]. However, vandetanib and erlotinib showed equivalent efficacy for PFS and OS in a pre-planned noninferiority analysis. Formal publication of the results are still awaited.

A randomized, placebo-controlled phase II study assessed vandetanib (100 or 300 mg) in combination with docetexal (75 mg/m^2) in platinum-refractory stage IIIB/IV NSCLC, including squamous cell histology [Heymach *et al.* 2007]. Although overall survival was not different across the groups, the PFS was longer in the vandetanib arms compared to the placebo arm (18.7, 17.0 and 12.0 weeks, respectively). The phase III ZODIAC (Zactima in Combination with Docetaxel In non-small cell lung cancer) trial assessing this combination in the second-line setting has recently completed accrual. In addition, based on the promising results of a phase I trial [deBoer *et al.* 2008], the phase III

ZEAL (Zactima Efficacy with Alimta in Lung cancer) trial is evaluating vandetanib (100 mg/day) combined with pemetrexed compared to pemetrexed alone in the second-line setting. Preliminary results of these two phase III trials have recently been announced by AstraZeneca [Phase III Studies Show That Vandetanib (ZACTIMA) Brings Clinical Benefits to Patients With Lung Cancer. http://www.astrazeneca.com/media/latest-press-releases/2008/4215815?itemId=4215815]. A statistically significant longer PFS was found when vandetanib was added to chemotherapy in the ZODIAC but not the ZEAL trial. This difference may be due to the larger number of patients enrolled in the ZODIAC ($n = 1391$) compared to the ZEAL trial ($n = 534$). In both studies, significantly greater response rates but no significant trends in overall survival were seen. Formal presentation of the results of these trials is eagerly awaited.

In the first-line setting, a randomized phase II trial compared vandetanib monotherapy (300 mg) or vandetanib plus paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with paclitaxel and carboplatin alone [Heymach *et al.* 2008b]. An interim analysis showed shorter PFS in the vandetanib alone *versus* the chemotherapy group and recruitment into this arm was stopped early. The addition of vandetanib to paclitaxel and carboplatin also did not improve PFS compared to chemotherapy alone (24 *versus* 23 weeks, $p = 0.098$).

Thalidomide

Thalidomide is an oral anti-angiogenic agent with immunomodulatory properties. It is thought to inhibit angiogenesis by interfering with basic fibroblast growth factor (bFGF) and/or VEGF [Paravar and Lee, 2008; D'Amato *et al.* 1994]. Results of thalidomide in the treatment of myeloma are promising but trials with NSCLC have so far been disappointing. A phase II study combining thalidomide (200 mg starting dose, escalated to maximum 1000 mg) with carboplatin (AUC 5) and irinotecan (50 mg/m^2) for stage IIIB/IV NSCLC did not demonstrate an improvement with the addition of thalidomide. The overall response rate did not meet the predetermined level of efficacy to merit further investigation of this combination [Miller *et al.* 2006]. Similarly a randomized, double-blind, placebo-controlled phase III trial found no difference in PFS or overall survival when thalidomide was added to gemcitabine (1200 mg/m^2) and carboplatin (AUC 5) [Lee *et al.* 2007]. Currently, a phase II trial is evaluating neoadjuvant thalidomide, carboplatin and gemcitabine in patients undergoing surgery for stage II or III NSCLC. A phase III trial is evaluating the efficacy of carboplatin, paclitaxel and radiotherapy with and without thalidomide for stage III NSCLC.

Unresolved issues

Despite the increasing amount of promising data there are still many unanswered questions concerning the use of angiogenesis inhibitors for the treatment of NSCLC. One of these concerns the optimal treatment regimen: what are the optimal dose, schedule, combination and duration of treatment? Jaine and colleagues introduced the idea of 'vasculature normalization' and a 'window of opportunity' when combining angiogenesis inhibitors with other systemic agents [Jain, 2001]. Tumor blood vessels are tortuous, dilated, poorly organised, hyperpermeable and increase interstitial pressure. This increases resistance to blood flow and impairs blood supply thereby compromising the delivery and effectiveness of systemic anticancer therapies. Angiogenesis inhibitors cause a normalisation of the tumor vasculature before its destruction. During this normalization phase, tumor blood supply and thus the delivery of systemic therapies is increased. The timing of treatment delivery must be fine-tuned to benefit from this increased vascular efficiency.

The normalization of the vasculature also increases tumor oxygenation, which is associated with radiosensitisation. Indeed, preclinical and clinical data show synergy when combining angiogenesis inhibitors with (chemo)radiotherapy and this combination is being investigated for NSCLC in a number of trials [O'Reilly, 2008]. However, there is a potential for increased toxicity. The timing and duration of antiangiogenic therapy required to give the optimal enhancement with radiation therapy remains unknown. Studies are needed to compare different sequences of radiation therapy and antiangiogenic agents.

Another issue concerns the applicability of these agents. As discussed, the pivotal phase II study of bevacizumab combined with carboplatin and paclitaxel found a higher incidence of bleeding, including major life-threatening pulmonary hemorrhage, which appeared to be associated with squamous cell histology. Subsequent trials

have therefore excluded squamous cell histology, and approval has only been granted for non-squamous NSCLC. However, a recent retrospective evaluation of the 13 patients with severe primary pulmonary hemorrhage treated with bevacizumab plus carboplatin and paclitaxel in the phase II and III trials identified baseline tumor cavitation as the only potential risk factor for severe pulmonary hemorrhage, regardless of location and histology [Sandler *et al*. 2009]. Patients with brain metastases and taking anticoagulant medication have similarly been excluded from trials with bevacizumab for fear of intracerebral hemorrhage. However, data from phase II studies of bevacizumab for the treatment of glioblastoma multiforme suggest this risk to be extremely low, reporting either no symptomatic intracerebral hemorrhages at all [Kreisl *et al*. 2009; Norden *et al*. 2008] or rates <3% [Cloughesy *et al*. 2008; Vredenburgh *et al*. 2007].

The restrictive eligibility criteria greatly limit patient access to bevacizumab and, in light of emerging data, may be unnecessarily stringent [Somer *et al*. 2008]. Ongoing trials are now evaluating the safety and efficacy of bevacizumab in patients previously excluded from trials. Preliminary results of the open-label SAIL trial, evaluating the safety of first-line bevacizumab combined with standard chemotherapy regimens in some 2000 patients, report no cases of intracerebral hemorrhage associated with metastases and no safety risk has been identified in patients receiving anticoagulants [Dansin *et al*. 2008; Griesinger *et al*. 2008]. Two phase II studies are evaluating the safety and efficacy of bevacizumab in patients with stable, treated brain metastases from NSCLC in combination with first- or second-line therapy (PASSPORT) and in combination with second-line pemetrexed. One phase II trial will combine bevacizumab with first-line paclitaxel and carboplatin (cohort 1) or second-line erlotinib (cohort 2) in patients with asymptomatic untreated brain metastasis. The phase II BRIDGE trial is assessing if delayed administration of bevacizumab to carboplatin and paclitaxel in subjects with advanced or recurrent squamous NSCLC reduces grade 3 pulmonary hemorrhage events. The phase II AVASQ trial is evaluating whether prophylactic radiotherapy prior to bevacizumab plus platinum-based chemotherapy (cisplatin and gemcitabine or carboplatin and paclitaxel) lowers pulmonary hemorrhage risk in patients with advanced or recurrent previously untreated squamous NSCLC. Similarly, a California Cancer Consortium phase II trial is investigating whether prophylactic chest radiotherapy prevents hemoptysis in patients at high risk for bevacizumab-associated hemoptysis who receive bevacizumab, paclitaxel, and carboplatin for advanced NSCLC.

Selection of patients most likely to respond to angiogenesis inhibitors remains a great challenge. A subgroup analysis of the ECOG 4599 trial combing bevacizumab with carboplatin and paclitaxel found a survival benefit in males but not females [Sandler *et al*. 2006]. However, in the vandetanib plus docetaxel and vandetanib plus carboplatin and paclitaxel trials there was a more pronounced benefit in PFS in females [Heymach *et al*. 2008b]. The influence of gender on outcome needs to be further elucidated in future trials.

As most anti-angiogenic drugs target the VEGF pathway, much research has focused on intratumoral and circulating VEGF levels and its receptors as potential biomarkers for predicting and/or reflecting efficacy to guide patient selection and monitor treatment effect. Results thus far are disappointing and conflicting. The dose-finding Japanese phase II study of vandetanib monotherapy found an increase in plasma VEGF and decrease in plasma VEGFR levels with treatment. Patients experiencing clinical benefit had lower baseline VEGF levels but there was no association with baseline VEGFR levels and outcome [Kiura *et al*. 2008]. Heymach and colleagues analysed baseline VEGF levels from 351 patients enrolled in the three aforementioned phase II trials of vandetanib and found a lower risk of disease progression in patients with low baseline VEGF levels receiving vandetanib monotherapy (300 mg) *versus* gefitinib or carboplatin and paclitaxel, or vandetanib (100 mg) in combination with docetaxel versus docetaxel alone [Heymach *et al*. 2008a]. Contrastingly, in the ECOG 4599 trial high baseline VEGF levels were predictive of response to bevacizumab, although not survival [Dowlati *et al*. 2008]. Similarly VEGF expression in metastatic colorectal cancer and advanced pancreatic cancer was not found to predict benefit from bevacizumab [Jubb *et al*. 2006; Kindler *et al*. 2005]. For sunitinib, higher baseline soluble VEGFR-2 levels were associated with tumor size reduction in patients with metastatic breast cancer, and, in patients with unresectable neuroendocrine

tumors, those with higher baseline VEFGR-2 and VEGFR-3 levels and decreases during treatment tended towards a longer PFS. On the other hand, in a phase II trial of sunitinib for metastatic renal cell carcinoma (mRCC) no association was found between baseline VEGF-A, VEGFR-2, PlGF or VEGFR-3 and response or survival. In another study, lower pretreatment VEGFR-3 levels were observed in patients with mRCC who responded to sunitinib [LeTourneau *et al*. 2008]. For sorafenib, a phase III trial in mRCC, a trend of longer PFS was seen in patients with high baseline VEGF. An exploratory analysis of preoperative pazopanib in early-stage NSCLC demonstrated a significant decrease in soluble VEGFR2. Moreover, a correlation was observed between changes in soluble VEGFR-2 and VEGF during pazopanib treatment and tumor shrinkage [Nikolinakos *et al*. 2008]. Most studies have shown an increase in VEGF and decrease in VEGFR-2 and VEGFR-3 during treatment with angiogenesis inhibitors [LeTourneau *et al*. 2008; DePrimo and Bello, 2007]. However, these changes do not consistently correlate with clinical benefit or survival and may simply represent a pharmacodynamic drug effect. More research is needed to establish whether levels of angiogenic factors can be used as valid biomakers of clinical benefit or survival.

Elevated levels of circulating endothelial progenitor cells (CEPs) and mature circulating endothelial cells (CECs) have been found in cancer patients and are associated with a poor prognosis. These cells are being investigated as biomarkers for response to angiogenesis inhibitors. Results are inconsistent and hampered by the lack of a clear definition and the absence of standardised assays [Strijbos *et al*. 2008]. In one study, CEPs increased in patients treated with sunitinib for renal cell carcinoma and in patients treated with bevacizumab and erlotinib for NSCLC. An increase correlated with response in the former group [Vroling *et al*. 2008]. Similarly, in a phase II trial of sunitinib in imatinib-restistant GIST, patients with clinical benefit had significantly greater increases in CECs after 3 weeks of treatment than patients with progression [Norden-Zfoni *et al*. 2007]. Contrastingly, a phase II trial in patients with recurrent glioblastoma treated with cediranib found that elevated levels of CECs correlated with disease progression. A phase I trial showed bevacizumab to decrease the levels of CECs and CEPs in patients with locally advanced rectal carcinoma [Willett *et al*. 2005]. Another study showed a differential effect of vandetanib on CEP and CEC levels [Beaudry *et al*. 2005]. Further research needs to clarify whether CECs and/or CEPs can be used as surrogate markers for efficacy.

In summary, currently no biomarker predicting or reflecting efficacy of anti-angiogenic agents has been consistently identified let alone validated. Further research into the field of such biomarkers is much needed. In addition, the optimal method to monitor response is an area of ongoing study. The current standard response evaluation in clinical trials uses the Response Evaluation Criteria in Solid Tumors (RECIST) [Therasse *et al*. 2000]. A response according to these criteria requires the sum of the longest diameters of measurable lesions to decrease by at least 30%. However, angiogenesis inhibitors are considered cytostatic not cytotoxic. Responses with monotherapy are, therefore, likely to be underestimated using RECIST. In addition, tumor cavitations frequently develop with angiogenic inhibitors. This often occurs without a change in the tumor diameter. Recently, Crabb and colleagues proposed an alternate response assessment for angiogenesis inhibitors in which the longest diameter of a cavity (zero if no cavity present) is subtracted from the longest diameter of the lesion to provide an alternate measurement of the target lesion [Crabb *et al*. 2008]. Whether this more accurately reflects drug activity will have to be evaluated in future studies. Other image-based response monitoring being investigated include vascular imaging by positron emission tomography (PET), perfusion computed tomography (CT), dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and single-photon emission computed tomography (SPECT).

Conclusion

Angiogenesis plays a major role in tumor growth and metastasis. The key player of angiogenesis is the VEGF pathway. Inhibition of this pathway, either by targeting VEGF directly or targeting its receptors, is theoretically attractive and has shown promise in the treatment of NSCLC. Currently bevacizumab is the only angiogenesis inhibitor that has been approved for the treatment of advanced NSCLC. The results of the many ongoing and planned clinical trials of angiogenesis inhibitors are eagerly awaited and will clarify the further role of these agents in the treatment of NSCLC. Establishing predictive biomarkers and response monitoring

techniques will also be essential for optimising the potential benefit gained from these agents.

Conflict of Interest Statement

None declared.

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