Review

Clinical Cancer Research

Exploring the Benefit/Risk Associated with Antiangiogenic Agents for the Treatment of Non–Small Cell Lung Cancer Patients

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Abstract

Following the approval of bevacizumab, an antibody targeting VEGF-A, for advanced non-squamous non–small cell lung cancer (NSCLC) in 2006, intensive efforts were put into the clinical development of antiangiogenic agents for NSCLC. Currently, the other antiangiogenic agents approved for NSCLC are ramucirumab, a VEGF receptor-2 (VEGFR-2)–targeting antibody indicated for both squamous and non-squamous NSCLC in the United States, and nintedanib, an anti–VEGFR-1/2/3, platelet-derived growth factor receptor-α/β, fibroblast growth factor receptor-1/2/3 angiokinase inhibitor indicated for adenocarcinoma of the lung in the European Union. Many other antiangiogenic agents are being evaluated in phase III trials for NSCLC, including aflibercept, sunitinib, sorafenib, cediranib, and vandetanib. Although many of the same signaling pathways are targeted by these novel agents, mixed efficacy results have been observed in these trials. Moreover, safety issues have raised concerns about using antiangiogenic agents in this patient population, and fatal bleeding events have been reported. Importantly, although no biomarker has yet been validated for antiangiogenic agents in NSCLC, biomarkers that show potential include circulating levels of short VEGF-A isoforms, expression of neuropilin-1 and VEGFR-1 in tumors and plasma, genetic variants in VEGF-A and VEGFR, and *tumor protein p53* mutations (with the latter having been shown to correlate with increased levels of VEGF-A transcripts). This review provides an overview of the clinical benefit and risk associated with the use of antiangiogenic agents for NSCLC, and summarizes the research to date on the identification of predictive biomarkers for antiangiogenic therapies. *Clin Cancer Res; 23(5); 1137–48. ©2016 AACR.*

Introduction

Lung cancer ranks as the leading cause of cancer-related death in the United States, accounting for approximately 150,000 deaths (about 27% of all cancer-related deaths) in 2015 alone (1), and is the second overall leading cause of death in the United States after heart disease (2). For the lung cancer population diagnosed between 2003 and 2009, the 1-year and 5-year survival rates were 43% and 17%, respectively (3), reflecting the high rate of surgically unresectable, advanced disease that is not amenable to curative treatment. Furthermore, patients with lung cancer exhibit lower survival rates at each stage (I–IV) than those of patients with other common cancers, such as breast and colon cancer (4–7).

Non–small cell lung cancer (NSCLC) accounts for approximately 84% of lung cancer diagnoses in the United States (3). In terms of targeted therapy for advanced NSCLC, initial success was observed with EGFR inhibitors in the setting of activating *EGFR* mutations (8). Another approach has been to target angiogenesis, which is important in tumor growth and metastasis (9), by directing agents against the VEGF family of growth factors and receptor tyrosine kinases, as well as other proangiogenic factors (10). Although VEGF is expressed by many types of cancer cells, including NSCLC (11), several proangiogenic factors also impact tumorigenesis, including platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF; Fig. 1; ref. 12).

The different types of NSCLC have exhibited different angiogenic vascular patterns. Microvascular density was consistently higher in adenocarcinoma than in squamous NSCLC (13–15), and was variable in large cell NSCLC (13, 14). As visualized by narrow band imaging videobronchoscopy, dotted blood vessels (short capillary loops visible as pinpoint dots) were more common in adenocarcinoma than in squamous NSCLC and were not observed in large cell NSCLC. Tortuous blood vessels were much more common in squamous NSCLC than in adenocarcinoma and large cell NSCLC, and abruptly ending blood vessels were more common in squamous NSCLC than in adenocarcinoma and were not observed in large cell NSCLC (16). The mean diameter of microvessels appeared to be greater in squamous cell and large cell NSCLC than in adenocarcinoma (15, 17).

Despite the impact of multiple proangiogenic factors on tumorigenesis, the anti-VEGF mAb bevacizumab, the anti–VEGF receptor-2 (VEGFR-2) mAb ramucirumab, and the anti–VEGFR-1/2/3, PDGF receptor (PDGFR)-α/β, and FGF receptor (FGFR)-1/2/3 multitargeted tyrosine kinase inhibitor (TKI) nintedanib are the only antiangiogenic agents approved for NSCLC in the United States and/or Europe as of this writing, with large clinical trials demonstrating efficacy in combination with chemotherapy (all containing taxanes) in advanced non-squamous NSCLC (bevacizumab and ramucirumab), squamous NSCLC (ramucirumab), or adenocarcinoma of the lung (nintedanib; refs. 18–22).

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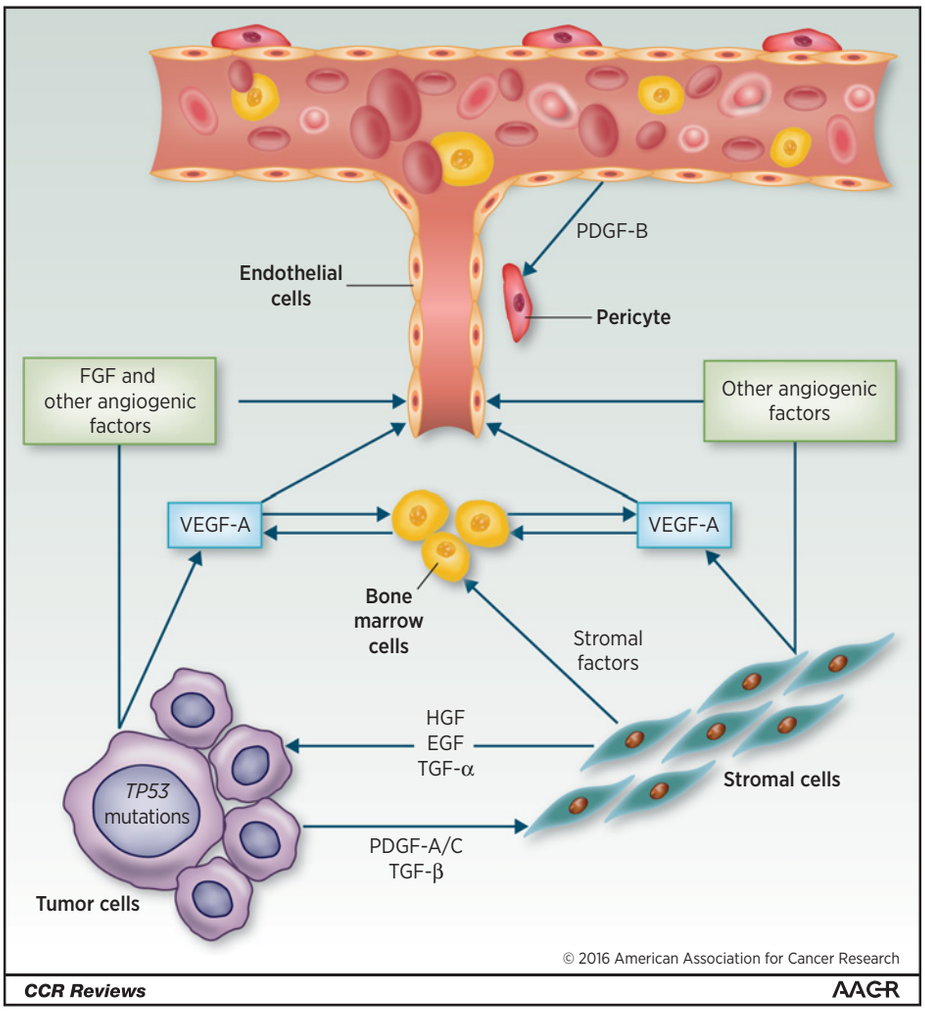

Figure 1.
Overview of tumor angiogenesis. Tumor cells promote angiogenesis through production of proangiogenic factors, which impact downstream angiogenic signaling that involves endothelial cells, stromal cells, and bone marrow cells. Factors secreted by these other cell types can further promote tumorigenesis. FGF, fibroblast growth factor; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TP53, tumor protein p53.

Although clinical development of other antiangiogenic therapies for advanced NSCLC remains an important priority in this field, identification of predictive biomarkers for antiangiogenic agents is still a source of unrealized clinical benefit for this class of agents.

The Benefits and Risks of Approved Antiangiogenic Therapy for Advanced NSCLC

A major limitation associated with antiangiogenic agents is that many of these drugs, including bevacizumab, are suitable only for patients with non-squamous disease (21). Concerns surrounding treatment of squamous NSCLC with antiangiogenic agents stemmed from an increased risk of serious bleeding events observed in an early randomized trial of bevacizumab (23), as well as reports of adverse safety signals in subsequent trials involving antiangiogenic agents (24, 25); at the same time, however, clinical development of other antiangiogenic agents has not been restricted on the basis of NSCLC histology (Table 1). In addition, the small population of patients with uncommon non-squamous tumors (those other than adenocarcinoma) precludes definitive conclusions regarding antiangiogenic agents for patients with these uncommon tumors (26). Therefore, most phase III trials with antiangiogenic agents have focused mainly on non-squamous advanced NSCLC (Tables 2 and 3). Additional insight into the relative efficacy of bevacizumab versus chemotherapy or multitargeted TKIs in advanced NSCLC have been provided elsewhere in recently published meta-analyses (27, 28).

Bevacizumab

Bevacizumab is a mAb that binds to VEGF-A and inhibits the interaction with its receptors, VEGFR-1 and VEGFR-2 (21). Approval for bevacizumab in advanced NSCLC (non-squamous) was based on the ECOG-4599 trial (paclitaxel/carboplatin with or without bevacizumab in first-line advanced NSCLC; ref. 19). At the 15-mg/kg dose (intravenously every 3 weeks), bevacizumab combined with paclitaxel/carboplatin was associated with improved overall survival [OS; 12.3 vs. 10.3 months; hazard ratio (HR), 0.79; 95% confidence interval (CI), 0.67–0.92; $P = 0.003$], progression-free survival (PFS; 6.2 vs. 4.5 months; HR, 0.66; 95% CI, 0.57–0.77; $P < 0.001$), and response rate (RR; 35% vs. 15%; $P < 0.001$) versus paclitaxel/carboplatin alone. More recent meta-analysis of phase II/III trials for bevacizumab in combination with platinum-based

Table 1. Antiangiogenic agents in squamous NSCLC

Agent	Phase (combination treatment)	Notes
Bevacizumab VEGF-A mAb FDA and EMA approved for non-squamous NSCLC, CRC, glioblastoma, RCC, cervical cancer, and ovarian cancer	Phase II (carboplatin/paclitaxel; ref. 23) Phase II (carboplatin/paclitaxel; ref. 24)	Major hemoptysis; 4 of 6 severe hemorrhages associated with squamous histology 1 of 31 (3.2%) patients with squamous histology had grade ≥3 pulmonary hemorrhage; 9 (29%) had grade 3 AEs
Ramucirumab VEGFR-2 mAb FDA approved for NSCLC (squamous and non-squamous)	Phase III (docetaxel; ref. 22)	No differences in efficacy and safety between squamous and non-squamous populations
Nintedanib Multitargeted TKI against VEGFR-1/2/3, PDGFR-α/β, FGFR-1/2/3, SRC family, and FLT3 EMA approved for NSCLC (adenocarcinoma histology); FDA and EMA approved for idiopathic pulmonary fibrosis	Phase III (docetaxel; ref. 18)	PFS but not OS benefit was observed with nintedanib in the squamous subgroup
Sunitinib Multitargeted TKI against VEGFR-1/2/3, PDGFR-α/β, KIT, FLT3, CSF1R, and RET Approved for RCC, GIST, and pNET	Phase III (erlotinib; ref. 40)	Incidences of treatment-related pulmonary hemorrhage and hemoptysis were similar between treatment arms, which included squamous patients (28% per arm)
Sorafenib Multitargeted TKI against VEGFR-1/2/3, PDGFR-β, KIT, FLT3, RET, and RAF Approved for HCC, RCC, and thyroid carcinoma	Phase III (carboplatin/paclitaxel; ref. 25)	Higher incidence of mortality was observed for patients with squamous histology treated with sorafenib; incidence of fatal bleeding events in the squamous cohort was similar between treatment groups
Cediranib Multitargeted TKI against VEGFR-1/2/3, PDGFR-α/β, and KIT	Phase II/III (carboplatin/paclitaxel; ref. 44)	No evidence of different outcomes was observed on the basis of histology
Vandetanib Multitargeted TKI against VEGFR-2, VEGFR-3, RET, and EGFR Approved for medullary thyroid cancer	Phase III (docetaxel; ref. 48) Phase III (erlotinib; ref. 50) Phase III (51)	PFS and OS were consistent between the squamous cohort and the overall population; no safety issues were observed specifically in the squamous subgroup Similar rates of hemoptysis were observed between treatment groups Difference in PFS benefit with vandetanib was observed between patients with adenocarcinoma and squamous histologies

Abbreviations: AE, adverse event; CRC, colorectal cancer; CSF1R, colony-stimulating factor 1 receptor; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FLT3, fms-related tyrosine kinase 3; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; RAF, Raf proto-oncogene, serine/threonine kinase; RCC, renal cell carcinoma; RET, ret proto-oncogene.

chemotherapy suggested that bevacizumab had a greater treatment effect on OS among patients with adenocarcinoma histology compared with other histologies, such as large cell (29). An increased incidence of clinically significant bleeding was observed with bevacizumab (4.4% vs. 0.7%; $P < 0.001$), and five deaths were reported with bevacizumab due to pulmonary hemorrhage. A retrospective analysis of a phase II and phase III study identified baseline tumor cavitation as a potential risk factor for pulmonary hemorrhage with bevacizumab in NSCLC (30).

A subsequent study, AVAiL, examined gemcitabine/cisplatin alone or with bevacizumab in first-line advanced NSCLC (20, 31). A lower dose (7.5 mg/kg) of bevacizumab was examined in addition to 15 mg/kg. Although a significant PFS benefit was observed with the addition of bevacizumab at both doses (7.5 mg/kg: 6.7 vs. 6.1 months; HR, 0.75; 95% CI, 0.62–0.91; $P = 0.003$; 15 mg/kg: 6.5 vs. 6.1 months; HR, 0.82; 95% CI, 0.68–0.98; $P = 0.03$), this did not translate into an OS benefit (7.5 mg/kg: 13.6 vs. 13.1 months; HR, 0.93; 95% CI, 0.78–1.11; $P = 0.420$; 15 mg/kg: 13.4 vs. 13.1 months; HR, 1.03; 95% CI, 0.86–1.23; $P = 0.761$). Incidences of grade ≥3 adverse events (AE) were similar between arms, and the only dose-related bevacizumab-associated AEs were hypertension and proteinuria. However, fatal pulmonary hemorrhage was observed in seven patients treated with bevacizumab compared with one patient receiving gemcitabine/cisplatin only.

The BeTa phase III trial examined bevacizumab in combination with the EGFR TKI erlotinib versus erlotinib alone in recurrent or refractory NSCLC after first-line treatment (32). Bevacizumab 15 mg/kg with erlotinib 150 mg/day did not improve OS versus

Table 2. Efficacy of antiangiogenic agents in phase III NSCLC trials

Study	*N*	Regimen	ORR	Median OS	Median PFS
ECOG-4599 (2006; ref. 19)	878	Bevacizumab + paclitaxel/carboplatin vs.	35%	12.3 mo	6.2 mo
		paclitaxel/carboplatin	15%	10.3 mo	4.5 mo
			$P < 0.001$	(HR, 0.79; 95% CI, 0.67–0.92; $P = 0.003$)	(HR, 0.66; 95% CI, 0.57–0.77; $P < 0.001$)
AVAiL (2009; refs. 20, 31)	1,043	7.5 mg/kg bevacizumab + gemcitabine/cisplatin vs.	37.8% ($P < 0.0001$)	13.6 mo (HR, 0.93; 95% CI, 0.78–1.11; $P = 0.420$)	6.7 mo (HR, 0.75; 95% CI, 0.62–0.91; $P = 0.003$)
		15 mg/kg bevacizumab + gemcitabine/cisplatin vs.	34.6% ($P = 0.0002$)	13.4 mo (HR, 1.03; 95% CI, 0.86–1.23; $P = 0.761$)	6.5 mo (HR, 0.82; 95% CI, 0.68–0.98; $P = 0.03$)
		placebo + gemcitabine/cisplatin	21.6%	13.1 mo	6.1 mo
BeTa (2011; ref. 32)	636	Bevacizumab + erlotinib vs.	13%	9.3 mo	3.4 mo
		placebo + erlotinib	6%	9.2 mo (HR, 0.97; 95% CI, 0.80–1.18; $P = 0.7583$)	1.7 mo (HR, 0.62; 95% CI, 0.52–0.75)
REVEL (2014; ref. 22)	1,253	Ramucirumab + docetaxel vs.	23%	10.5 mo	4.5 mo
		placebo + docetaxel	14% (OR, 1.89; 95% CI, 1.41–2.54; $P < 0.0001$)	9.1 mo (HR, 0.86; 95% CI, 0.75–0.98; $P = 0.023$)	3.0 mo (HR, 0.76; 95% CI, 0.68–0.86; $P < 0.0001$)
VITAL (2012; ref. 38)	913	Aflibercept + docetaxel vs.	23.3%	10.1 mo	5.2 mo
		placebo + docetaxel	8.9% ($P < 0.001$)	10.4 mo (HR = 1.01; 95% CI, 0.87–1.17; $P = 0.90$)	4.1 mo (HR = 0.82; 95% CI, 0.72–0.94; $P = 0.0035$)
Sunitinib (2012; ref. 40)	960	Sunitinib + erlotinib vs.	10.6%	9.0 mo	3.6 mo
		placebo + erlotinib	6.9% ($P = 0.047$)	8.5 mo (HR, 0.92; 95% CI, 0.80–1.07; $P = 0.1388$)	2.0 mo (HR, 0.81; 95% CI, 0.70–0.94; $P = 0.0023$)
ESCAPE (2010; ref. 25)	926	Sorafenib + paclitaxel/carboplatin vs.	27%	10.7 mo	4.6 mo
		placebo + paclitaxel/carboplatin	24% ($P = 0.1015$)	10.6 mo (HR, 1.15; 95% CI, 0.94–1.41; $P = 0.915$)	5.4 mo (HR, 0.99; 95% CI, 0.84–1.16; $P = 0.433$)
NExUS (2012; ref. 42)	904	Sorafenib + gemcitabine/cisplatin vs.	28%	12.4 mo	6.0 mo
		placebo + gemcitabine/cisplatin	26% ($P = 0.27$)	12.5 mo (HR, 0.98; 95% CI, 0.83–1.16; $P = 0.401$)	5.5 mo (HR, 0.83; 95% CI, 0.71–0.97; $P = 0.008$)
NCIC CTG BR29 (2014; ref. 45)	306	Cediranib + carboplatin/paclitaxel vs.	52%	12.2 mo	5.5 mo
		placebo + carboplatin/paclitaxel	34% $P = 0.001$	12.1 mo (HR, 0.94; 95% CI, 0.69–1.30; $P = 0.72$)	5.5 mo (HR, 0.91; 95% CI, 0.71–1.18; $P = 0.49$)
ZODIAC (2010; ref. 48)	1,391	Vandetanib + docetaxel vs.	17%	10.6 mo	4.0 mo
		placebo + docetaxel	10% $P = 0.0001$	10.0 mo (HR, 0.91; 97.52% CI, 0.78–1.07; $P = 0.196$)	3.2 mo (HR, 0.79; 97.58% CI, 0.70–0.90; $P < 0.0001$)
ZEAL (2011; ref. 49)	534	Vandetanib + pemetrexed vs.	19%	10.5 mo	17.6 wk
		placebo + pemetrexed	8% $P < 0.001$	9.2 mo (HR, 0.86; 97.54% CI, 0.65–1.13; $P = 0.219$)	11.9 wk (HR, 0.86; 97.58% CI, 0.69–1.06; $P = 0.108$)

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Table 2. Efficacy of antiangiogenic agents in phase III NSCLC trials (Cont'd)

Study	*N*	Regimen	ORR	Median OS	Median PFS
ZEST (2011; ref. 50)	1,240	Vandetanib vs. erlotinib	12% 12% $P = 0.98$	6.9 mo 7.8 mo (HR, 1.01; 95.08% CI, 0.89–1.16; $P = 0.830$)	2.6 mo 2.0 mo (HR, 0.98; 95.22% CI, 0.87–1.10; $P = 0.721$)
ZEPHYR (2012; ref. 51)	924	Vandetanib vs. placebo	2.6% 0.7% $P = 0.028$	8.5 mo 7.8 mo (HR, 0.95; 95.2% CI, 0.81–1.11; $P = 0.527$)	1.9 mo 1.8 mo (HR, 0.63; 95% CI, 0.54–0.74; $P < 0.001$)
LUME-Lung 1 (2014; ref. 18)	655	Nintedanib + docetaxel vs. placebo + docetaxel	4.4% 3.3% (OR, 1.34; 95% CI, 0.76–2.39; $P = 0.3067$)[a]	Overall: 10.1 mo 9.1 mo (HR, 0.94; 95% CI, 0.83–1.05; $P = 0.2720$); Adenocarcinoma: 12.6 mo 10.3 mo (HR, 0.83; 95% CI, 0.70–0.99; $P = 0.0359$)[b]	3.4 mo 2.7 mo (HR, 0.79; 95% CI, 0.68–0.92; $P = 0.0019$)

Abbreviation: CI, confidence interval; HR, hazard ratio; mo, month; NSCLC, non–small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; wk, week.
[a]Patients with adenocarcinoma histology who progressed within 9 months after treatment demonstrated higher ORR with nintedanib versus placebo (4.9% vs. 1.5%; OR, 3.54; 95% CI, 1.06–16.03; $P = 0.0393$).
[b]Patients with adenocarcinoma histology who progressed within 9 months after treatment also demonstrated improved OS with nintedanib versus placebo (10.9 vs. 7.9 months; HR, 0.75; 95% CI, 0.60–0.92; $P = 0.0073$).

erlotinib alone (9.3 vs. 9.2 months; HR, 0.97; 95% CI, 0.80–1.18; $P = 0.7583$). Incidences of grade 3/4 AEs (60% vs. 48%) or grade 5 AEs (6% vs. 4%; *P* values not reported) were slightly higher with bevacizumab versus control, and two bleeding-related deaths (pulmonary hemorrhage and gastrointestinal hemorrhage) were reported with bevacizumab.

Ramucirumab

Ramucirumab, an anti–VEGFR-2 mAb, was approved for metastatic NSCLC in December 2014 based on the results of the REVEL trial (ramucirumab combined with docetaxel in previously treated squamous or non-squamous NSCLC; ref. 22). The addition of 10-mg/kg ramucirumab to docetaxel improved both OS (10.5 vs. 9.1 months; HR, 0.86; 95% CI, 0.75–0.98; $P = 0.023$) and PFS (4.5 vs. 3.0 months; HR, 0.76; 95% CI, 0.68–0.86; $P < 0.0001$) versus docetaxel alone. Incidences of common grade $\geq$3 AEs were slightly higher with ramucirumab versus control, for example, febrile neutropenia (16% vs. 10%) and hypertension (6% vs. 2%). Rates of fatal AEs were similar between the ramucirumab and control arms; notably, drug-related hemorrhagic events led to death in five patients in the ramucirumab group and three in the control group.

Subgroup analyses revealed that the improvement in OS was driven primarily by the treatment effects on patients with non-squamous pathology. Patients with squamous histology did not show a statistically significant OS improvement (9.5 vs. 8.2 months; HR, 0.88; 95% CI, 0.69–1.13; $P = 0.319$); patients with non-squamous histology showed a significant OS improvement (11.1 vs. 9.7 months; HR, 0.83; 95% CI, 0.71–0.97; $P = 0.020$). Patients with squamous and non-squamous NSCLC treated with ramucirumab demonstrated similar safety in both populations, including similar rates of pulmonary hemorrhage with ramucirumab versus control (any grade, 8% vs. 7%, respectively; grade $\geq$3, 1% in each group). This study's results raise the question of whether there is a real difference between bevacizumab and ramucirumab in terms of pulmonary hemorrhage risk, or if it is a matter of different study constructs.

Nintedanib

Nintedanib is an oral triple angiokinase inhibitor targeting VEGFR-1/2/3, PDGFR-α/β, FGFR-1/2/3, SRC proto-oncogene, non-receptor tyrosine kinase family, fms-related tyrosine kinase 3 (FLT3), and the ret proto-oncogene (RET; ref. 33) and was approved for treatment of NSCLC of adenocarcinoma histology after first-line chemotherapy in November 2014 by the European Medicines Agency (EMA; ref. 34). Nintedanib 200 mg twice daily combined with docetaxel versus docetaxel plus placebo was evaluated in previously treated NSCLC in the LUME-Lung 1 trial (18) and demonstrated significantly improved PFS compared with docetaxel plus placebo in the overall patient population (3.4 vs. 2.7 months; HR, 0.79; 95% CI, 0.68–0.92; $P = 0.0019$). Nintedanib also demonstrated significantly improved OS in hierarchical testing first in patients with adenocarcinoma histology who progressed within 9 months after treatment (10.9 vs. 7.9 months; HR, 0.75; 95% CI, 0.60–0.92; $P = 0.0073$) and second in patients with adenocarcinoma histology (12.6 vs. 10.3 months; HR, 0.83; 95% CI, 0.70–0.99; $P = 0.0359$), but not in the total patient population (10.1 vs. 9.1 months; HR, 0.94; 95% CI, 0.83–1.05; $P = 0.2720$) versus docetaxel alone. Grade $\geq$3 AEs associated more frequently with nintedanib plus docetaxel were diarrhea

Table 3. Safety of antiangiogenic agents in phase III NSCLC trials

Study	*N*	Regimen	Common AEs ≥grade 3	Percentage or number of patients with AEs: Control arm	Antiangiogenic arm	*P*
Approved						
ECOG-4599 (2006; ref. 19)	878	Paclitaxel/carboplatin ± bevacizumab	Neutropenia	17	26	0.002
			Hypertension	1	7	< 0.001
			Febrile neutropenia	2	5	0.02
			AEs leading to death:			
			Any	$n = 2$	$n = 15$	0.001
			Pulmonary hemorrhage	$n = 0$	$n = 5$	NR
			Cerebrovascular event	$n = 0$	$n = 2$	NR
			GI hemorrhage	$n = 1$	$n = 2$	NR
			Probable pulmonary embolus	$n = 0$	$n = 1$	NR
			Febrile neutropenia	$n = 1$	$n = 5$	NR
AVAiL (2009; refs. 20, 31)	1,043	Gemcitabine/cisplatin ± bevacizumab 7.5 mg/kg vs. 15 mg/kg	Neutropenia	32	40 vs. 36	NR
			Thrombocytopenia	23	27 vs. 23	NR
			Anemia	13	10 vs. 10	NR
			Asthenia	3	5 vs. 5	NR
			Vomiting	4	7 vs. 9	NR
			Hypertension	2	6 vs. 9	NR
			Ischemic events	5	2 vs. 3	NR
			Venous thromboembolic events	6	7 vs. 7	NR
			Pulmonary hemorrhage	1	2 vs. 1	NR
			AEs leading to death (any)[a]	4	4 vs. 5	NR
BeTa (2011; ref. 32)	636	Erlotinib ± bevacizumab	Rash	6	16	NR
			Hypertension	1	5	NR
			AEs leading to death:			
			Any	4	6	NR
			Pulmonary hemorrhage	$n = 0$	$n = 1$	NR
			GI hemorrhage	$n = 0$	$n = 1$	NR
REVEL (2014; ref. 22)	1,253	Docetaxel ± ramucirumab	Neutropenia	39	49	NR
			Febrile neutropenia	10	16	NR
			Leukopenia	12	14	NR
			Fatigue	10	14	NR
			Hypertension	2	6	NR
			Diarrhea	3	5	NR
			Dyspnea	8	4	NR
			Anemia	6	3	NR
			AEs leading to death (any)	6	5	NR
LUME-Lung 1 (2014; ref. 18)	658 (adenocarcinoma histology only)	Docetaxel ± nintedanib	Decreased neutrophils[b]	35	36	NR
			Decreased white blood cell count[b]	18	20	NR
			Neutropenia[b]	14	12	NR
			Increased ALT[b]	1	12	NR
			Diarrhea[b]	4	6	NR
			Fatigue[b]	4	5	NR
			Dyspnea[b]	6	5	NR
			Increased AST[b]	1	4	NR
			Decreased appetite[b]	2	1	NR
			Stomatitis[b]	<1	1	NR
			Nausea[b]	1	1	NR
			Vomiting[b]	1	1	NR
			Cough[b]	1	1	NR
			Pyrexia[b]	<1	1	NR
			Decreased hemoglobin[b]	2	1	NR
			AEs leading to death (any)[b]	10	18	NR
Investigational						
VITAL (2012; ref. 38)	913	Docetaxel ± aflibercept	Neutropenia	21	28	NR
			Fatigue	4	11	NR
			Stomatitis	1	9	NR
			Febrile neutropenia	4	7	NR
			Hypertension	1	7	NR
			Dyspnea	6	6	NR
			Asthenia	3	5	NR
			AEs leading to death:			
			Neutropenia	$n = 1$	$n = 6$	NR
			Pulmonary embolism	$n = 0$	$n = 2$	NR
			Arterial thromboembolic events	$n = 3$	$n = 0$	NR

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Table 3. Safety of antiangiogenic agents in phase III NSCLC trials (Cont'd)

Study	*N*	Regimen	Common AEs ≥grade 3	Percentage or number of patients with AEs: Control arm	Antiangiogenic arm	*P*
Sunitinib (2012; ref. 40)	960	Erlotinib ± sunitinib	Rash/acne[c]	10	17	NR
			Diarrhea[c]	3	16	NR
			Hypophosphatemia[c]	4	13	NR
			Lymphopenia[c]	7	11	NR
			Asthenia/fatigue[c]	3	8	NR
			Hyponatremia[c]	4	6	NR
			Hypokalemia[c]	2	6	NR
			Anemia[c]	4	5	NR
			Neutropenia[c]	1	5	NR
			AEs leading to death:			
			Meningorrhagia	$n = 0$	$n = 1$	NR
			Respiratory tract infection	$n = 0$	$n = 1$	NR
			Hemoptysis	$n = 0$	$n = 1$	NR
			Unknown cause	$n = 0$	$n = 1$	NR
			Pulmonary hemorrhage	$n = 1$	$n = 0$	NR
			Interstitial lung disease	$n = 2$	$n = 0$	NR
			Subdural hemorrhage	$n = 1$	$n = 0$	NR
ESCAPE (2010; ref. 25)	926	Paclitaxel/carboplatin ± sorafenib	Rash/desquamation[c]	1	9	NR
			Neutropenia[c]	6	9	NR
			Hand–foot skin reaction[c]	<1	8	NR
			Fatigue[c]	3	5	NR
			AE leading to death (bleeding)	$n = 2$	$n = 4$	NR
NExUS (2012; ref. 42)	904	Gemcitabine/cisplatin ± sorafenib	Thrombocytopenia	6	10	NR
			Hand–foot skin reaction	<1	9	NR
			Fatigue	4	7	NR
			Rash/desquamation	1	6	NR
			Neutropenia	6	5	NR
			AEs leading to death:			
			Any	1	1	NR
			Vascular (thrombotic)	0	1	NR
			GI perforation	0	<1	NR
			Lung hemorrhage	0	<1	NR
			Abdominal hemorrhage NOS	0	<1	NR
			CNS hemorrhage	<1	0	NR
			Constitutional (other)	<1	0	NR
NCIC CTG BR29 (2014; ref. 45)	306	Carboplatin/paclitaxel ± cediranib	Neutropenia	57	64	NR
			Fatigue	13	21	0.09
			Diarrhea	1	16	< 0.0001
			Hypertension	3	15	0.0002
			Venous thrombosis	10	11	NR
			Anemia	8	11	NR
			Thrombocytopenia	7	10	NR
			Dyspnea	6	10	NR
			Febrile neutropenia	5	9	NR
			Sensory neuropathy	6	7	NR
			Anorexia	1	7	0.02
			AEs leading to death:			
			Any	$n = 0$	$n = 2$	NR
			Leukoencephalopathy	$n = 0$	$n = 1$	NR
			Pulmonary or GI hemorrhage	$n = 0$	$n = 1$	NR
ZODIAC (2010; ref. 48)	1,391	Docetaxel ± vandetanib	Neutropenia	24	29	NR
			Leukopenia	11	14	NR
			Rash	1	9	NR
			Dyspnea	7	6	NR
			Fatigue	5	5	NR
			Diarrhea	4	5	NR
			AEs leading to death:			
			Any	6	6	NR
			Febrile neutropenia	6	7	NR
ZEAL (2011; ref. 49)	534	Pemetrexed ± vandetanib	Dyspnea	8	6	NR
			Fatigue	7	6	NR
			Rash	3	6	NR
			Anemia	6	1	NR

(Continued on the following page)

Table 3. Safety of antiangiogenic agents in phase III NSCLC trials (Cont'd)

Study	*N*	Regimen	Common AEs ≥grade 3	Percentage or number of patients with AEs: Control arm	Antiangiogenic arm	*P*
			AEs leading to death:			
			Any	4	5	NR
			Hemoptysis	$n = 2$	$n = 2$	NR
			Pulmonary embolism	$n = 1$	$n = 1$	NR
ZEST (2011; ref. 50)	1,240	Vandetanib vs. erlotinib	Diarrhea	3	5	NR
			Dyspnea	6	4	NR
			AEs leading to death:			
			Any	3	6	NR
			Pneumonia	$n = 5$	$n = 9$	NR
			Dyspnea	$n = 3$	$n = 6$	NR
			Cerebrovascular accident	$n = 2$	$n = 0$	NR
			Pneumonia aspiration	$n = 0$	$n = 2$	NR
			Pulmonary embolism	$n = 0$	$n = 2$	NR
			Respiratory failure	$n = 0$	$n = 2$	NR
			Respiratory tract infection	$n = 0$	$n = 2$	NR
ZEPHYR (2012; ref. 51)	924	Vandetanib vs. placebo	Rash	<1	6	NR
			Diarrhea	<1	5	NR
			Hypertension	0	5	NR
			AEs leading to death (any)	4	4	NR

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; GI, gastrointestinal; NR, not reported; NOS, not otherwise specified.

[a]Most common non–progression-related deaths were cardiopulmonary failure, respiratory failure, hemoptysis, and pulmonary embolism.

[b]Reported for patients with adenocarcinoma histology only.

[c]Treatment-related AEs.

and increases in alanine and aspartate aminotransferase. The most common fatal AEs (not necessarily drug related) for the nintedanib and placebo arms, respectively, included sepsis (5 vs. 1), pneumonia (2 vs. 7), respiratory failure (4 vs. 0), and pulmonary embolism (0 vs. 3). Nintedanib has also been approved by the EMA and the U.S. Food and Drug Administration for the treatment of patients with idiopathic pulmonary fibrosis (35, 36).

Investigational Agents for NSCLC

A wide variety of antiangiogenic TKIs and mAbs have been evaluated in phase III studies.

Aflibercept

Aflibercept, approved for colorectal cancer, is a recombinant human fusion protein that acts as a decoy receptor for VEGF-A/B ligands (37). In a randomized phase III trial of aflibercept plus docetaxel versus docetaxel alone in previously treated advanced NSCLC (38), the addition of 6-mg/kg aflibercept to docetaxel did not significantly prolong OS (10.1 vs. 10.4 months; HR, 1.01; 95% CI, 0.87–1.17; $P = 0.90$). However, exploratory analyses revealed significant improvements with aflibercept versus placebo in PFS (5.2 vs. 4.1 months; HR, 0.82; 95% CI, 0.72–0.94; $P = 0.0035$) and RR (23.3% vs. 8.9%; $P < 0.001$). Grade ≥3 AEs with higher incidence in the aflibercept group included neutropenia, fatigue, stomatitis, and hypertension. Rates of fatal AEs (e.g., neutropenic complications and pulmonary embolism) were higher with aflibercept than placebo (7.1% vs. 4.0%).

Sunitinib

Sunitinib is a multitargeted TKI directed against VEGFR-1/2/3, PDGFR-α/β, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), FLT3, colony-stimulating factor 1 receptor, and RET (39). Sunitinib plus erlotinib demonstrated improved PFS (3.6 vs. 2.0 months; HR, 0.81; 95% CI, 0.70–0.94; $P = 0.0023$) and RR (10.6% vs. 6.9%; $P = 0.0471$), but not OS (9.0 vs. 8.5 months; HR, 0.92; 95% CI, 0.80–1.07; $P = 0.1388$), versus erlotinib alone in a phase III trial in previously treated patients with NSCLC (40). High toxicity with sunitinib was noted, with rash/dermatitis and diarrhea being most frequent. Treatment-related deaths occurred in four patients, each in the sunitinib and control arms.

Sorafenib

Sorafenib is a multitargeted TKI with inhibitory activity against VEGFR-1/2/3, PDGFR-β, KIT, FLT3, RET, and Raf proto-oncogene, serine/threonine kinases (41). Evaluation of sorafenib in NSCLC has revealed limited efficacy. The ESCAPE phase III trial (paclitaxel/carboplatin alone or with sorafenib 400 mg twice daily) in first-line advanced NSCLC was terminated prematurely after an interim analysis showed that median OS was not significantly improved (10.7 vs. 10.6 months; HR, 1.15; 95% CI, 0.94–1.41; $P = 0.915$; ref. 25). Interestingly, a prespecified exploratory analysis showed greater mortality among patients with squamous histology treated with the combination versus paclitaxel/carboplatin alone (HR, 1.85; 95% CI, 1.22–2.81), but this was not due to pulmonary hemorrhage, as no differences in fatal bleeding events were observed in the squamous subgroup. On the basis of this observation, patients with squamous histology were excluded from the NExUS trial (gemcitabine/cisplatin alone or with sorafenib 400 mg twice daily) in the first-line treatment of advanced NSCLC (42). Consistent with the ESCAPE trial, no improvement in OS was seen with sorafenib combined with gemcitabine/cisplatin (12.4 vs. 12.5 months; HR, 0.98; 95% CI, 0.83–1.16; $P = 0.401$), although sorafenib was associated with longer PFS (6.0 vs. 5.5 months; HR, 0.83; 95% CI, 0.71–0.97; $P = 0.008$). Grade ≥3 drug-related AEs that were more frequently observed in the sorafenib treatment arm included hand–foot skin reaction, fatigue, rash, and hypertension.

Cediranib

Cediranib is a TKI that targets VEGFR-1/2/3, PDGFR-α/β, and KIT (43). In the phase II/III NCIC CTG BR24 trial of paclitaxel/carboplatin plus cediranib 30 mg once daily for first-line advanced NSCLC (44), median PFS was 5.6 months for cediranib versus 5 months for placebo (HR, 0.77; 95% CI, 0.56–1.08; $P = 0.13$). Although higher RRs were observed with cediranib (38% vs. 16%; $P < 0.001$), the trial was halted because more deaths were attributed to cediranib versus placebo (13% vs. 0%; P value not reported). Fatal AEs observed in the cediranib arm included febrile neutropenia, hemoptysis, disseminated/intravascular coagulation, infection, hepatorenal failure, and dehydration/dyspnea/renal failure (observed in a single patient). Subsequently, the NCIC CTG BR29 trial evaluated reduced-dose cediranib (20 mg once daily) plus paclitaxel/carboplatin for advanced NSCLC (45). However, the trial was halted for futility at interim analysis, as no significant differences in PFS (5.5 vs. 5.5 months; HR, 0.91; 95% CI, 0.71–1.18; $P = 0.49$) or OS (12.2 vs. 12.1 months; HR, 0.94; 95% CI, 0.69–1.30; $P = 0.72$) were observed. Grade ≥3 AEs that were more frequent with cediranib versus placebo were hypertension, fatigue, anorexia, and diarrhea.

Vandetanib

The TKI vandetanib inhibits VEGFR-2, VEGFR-3, RET, and EGFR (46, 47). In the ZODIAC trial of previously treated advanced NSCLC, patients receiving vandetanib 100 mg/day plus docetaxel demonstrated improved PFS (4.0 vs. 3.2 months; HR, 0.79; 97.58% CI, 0.70–0.90; $P < 0.0001$) versus those receiving docetaxel alone (48). However, the ZEAL, ZEST, and ZEPHYR trials showed that vandetanib 100 to 300 mg/day does not provide clinical benefit (as measured by PFS and/or OS) when combined with pemetrexed as second-line treatment, when compared with erlotinib in previously treated NSCLC, or compared with placebo in patients previously treated with an EGFR TKI, respectively (49–51). Grade ≥3 AEs that were frequently associated with vandetanib included rash, fatigue, diarrhea, dyspnea, cough, and hypertension. Generally, rates of fatal AEs were similar between the vandetanib and placebo arms (48, 49, 51).

Role of Predictive Biomarkers in the Treatment of NSCLC

Although predictive biomarkers have emerged to guide treatment of advanced NSCLC with targeted agents, their applicability has mainly been limited to nonangiogenic agents. Consequently, efforts have been made to identify predictive biomarkers for antiangiogenic therapy (52). Tumor-derived tissue biomarkers that have been examined include intratumoral microvascular density (53) and VEGFR-2 (54), whereas circulating plasma or serum biomarkers examined to date include VEGF-A (55–57), interleukins (58, 59), endothelial selectin (55), intercellular adhesion molecule-1 (55), and circulating endothelial cells (52). Although inconsistent observations have raised doubts on the use of VEGF-A plasma levels as a predictive biomarker for bevacizumab (60), an analysis of recent data supports further assessment of the role of circulating levels of short VEGF-A isoforms, expression of neuropilin-1 and VEGFR-1 in tumors and plasma, and genetic variants in VEGF-A and VEGFR as biomarker candidates for benefit from VEGF/VEGFR-targeting agents (61). AEs following treatment have also been studied as candidate biomarkers; early data suggested that the development of hypertension on paclitaxel/carboplatin plus bevacizumab may be associated with improved outcomes in NSCLC, but this finding has not been supported by a more recent study (62). Finally, mutant but not wild-type *tumor protein p53 (TP53)* was identified as a possible predictive biomarker of longer PFS in patients treated with bevacizumab (63), and our results from a recent multivariate analysis of the transcriptome further suggest that mutant *TP53* is associated with increased VEGF-A expression, with VEGF-A being a target of bevacizumab (64).

No predictive biomarkers for antiangiogenic therapy have been prospectively validated and widely recognized as a reliable tool for patient selection (9, 65, 66). The use of a survival endpoint as the outcome variable for the discovery of predictive biomarkers contributes to the current lack of validated biomarkers for antiangiogenic agents (67). Survival as an endpoint is often affected by factors that are not related to therapeutic efficacy, cannot distinguish efficacy at the individual patient level, require a randomized trial to distinguish predictive factors from prognostic factors, require long-term follow-up and large patient numbers to detect an association with a biomarker, and can be confounded by crossover on trial as well as by posttrial treatments. In contrast, for agents that, as single agents, can induce tumor regression, use of tumor regression/response as the outcome variable offers several advantages for biomarker studies, including detection of drug effect at the individual patient level via tumor shrinkage, as well as a requirement of a shorter follow-up period. As most clinical trials of antiangiogenic agents have been done as combination trials, it is unclear whether there would be sufficient activity to use single-agent response as an outcome for the exploration of predictive markers. However, bevacizumab, as an example, has demonstrated capability of inducing responses when used as a single agent in NSCLC (as neoadjuvant treatment), renal cell carcinoma, and ovarian carcinoma (68–72).

An additional aspect that hinders the development of clinically useful biomarkers for antiangiogenic agents is the current focus on biomarkers that are continuous (e.g., degree of protein or gene expression) rather than dichotomous (e.g., gene mutation, deletion, and amplification) variables (67); using continuous variables as biomarkers is challenging due to variations in measurement, temporal fluctuations in expression, and the utilization of biologically irrational cutoff points. Nevertheless, the search for predictive biomarkers is ongoing.

Limitations of Current Antiangiogenic Therapy and Possible Future Directions

Despite the documented benefits of antiangiogenic therapy, the summary of results from phase III NSCLC clinical trials in Table 2 shows that treatment with these agents has been associated with relatively modest increases in median OS; in some instances, median OS has decreased. Likewise, increases in median PFS have typically been modest. Median PFS was similar with and without antiangiogenic therapy in one trial and shorter with antiangiogenic therapy in another trial.

Vasculogenic mimicry (VM), the process by which tumor cells imitate endothelial cells and form vascular networks, may contribute to the failure of antiangiogenic therapy to markedly increase OS in NSCLC (73, 74). Antiangiogenic treatment inhibits endothelium-dependent vessels, resulting in hypoxia within tumors (73). Hypoxia promotes VM, which maintains the tumor's blood supply and facilitates tumor metastasis (73). VM has been

observed in many types of cancers, including NSCLC (75); in NSCLC, it occurs most frequently in large cell lung cancer, followed by lung adenocarcinoma and squamous carcinoma (76). The presence of VM in NSCLC tumors is associated with poor differentiation, advanced stage, and distant metastasis (76). As in many other types of cancer, VM in NSCLC is also associated with shorter survival (76, 77).

Given the potential of VM to compromise the effectiveness of antiangiogenic therapy, it has been suggested that administering an antiangiogenic agent in combination with VM-targeted therapy might effectively block the supply of oxygen and nutrition to tumor cells, improving outcomes in selected patients (74, 78). Because the mechanisms of VM are highly complex and involve multiple signaling pathways, further studies on VM are needed to determine the potential for translational studies and clinical applications (78) in the treatment of NSCLC.

As for many targeted agents, biomarkers that predict response might also be helpful in improving response rates. Several recent studies suggest that isoforms of VEGF-A or mutations in *TP53*, with the latter increasing VEGF-A levels, correlate with better outcomes with antiangiogenic agents. Hence, patient selection may be a key to enhancing the modest clinical benefits seen to date (68–72).

Conclusions

Documented benefits and shortcomings of antiangiogenic therapy, some applying to the entire class and others specific to individual agents, have been summarized in this review. Although the toxicity of bevacizumab and other multitargeted antiangiogenic TKIs, especially in patients with squamous histology, limits their clinical benefit to specific patient populations, several recently developed antiangiogenic agents, such as ramucirumab or nintedanib, have shown promising efficacy and safety results either independent of tumor histology or in the adenocarcinoma patient population. Nevertheless, the lack of validated predictive biomarkers ranks high as a major class-wide limitation and may be due, in part, to the use of suboptimal clinical trial strategies to identify them (67). Further exploration of single-agent activity (using response as the clinical outcome of interest) might help in biomarker development, as might more extensive exploration of dichotomous (present vs. absent) factors. Specific biomarkers that merit additional investigation include circulating levels of short VEGF-A isoforms, neuropilin-1 and VEGFR-1 expression in tumors and plasma, genetic variants in VEGF-A and VEGFR, and *TP53* mutations (which are associated with increased VEGF-A transcript levels).

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