Current Treatment Options in Oncology (2007) 8:15–27
DOI 10.1007/s11864-007-0022-4

Lung Cancer

Role of Anti-angiogenesis Agents in Treating NSCLC: Focus on Bevacizumab and VEGFR Tyrosine Kinase Inhibitors

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Opinion statement

Successful inhibition of angiogenesis with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab has improved the efficacy seen with standard cytotoxic therapy in NSCLC. The addition of bevacizumab to first-line chemotherapy improved response rate and progression free survival and added 2 months to median overall survival for those patients with advanced stage NSCLC on the treatment arm of E4599. Bevacizumab is now a standard agent to add to frontline carboplatin and paclitaxel for patients with newly diagnosed NSCLC who meet the eligibility criteria from the landmark E4599 trial. Unfortunately about half of all patients are not eligible either because they have squamous histology, brain metastases, or are on anti-coagulation. Ongoing trials are further exploring the safety of bevacizumab in these patient populations, as well as in combination with other cytotoxic regimens. Exploration of other applications of bevacizumab in the second-line and adjuvant setting are ongoing as well. The largest class of drugs that block angiogenesis are the multi-targeted tyrosine kinase inhibitors (TKIs) that target the VEGF receptor (VEGFR). These drugs are still in development, and though two are now on the market for treating other malignancies, their role in NSCLC is under investigation. These agents have the advantages of hitting multiple targets, convenient oral administration, and potential for lower cost. Their lack of target specificity leads to unexpected toxicity, but also promising efficacy. For example, the overall objective response rate of 9.5% with single agent sunitinib compares similarly to that of pemetrexed or docetaxel in previously treated NSCLC patients, but toxicity, notably fatigue, lead to discontinuation in 38% of patients. Hypertension, hemorrhage and cavitation are common toxicities amongst this class of agents. Rash, fatigue, myalgia, and hand-foot syndrome are more specifically seen with TKIs. These compounds may also be synergistic or additive with traditional cytotoxic chemotherapy drugs and other novel compounds. In early trials sorafenib as a single agent has shown no clinical response in previously treated NSCLC patients, whereas clinical benefit in combination with erlotinib or chemotherapy has been seen

in early studies. Vandetanib has demonstrated objective responses as a single agent and in combination with chemotherapy in previously treated NSCLC patients. A phase I trial of AZD2171 with carboplatin and paclitaxel in newly diagnosed advanced stage NSCLC also demonstrated promising results with 6 of 15 patients achieving partial responses. NSCLC specific trials are also underway, or in development for pazopanib, axitinib, AMG 706, XL647, enzastaurin, and other TKIs. Other anti-angiogenesis agents with different mechanisms of action include thalidomide and its derivatives, monoclonal antibodies to the VEGFRs, and VEGF Trap, a chimeric molecule which combines extracellular portions of VEGFR1 and VEGFR2 with the Fc portion of immunoglobulin G1 to form a molecule that binds and "traps" VEGF. Despite modest improvements, prognosis continues to be poor for patients with advanced NSCLC. Bevacizumab is a first step into the world of angiogenesis inhibitors for NSCLC and though it only offers a modest survival benefit in a limited patient population, it paves the way for the development of the next generation of anti-angiogenesis inhibitors. We can hope that further improvements in survival will follow.

Introduction

Lung cancer is the leading cause of cancer-related death in the United States with an expected 174,470 newly diagnosed patients and 162,460 deaths in 2005 [1]. Despite modern advances in detection and treatment of non-small cell lung cancer (NSCLC), the mortality from this disease remains dismal. Five-year survival rates for patients with NSCLC range from 60 to 80% in Stage I disease down to <5% in patients with Stage IV disease [2]. Although there have been developments in both innovative treatment approaches and newer generation chemotherapies, novel approaches are gravely needed.

Pre-clinical work has spawned recent advances in biologically targeted agents aimed at angiogenesis. Solid tumor growth and metastasis are dependent on development of new blood vessels (neovascularization), thus inhibition of tumor-induced angiogenesis should prevent the growth of solid tumors and reduce development of metastases [3•–6]. The vascular endothelial growth factor (VEGF) family plays a key pro-angiogenic role in vasculature development [7]. The development of bevacizumab, a monoclonal antibody to the VEGF ligand, is the first successful anti-angiogenesis approach in lung cancer. In October 2006, bevacizumab was granted a labeling extension by the Food and Drug Administration for the initial treatment of advanced stage NSCLC, in combination with carboplatin and paclitaxel. Bevacizumab is a proof in principle of the efficacy of angiogenesis inhibition and has generated guarded optimism for the role of other angiogenesis inhibitors in the treatment of NSCLC.

This review aims to describe the role and rationale for exploring anti-angiogenic therapies in the treatment of NSCLC. We will summarize prior and current clinical studies of bevacizumab as well as early clinical data of other small molecule inhibitors of angiogenesis in their application to the treatment of NSCLC.

Vascular endothelial growth factor (VEGF) signaling pathway

- Three decades have passed since Judah Folkman first described the importance of tumor neo-angiogenesis in tumor growth and proposed that inhibition of this pathway could be a means to treat cancer [6]. Angiogenesis is a tightly regulated process of endothelial cell division and migration with resultant formation of new capillaries. In the malignant state, the balance of endothelial growth is shifted towards the "angiogenic phenotype" with increased proliferation of new aberrant capillaries. This eventually leads to the establishment of a new vascular bed encouraging tumor progression and metastases [8].
- The VEGF signaling pathway plays a critical role in the angiogenic processes. VEGF ligands are secreted by tumor cells and macrophages [9–11]. Three cell surface receptors for VEGF: [VEGFR1 (Flt-1), VEGFR2

(KDR/flk-1), and VEGFR3 (Flt-4)] are located on the host vascular endothelial cells, monocytes, and hematopoietic precursors. VEGFR2, which is commonly over-expressed by tumor vasculature is the most important of these receptors [12••]. VEGFR2 signal transduction activates pathways that promote endothelial cell proliferation, survival, and migration [13]. VEGF expression is induced by hypoxia-inducible factor 1 (HIF-1); platelet derived growth factor (PDGF), tumor necrosis factor α (TNF-α), and transforming growth factor-β (TGF-β) and by inactivation of the von Hippel-Lindau (vHL) tumor suppressor gene [14]. VEGFR1 is less understood and may play a regulatory role by VEGF sequestration or stimulation of hematopoietic stem cell migration. The VEGFR3 signal transduction pathway mediates lymphangiogenesis and has been associated with lymph node metastasis.

- Angiogenesis is critical to both tumor growth and metastasis and thus blocking angiogenesis via VEGF blockade offers a unique treatment strategy [15]. Inhibition of VEGF-induced angiogenic and lymphangiogenic signals may selectively target the tumor-associated vessels given the lack of organization of these vessels and their increased permeability [16, 17]. There are various anti-angiogenic agents currently in clinical development for the treatment of NSCLC with a majority of agents directed either at the VEGF molecule or the VEGF receptor tyrosine kinase.

Bevacizumab

- Bevacizumab, a recombinant humanized monoclonal antibody that binds to VEGF, is the first angiogenesis inhibitor to demonstrate efficacy in solid tumors [18]. A randomized phase II trial of patients with newly diagnosed advanced NSCLC treated with standard platinum based chemotherapy with placebo or bevacizumab (at either 7.5 mg/kg versus 15 mg/kg) demonstrated a higher response rate and increase in overall survival with the higher dose of bevacizumab compared to placebo [19]. Patients whose tumors were centrally located or were of squamous cell histology were found to have a higher risk of fatal tumor related bleeding episodes. Subsequently a randomized phase III trial, ECOG 4599, evaluated standard chemotherapy (carboplatin at an area under the concentration curve (AUC) of six with paclitaxel at 200 mg/m^2 every 3 weeks for six cycles) with or without bevacizumab (15 mg/kg every 3 weeks continued for up to 1 year) in untreated advanced stage NSCLC patients [20••]. This trial randomized 878 patients to receive chemotherapy with or without bevacizumab. To reduce the risk of bleeding it excluded patients with squamous cell histology, brain metastasis, anti-coagulant use, or history of gross hemoptysis. Response rate (35 versus 15%), progression free survival (PFS) (6.2 versus 4.5 months), and overall survival (OS) (12.3 versus 10.3 months) were all statistically superior in the bevacizumab arm of the study. This is the first agent to date to show a survival benefit when added to a doublet chemotherapy regimen in the first-line treatment of advanced NSCLC. However, a higher incidence of grade 3 or greater bleeding was associated with bevacizumab administration (4.4 versus 0.7%) as were grade 3 or greater hypertension (7 versus <1%), and grade 4 neutropenia (26 versus 17%). At final publication, a total of 15 patients on the bevacizumab arm died on therapy: five from pulmonary hemorrhage, five from complications of febrile neutropenia, two from gastrointestinal bleed, two from cerebrovascular events, and one from probable pulmonary embolus.

In comparison, on the chemotherapy alone arm there were two deaths: one gastrointestinal bleed, one neutropenic fever. Pulmonary hemorrhage was noted in 2.3% of bevacizumab treated patients [21]. Similar toxicity profiles have been documented with several of the VEGFR targeted agents as will be discussed in further sections. (Table 1) This trial has established the paradigm of angiogenesis inhibition as frontline treatment for NSCLC.

- Bevacizumab continues to be appraised in NSCLC in different settings as well as in combination with other chemotherapies. An ongoing phase III European trial is looking at the combination of bevacizumab with cisplatin and gemcitabine in advanced stage NSCLC. Additionally, other investigators are examining the safety of bevacizumab in patients with treated brain metastases, and those with squamous cell carcinoma that have previously been irradiated. Bevacizumab has also been combined with the epidermal growth factor receptor inhibitor erlotinib. Erlotinib is a small molecule tyrosine kinase inhibitor of EGFR active for previously treated NSCLC [31]. A phase I/II trial is comparing chemotherapy alone versus bevacizumab with chemotherapy (either pemetrexed or docetaxel) or erlotinib [32]. Preliminary data has demonstrated higher efficacy in the bevacizumab containing arms with higher response rates and median PFS in combination with erlotinib or chemotherapy compared to the chemotherapy alone arm.
- Eastern Cooperative Oncology Group (ECOG) 1505, to open in early 2007, is an intergroup phase III randomized trial evaluating the use of bevacizumab in combination with a platinum-containing regimen in the adjuvant setting in resected early stage disease. The role of bevacizumab in locally advanced NSCLC after definitive chemotherapy and radiation is also being investigated.

Small molecule tyrosine kinase inhibitors against VEGFR

- Tyrosine kinase inhibitors of VEGFR are small molecules that bind to the ATP pocket of the tyrosine kinase residues of the internal domain of the receptor. As a result of their effects on the receptor and downstream signaling, these inhibitors interfere with a number of key biologic functions associated with VEGFR activation. Although results with bevacizumab have been encouraging, redundancy in the angiogenesis pathways makes multiple targeted agents appealing. Promising TKIs that target the VEGFRs as well as other receptors are under development for lung cancer and we will discuss a few of these

Table 1. Selected angiogenesis inhibitors and their common toxicities

Agent	Common toxicities
Bevacizumab [20••]	Hypertension, Bleeding, Neutropenia,
Sorafenib [22]	Diarrhea, Fatigue, Skin Toxicity, Nausea, Hypertension, and Hand-Foot Syndrome
Sunitinib [23]	Asthenia, Myalgia, Nausea, Stomatitis, Diarrhea, Neutropenia, Thrombocytopenia
Vandetanib [24]	Diarrhea, Rash, Nausea, Hypertension, Headache, and Asymptomatic prolonged QTc interval
AZD2171 [25]	Hypertension, Headache, Voice Hoarseness, and Diarrhea
Pazopanib [26]	Nausea, Vomiting, Diarrhea, Fatigue, Anorexia, and Hypertension
Axitinib [27]	Fatigue, Nausea, Vomiting, Diarrhea, and Hypertension
AMG 706 [28]	Hypertension, Fatigue, Diarrhea, and Headache
XL647 [29]	Fatigue, Nausea, Diarrhea, and Rash
Enzastaurin [30]	Fatigue, Cough, Diarrhea, Nausea, Constipation, Peripheral Edema, and Chromaturia

agents including sorafenib, sunitinib, vandetanib, AZD2171, pazopanib, axitinib, AMG 706, XL6474, and enzastaurin. (Table 2)

Sorafenib

- Sorafenib is an inhibitor of raf-kinase, VEGFR1, VEGFR2, VEGFR3, PDGFR- Beta, Flt-3, c-kit, and p38-alpha with activity in various preclinical models [33]. Mutations of the ras/raf kinase pathways have been noted in up to 20% of NSCLC [34]. A phase I clinical trial, which enrolled 69 patients found the maximum tolerated dose to be 400 mg twice daily with the dose limiting adverse events including diarrhea, fatigue, and skin toxicity. A partial response was seen in a patient with hepatocellular carcinoma and 25 other patients with various tumor types demonstrated disease stability, including one NSCLC patient for just over 300 days. In a phase III trial in metastatic renal cell cancer, sorafenib was well tolerated, with manageable side effects including rash, diarrhea, hand-foot skin reactions, fatigue, and hypertension and the drug now has FDA approval for this disease.
- Sorafenib, given continuously at 200 mg orally twice daily, was studied in a phase II trial of patients with advanced NSCLC [22]. Patients with brain metastases and squamous cell histology (up to 31% of patients) were allowed to enroll. Most common drug-related adverse events include diarrhea, hand-foot skin reaction, fatigue, and hypertension. Grade 3 or greater adverse events include hand-foot skin reaction (9.6%), fatigue (1.9%), diarrhea (1.9%), and hypertension (3.6%). Radiographic evidence of tumor cavitation was seen in four patients. Study drug-related hemorrhage was seen in 8% of patients in the study. Epistaxis was seen in three patients and one patient with a central cavitary lesion of squamous cell histology had a fatal pulmonary hemorrhage following radiation therapy one month after sorafenib. Median progression free survival of 2.7 months and median overall survival of 6.7 months was reported on 51 patients. Of 51 evaluable patients, stable disease was found in 59% of patients with a median progression free survival of 5.5 months. Health-related quality of life was minimally affected on treatment [35]. Higher VEGF levels (>161 pg/ml) at baseline correlated with shorter median survival (184 days versus 292 days, $P < 0.05$). Plasma soluble VEGFR-2 decreased during treatment however baseline levels or changes during

Table 2. Selected angiogenesis inhibitors and their targets in clinical development for the treatment of NSCLC

Agent	VEGF-A Ligand	VEGFR-1	VEGFR-2	VEGFR-3	PDGF-R	c-Kit	EGF-R	Protein Kinase C-Beta	Other
Bevacizumab [20••]	+								
Sorafenib [22]			+	+	+	+	+		Raf
Sunitinib [23]		+	+		+	+			FGFR
Vandetanib [24]		+	+	+	+/−		+		
AZD2171 [25]		+	++	+	+				
Pazopanib [26]		+	+	+					
Axitinib [27]		+	+	+	+	+			
AMG 706 [28]		+	+	+	+	+			Ret
XL647 [29]			+			+	+		ErbB2, EphB4
Enzastaurin [30]								+	

treatment were not significantly correlated with clinical outcome.

- ECOG is currently conducting a phase II study of sorafenib in patients with advanced stage NSCLC who have received at least two prior regimens. In addition, sorafenib has also been evaluated for use in combination with other agents. A NSCLC specific trial of 32 patients looked at the combination of gefitinib with sorafenib [36]. Dose escalation in the first 12 patients established a recommended dose of of 400 mg sorafenib orally twice daily with 250 mg gefitinib daily. An additional 20 patients were enrolled at that dose. One patient achieved a partial response and 20 had stable disease (63%). Adverse events included hypertension (12.5%), fatigue (37.5%), and diarrhea (53%). Promising results have also been seen using sorafenib in combination with carboplatin and paclitaxel in advanced NSCLC [37]. A phase I subset safety analysis of 15 patients demonstrated common drug-related events of hand-foot skin reaction, rash, diarrhea, and anorexia. Bleeding events were of grade 1–2 nature seen in three patients. There were four patients with a partial response and seven patients with stable disease.

Sunitinib

- Sunitinib is an oral multi-targeted TKI against VEGFR2, PDGFR, c-KIT, and FLT-3. PDGFR-Beta is expressed on perivascular stromal cells. Preclinical data suggest that a combined blockade of both PDGFR and VEGFR-2 can lead to particularly potent anti-angiogenic effects [38]. Tumor angiogenesis and poor prognosis is seen with abnormal VEGF and PDGF signaling in NSCLC [39]. Two phase I studies of single agent sunitinib in patients with advanced solid cancers have been reported. The larger trial included 41 patients and found a recommended phase II dose of 50 mg orally daily for 4 weeks followed by a 2-week rest period [40]. Dose-limiting toxicities were seen 3–4 weeks after initiation of treatment and included reversible grade 3 asthenia, grade 3 hypertension, and grade 2 bullous skin toxicity. Six of 23 patients had a response to treatment: three renal cell carcinomas, one neuroendocrine tumor, one GIST, and one adenocarcinoma of unknown primary. Substantial activity has been demonstrated with sunitinib in renal cell carcinoma and in imatinib resistant gastrointestinal stromal tumor (GIST) [41]. On January 26, 2006, the United States Federal Drug Administration granted approval for sunitinib for the treatment of GIST after disease progression on or intolerance to imatinib mesylate. Approval was also granted for the treatment of advanced renal cell carcinoma based on partial response rates and response duration under accelerated approval regulations.
- Sunitinib was evaluated in a multicenter open-label, single arm phase II trial in previously treated, advanced NSCLC [23]. Primary endpoint was overall confirmed objective response rate. Key exclusion criteria included prior anti-angiogenesis inhibitors, recent gross hemoptysis, recent grade 3 hemorrhage, brain metastases, and history of cardiac disease, pulmonary hemorrhage, or cerebrovascular accident. The most recent update of 63 patients was presented. Common adverse events included fatigue, nausea, and diarrhea. Grade 3 or higher events included fatigue, myalgia, nausea/vomiting, dyspnea, hypertension, peripheral edema, and depression. Hematologic toxicities grade 3 or higher included neutropenia (5%) and thrombocytopenia (5%). Approximately 20–30% had dose interruptions or reductions with 38% discontinuation due to adverse events. Three hemorrhagic-

related deaths were seen on study of which two were related to the study drug (one pulmonary hemorrhage and one cerebral hemorrhage). Overall response rate was 9.5% (95% CI of 3.6–19.6%) with stable disease seen in 27 patients. Median progression free survival was 11.3 weeks (95% CI of 10.0–15.7 weeks). Median overall survival was 23.9 weeks (95% CI 17–28.3 weeks). NSCLC-specific clinical trials are evaluating the use of sunitinib in combination with chemotherapy or other agents as well as an ongoing continuous dosing schedule of 37.5 mg per day.

Vandetanib

- Vandetanib is an oral anilinoquinazoline, tyrosine kinase inhibitor of VEGFR2, VEGFR3, RET, and the epidermal growth factor receptor (EGFR) [42]. Phase I studies of vandetanib in patients with advanced solid tumors have demonstrated that the once-daily oral administration of vandetanib at less than 300 mg/day is well tolerated with a terminal half-life of about 120 h [43]. Dose limiting toxicity included diarrhea at the 600 mg daily dosing. Asymptomatic QTc prolongation was noted in 9% of patients. Other notable adverse events found were rash, diarrhea, nausea, hypertension and fatigue. Grade 3 rash and diarrhea were also seen at the 500 mg dose. In the phase I Japanese study, four partial responses were observed in nine patients with refractory NSCLC [44].
- The combination of vandetanib with chemotherapy has been evaluated in two randomized phase II trials in advanced NSCLC patients. In the first study, 127 patients with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. Patients were randomized to treatment with a standard dose of docetaxel and either placebo or 100 or 300 mg of vandetanib [24]. The study met its efficacy end point with a hazard ratio for time to progression compared to docetaxel alone of 0.635 for vandetanib at 100 mg daily and 0.829 for vandetanib at 300 mg daily. The estimated median TTP was 18.7 weeks for docetaxel plus vandetanib at 100 mg, 17 weeks for docetaxel plus vandetanib at 300 mg, and 12 weeks for docetaxel alone. A phase III trial of this combination is under development. In the second ongoing study, vandetanib (at 200 or 300 mg) is being investigated in combination with carboplatin (AUC of 6) and paclitaxel (200 mg/m^2) as first-line therapy for NSCLC patients [45]. Objective responses were observed in 7 of 18 patients at both dose levels. The randomized component of the study has been initiated and continues to recruit. The side effects reported with vandetanib in these studies were manageable and included diarrhea, rash, fatigue, and asymptomatic grade I prolongation of the QTc (generally observed with doses >500 mg/day).
- Recently, a phase II randomized trial of 165 patients also compared vandetanib (300 mg daily) with gefitinib (250 mg daily) in advanced previously treated NSCLC patients [46]. Patients were assigned to either gefitinib (250 mg daily) or vandetanib (300 mg daily) until disease progression or toxicity was seen and then they were allowed to cross over. Unlike other trials with angiogenesis inhibitors, patients who had brain metastases, hemoptysis, thromboses, or squamous cell histology were not excluded in this study. Preliminary data demonstrated a statistically significant longer PFS duration in the cohort initially treated with vandetanib than with gefitinib (11.9 versus 8.1 weeks, respectively, HR 0.69; $P = 0.025$). Objective response was higher (8 versus 1%) in the vandetanib treated group

compared to gefitinib. Common adverse events in the vandetanib versus the gefitinib treated groups were diarrhea, rash, nausea, headache, dizziness, QT related events, and hypertension. Grade 3 or greater adverse events of hypertension, diarrhea, rash, and headache were seen in the vandetanib treated group. Close to 40% of patients in each cohort subsequently switched over to the alternative cohort. Of those patients who switched from vandetanib to gefitinib, 25% had disease control at >8 weeks with one objective response. Of the patients who switched from gefitinib to vandetanib, disease control for at least 8 weeks was seen in 43% of patients with no objective responses. Of those who switched over there was a non-statistically significant greater improvement in overall survival in the group that crossed over to gefitinib (7.4 versus 6.1 months).

AZD2171

- AZD2171 is a small molecule, tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR-Beta and c-Kit [25]. In human umbilical vein endothelial cells, AZD2171 inhibited VEGF-stimulated proliferation and KDR phosphorylation. The first phase I study evaluated 36 patients in a standard dose escalation scheme at doses of 0.5–60.0 mg given orally daily (after an initial single dose and washout period) [47]. AZD2171 was generally well tolerated at <45 mg/days with common side effects of fatigue, nausea, diarrhea, and vomiting. In the second portion of the study, an additional 47 patients were enrolled at 20, 30 or 45 mg orally daily. All patients had liver metastases and six patients had NSCLC. The major toxicities include hypertension, headache, diarrhea, and voice hoarseness. Three patients in the 60 mg cohort each experienced one serious adverse event possibly related to AZD2171: grade 4 cerebral hemorrhage, grade 4 hypoglycemia, and grade 3 hypertension. Of the 83 patients enrolled, early reports of two unconfirmed partial responses were seen: one in prostate and one in renal cancer. Stable disease was seen in 23 patients including one of the six NSCLC patients enrolled.
- The National Cancer Institute of Canada Clinical Trials Group conducted a phase I study of daily oral AZD2171 in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer (NSCLC) [48]. Patients with stage IIIB or IV NSCLC of any histology and no significant history of hemoptysis or bleeding were eligible. Patients with treated brain metastases were allowed. Carboplatin (AUC 6) and paclitaxel (200 mg/m^2) were administered every 3 weeks. AZD2171 was initiated on the second day of cycle 1 at a dose of 30 or 45 mg orally daily. Preliminary results on 20 patients were presented. Common toxicities include fatigue, anorexia, mucositis, and diarrhea. No significant bleeding episodes were seen. Of 15 patients evaluable for response, there were six patients with partial responses and eight patients with stable disease. Given this promising early data, National Cancer Institute of Canada Clinical Trials Group has commenced a phase II/III trial of carboplatin and paclitaxel with AZD2171 or placebo.

Pazopanib

- Pazopanib is a small molecule tyrosine kinase inhibitor of the VEGFR1, VEGFR2, and VEGFR3, PDGFR, and c-kit pathways. Preliminary results on a phase I study of 43 patients who were enrolled in

a dose escalation schema with a range of 50–2000 mg daily were presented [26]. The maximum tolerated dose was not achieved. Common adverse events were mostly grade 2 or less and included nausea, diarrhea, fatigue, hypertension, and vomiting. Drug related events that were grade 3 or higher included hypertension, nausea, vomiting, fatigue, and diarrhea. Hypertension was manageable and reversible after discontinuation of the study drug. Plasma peak levels were attained at 800 mg per day and at doses greater than 800 mg per day, hair depigmentation was observed. Dose limiting toxicity of fatigue was seen in one patient at the 2000 mg per day dose. Partial responders included one patient with renal cell cancer and one patient with Hurthle cell cancer. Of the six additional patients with stable disease, one patient had NSCLC. Currently, the 800 mg once daily and 300 mg twice-daily cohorts are being expanded.

Axitinib

- Axitinib is another small molecule tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR, and c-kit that has recently been studied in early phase clinical trials. In a phase I trial, axitinib was given orally (2 h prior to meals) in escalating doses on a daily or twice daily dosing schedule every 28 days [27]. Preliminary results of 30 patients were presented with four NSCLC patients enrolled. Common adverse events were nausea, vomiting, and diarrhea. The maximum tolerated dose was 5 mg twice daily with dose-limiting toxicities of hypertension (HTN), seizures associated with HTN, elevated liver function tests, and mesenteric vein thrombosis with pancreatitis. Hypertension was manageable with antihypertensive medications. Of the five NSCLC patients, two patients had cavitation of the tumor. One death was seen in a patient who suffered from hemoptysis secondary to a cavitating lung lesion. Partial response was seen in a patient with renal cell cancer and adenoid cystic cancer. Stable disease was seen in seven patients. Tumor vascular response (>50% decrease from baseline parameter values to day 2) was seen on one-third of patients based on dynamic contrast enhanced MRI. Phase II trials as a single-agent or in combination with chemotherapy in NSCLC are being designed.

AMG 706

- AMG 706 is an oral, multi-kinase inhibitor which targets vascular endothelial growth factor (VEGF) receptors 1–3, platelet derived growth factor (PDGF) receptor, Ret, and Kit. AMG 706 was shown to inhibit human endothelial cell proliferation in preclinical models. Demonstration of VEGF inhibition with oral administration of AMG 706 was also confirmed in a rat corneal model [49]. As early as 24 h into treatment, AMG 706 produced a statistically significant reduction in vascular blood flow and/or permeability in A431 epidermoid xenograft models [50]. A phase I trial of patients with advanced solid tumors found 125 mg daily as the maximum tolerated dose [28]. Most mild to moderate adverse events were hypertension, fatigue, diarrhea, and headache. Three partial responses were seen in renal cell carcinoma, thyroid cancer, and sarcoma and approximately half of the patients had stable disease. Reductions of up to 61% were seen on dynamic contrast enhanced magnetic resonance imaging at day 21 of treatment.

- AMG 706 has been evaluated in combination with panitumumab (a fully human monoclonal antibody directed against the epidermal growth factor receptor) cisplatin, and gemcitabine [51]. A preliminary report on 15 patients demonstrated adverse events of rash, fatigue, nausea, thrombocytopenia, anemia, and neutropenia. AMG 706 has also been evaluated with panitumumab, carboplatin, and paclitaxel [52]. Early reports of safety of the combination were demonstrated in this study with no significant effect on pharmacokinetics. Hypertension, fatigue, and dyspnea were common adverse events. A phase II trial in advanced thyroid cancer is on-going and lung cancer trials are in development.

XL647

- XL647 is a novel small molecule, tyrosine kinase inhibitor of VEGFR2, EGFR, erbB2, and EphB4. XL647 has been shown to be effective in vitro in a number of human tumor cell lines including NSCLC. A recent update of a phase I clinical trial of monotherapy in advanced solid malignancies has been presented [29]. A total of 40 patients were enrolled in successive cohorts across nine dose levels ranging from 0.06 to 7.0 mg/kg of XL647 orally for five consecutive days, followed by a break, with cycles repeating every 14 days. Dose limiting toxicity of asymptomatic QTc prolongation at the 3.12 mg/kg level was seen. Grade 3 diarrhea was seen in the first two patients in the 7.0 mg/kg cohort which required dose reduction and the 4.68 mg/kg dose was considered the maximum tolerated dose. Most frequent adverse events include fatigue, nausea, diarrhea, and rash. Grade 3 or 4 anemia was seen in 6% of patients. At the 0.28 mg/kg dose, a serious event of a grade 4 pulmonary embolism was found possibly related to the investigational drug. One non-small cell lung cancer patient had a partial response with seven other patients having prolonged stable disease (>3 months). Additional dosing schedules are ongoing including a continuous daily dosing. An ongoing phase II NSCLC trial is exploring the intermittent dosing regimen further.

Enzastaurin

- Enzastaurin is a competitive selective inhibitor of protein kinase C beta (PKCB) and also targets the PI3K/AKT pathway and inhibits GSK3 phosphorylation. In vitro studies demonstrated decreased proliferation and induced apoptosis in tumor models [53]. Enzastaurin has also been shown to inhibit angiogenesis with decreased microvessel density in human tumor xenografts as well as in a rat corneal micropocket assay [54, 55]. In lung cancer models, enzastaurin demonstrated anti-tumor activity and inhibition of angiogenesis [56–58]. A phase I trial of enzastaurin in advanced malignancies has been conducted [30]. Enzastaurin was administered at escalating dose levels ranging from 20 to 700 mg orally, once daily for a 28-day cycle. Several patients enrolled onto the study were heavily pretreated with approximately ten NSCLC candidates out of the 47 patients. Although a MTD was not determined, pharmacokinetic studies determined 525 mg as the recommended phase II dose. DLT included asymptomatic QTc prolongation with two deaths on study unrelated to enzastaurin. A majority of patients had stable disease with no objective responses demonstrated during study. A recent safety evaluation of phase I and II trials of 135 patients treated with enzastaurin found

common adverse drug events included fatigue, cough, diarrhea, nausea, constipation, peripheral edema, and chromaturia [59]. Combination studies of enzastaurin with gemcitabine, pemetrexed, cisplatin, capecitabine, and erlotinib are on-going.

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