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Targeting Angiogenesis in Advanced Non-Small Cell Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer-related mortality in the United States. Over the past 40 years, treatments with standard chemotherapy agents have not resulted in substantial improvements in long-term survival for patients with advanced lung cancer. Therefore, new targets have been sought, and angiogenesis is a promising target for non-small cell lung cancer (NSCLC). Bevacizumab, a monoclonal antibody targeted against the vascular endothelial growth factor, is the only anti-angiogenic agent that is currently recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of advanced NSCLC. However, a number of antibody-based therapies and multi-targeted tyrosine kinase inhibitors are currently under investigation for the treatment of patients with NSCLC. This review summarizes the available clinical trial data on the efficacy and safety of these agents in advanced lung cancer patients.

Keywords

angiogenesis; non-small cell lung cancer; bevacizumab; adverse events

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States with an estimated 228,190 new cases and an estimated 159,480 deaths in 2013.[1] Over two-thirds of patients with lung cancer will present with advanced disease.[2] The 5-year survival rate is approximately 15%. Standard platinum-based chemotherapy regimens are associated with survival of approximately 1 year in patients with advanced lung cancer.[3] Approximately 60% of patients with stage IIIB/IV adenocarcinoma have a molecular mutation thought to drive tumor growth.[4] However, only those patients with epidermal growth factor receptor (EGFR) mutations (approximately 10–15%) or anaplastic lymphoma kinase (ALK) rearrangements (approximately 5%) have a Food and Drug Administration (FDA)-approved therapy available. Other potential targets such as c-ros oncogene 1 (ROS1) gene fusions and

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Note: For consistency, efficacy data have been converted to months using the following: 1 month = 4.2 weeks for data reported in weeks; 12 months = 365 days for data reported in days. For consistency, where necessary, PFS and OS values have been rounded to the nearest tenth, and HR, CI, and *P* values have been rounded to 2 decimal places.

BRAF mutations have been identified and clinical trials using targeted agents are ongoing. Alternative targets continue to be investigated, one of which is angiogenesis, a necessary step in the growth and metastasis of solid tumors.[5] Bevacizumab is the only anti-angiogenic therapy FDA-approved for NSCLC,[6] but other agents have been tested in advanced NSCLC. At the present time, the National Comprehensive Cancer Network (NCCN) recommends consideration of the use of bevacizumab in the first-line treatment setting for stage IV disease in combination with a platinum doublet with continuation of bevacizumab until progression. The use of anti-angiogenic agents is a rational approach to treat lung cancer but needs to be balanced against the potential risks involved, which can be life-threatening. Researchers have been searching for potential biomarkers to identify patients for whom therapy with anti-angiogenic inhibitors may be most beneficial. The current data for anti-angiogenic agents varies widely among the studied drugs, and safety data are especially limited for many of the agents studied. This review covers efficacy and safety/tolerability data from clinical trials of anti-angiogenic agents in advanced NSCLC.

Efficacy and Safety of Anti-angiogenic Agents for NSCLC

Antibody-Based Therapeutics

Bevacizumab—Bevacizumab is a humanized monoclonal antibody with a high affinity for vascular endothelial growth factor (VEGF).[7] Bevacizumab binds to circulating VEGF, preventing it from binding to the VEGF receptor (VEGFR) and thereby inhibiting downstream signaling. The sites of action of bevacizumab and other anti-angiogenic agents described in the text are depicted in Figure 1. Bevacizumab has been studied extensively in various malignancies and certain adverse events (AEs), such as bleeding and thrombosis, are known to be associated with its use. In addition, hypertension and proteinuria are common throughout treatment, although these are generally manageable with anti-hypertensive therapies.

Bevacizumab is the most studied anti-angiogenic agent in advanced NSCLC (Table 1 and 2). Following promising results from a phase II study,[8] ECOG 4599 was conducted as a randomized phase III trial that compared carboplatin/paclitaxel with or without bevacizumab in 878 patients with recurrent or advanced nonsquamous NSCLC.[9] Improvements in median overall survival (OS), median progression-free survival (PFS), and response rate (RR) occurred in bevacizumab-treated patients compared with the chemotherapy arm: 12.3 versus 10.3 months, 6.2 versus 4.5 months, and 35% versus 15%, respectively. In an unplanned subset analysis, median PFS and RR were significantly improved with bevacizumab versus chemotherapy for both sexes; however, median OS was not improved in the female cohort but was improved among men (11.7 vs 8.7 months with chemotherapy).[10] In another unplanned subset analysis, elderly (age ≥70 years) patients had improved median PFS and RR, but no improvement in median OS.[11] The most common grade ≥3 AEs in the bevacizumab arm were neutropenia (26%), hypertension (7%), febrile neutropenia (5%), and bleeding events (4%).[9] Compared with chemotherapy alone, bevacizumab plus chemotherapy was associated with higher rates of grade 4 neutropenia (26% vs 17%), grade 4 thrombocytopenia (1.6% vs 0.2%), and grade 3/4 febrile neutropenia (4.0% vs 1.8%),

hyponatremia (3.5% vs 1.1%), hypertension (7.0% vs 0.7%), headache (3.0% vs 0.5%), rash or desquamation (2.3% vs 0.5%), and bleeding events (4.4% vs 0.7%).

The AVAIL trial was a similarly designed phase III trial conducted in Europe and Canada to evaluate the efficacy of cisplatin and gemcitabine with or without bevacizumab (7.5 or 15 mg/kg) in 1,043 patients with advanced or recurrent nonsquamous NSCLC.[12] Median PFS (6.7 months in bevacizumab 7.5 mg/kg arm and 6.5 months in bevacizumab 15 mg/kg arm vs 6.1 months in placebo arm) and RR (38% in bevacizumab 7.5 mg/kg arm and 35% in bevacizumab 15 mg/kg arm vs 22% in placebo arm) were significantly improved in both bevacizumab-containing arms, but OS was not improved in either bevacizumab-containing arm compared with placebo (13.6 months, 13.4 months, and 13.1 months, respectively).[13] Grade 3/4 AEs in the bevacizumab 15-mg/kg arm included hypertension (9%), vomiting (9%), neutropenia (36%), bleeding (4%), and proteinuria (1%). Grade 3/4 AEs in the bevacizumab 7.5-mg/kg arm included hypertension (6%), vomiting (7%), neutropenia (40%), bleeding (4%), and proteinuria (<1%). Pulmonary hemorrhage was observed in 1.5% of patients in the bevacizumab 7.5-mg/kg arm, 0.9% in the bevacizumab 15-mg/kg arm, and 0.6% in the placebo arm.

A phase II study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed and bevacizumab showed impressive results[14] and led investigators to conduct a large randomized phase III trial of 939 patients to evaluate for superiority of pemetrexed/carboplatin/bevacizumab followed by pemetrexed/bevacizumab maintenance compared with paclitaxel/carboplatin/bevacizumab followed by single-agent bevacizumab maintenance.[15] Only PFS was statistically superior in the pemetrexed/carboplatin/bevacizumab arm (6.0 vs 5.6 months for paclitaxel/carboplatin/bevacizumab), but RR (34.1% vs 33.0%) and OS (12.6 vs 13.4 months) did not show superiority. The toxicities differed between arms; there was more grade 3/4 thrombocytopenia (23.3% vs 5.6%), anemia (14.5% vs 2.7%), and fatigue (10.9% vs 5.0%) in the pemetrexed group, whereas there was more grade 3/4 neutropenia (40.6% vs 25.8%), febrile neutropenia (4.1% vs 1.4%), and sensory neuropathy (4.1% vs 0%) in the paclitaxel group.

Several studies have evaluated bevacizumab in patients who have historically been excluded from other trials. The phase II BRIDGE trial studied carboplatin/paclitaxel and delayed bevacizumab in 31 previously untreated patients with advanced squamous NSCLC.[16] Efficacy results have not been published, but the 4 most common grade 3/4 AEs were hypertension (16%), dyspnea (10%), deep vein thrombosis (7%), and arthralgia (7%). One patient had grade ≥3 pulmonary hemorrhage and another had grade 1 pulmonary hemorrhage.

The phase II BRAIN trial evaluated the safety of bevacizumab given in the first-line setting with carboplatin/paclitaxel or in the second-line setting in combination with erlotinib in patients with nonsquamous NSCLC and asymptomatic, untreated brain metastases. Grade 1 intracranial hemorrhage occurred in 1 of 67 patients in the first-line setting and 0 of 24 patients in the second-line setting, and the RR for intracranial metastases was 61% in first-line therapy and 21% in second-line therapy.[17]

Ramucirumab—Ramucirumab (IM-1121B), a human monoclonal anti-VEGFR-2 antibody,[18] is currently being evaluated in patients with diverse histological subtypes of NSCLC, including those with squamous cell histology and/or treated brain metastases. Results from a single-arm phase II trial of 40 patients treated with carboplatin, paclitaxel, and ramucirumab reported a RR of 55% and median PFS of 7.9 months.[19] Grade 3/4 AEs included thrombocytopenia (10%), febrile neutropenia (7.5%), peripheral neuropathy and pulmonary embolism (5% each).

In a separate phase II randomized study in patients with nonsquamous NSCLC, ramucirumab plus pemetrexed was given in combination with either carboplatin or cisplatin versus single-agent pemetrexed in combination with carboplatin or cisplatin.[20] An interim analysis showed a RR of 44% and PFS of 6.3 months in the ramucirumab arm versus a RR of 37% and PFS of 4.3 months in the chemotherapy alone arm. Grade 3 AEs in the ramucirumab arm included thrombocytopenia (15%), neutropenia (13%), fatigue (12%), and nausea (10%).

Bavituximab—Bavituximab is a monoclonal antibody against phosphatidylserine that causes selective shutdown of existing tumor blood vessels.[21] A randomized phase II study of 86 patients with nonsquamous histology compared carboplatin/paclitaxel with or without bavituximab.[22] In the bavituximab group, the RR was 32% and PFS was 5.8 months, and in the chemotherapy alone group, the RR was 31% and PFS was 4.6 months. OS was not yet reached at the time of reporting. The most common grade 3/4 AEs were anemia (6.8% with bavituximab vs 7.1% with chemotherapy alone), neutropenia (6.8% vs 9.5%), and thrombocytopenia (6.8% vs 2.4%).

Aflibercept—Aflibercept (AV0005), an angiogenesis inhibitor composed of portions of the extracellular domains of human VEGFR-1 and VEGFR-2 fused to the Fc portion of human immunoglobulin G, is currently being evaluated in NSCLC.[23] In a single-arm, phase II trial, aflibercept was administered to 98 patients with platinum- and erlotinib-resistant lung adenocarcinoma, and results showed a RR of 2%, median PFS of 2.7 months, and median OS of 6.2 months.[24] Most common grade 3/4 AEs were hypertension (23%), dyspnea (21%), proteinuria (10%), and fatigue (7%). A phase III trial (VITAL) of docetaxel plus aflibercept vs docetaxel alone as second-line therapy in advanced NSCLC showed an improvement in RR (23% vs 9%), median PFS (5.2 months vs 4.1 months), but OS was not improved (10.1 months vs 10.4 months).[25] The most common grade 3/4 AEs were neutropenia (28% in aflibercept arm vs 21% in chemotherapy alone arm), fatigue (11% vs 4%), and stomatitis (9% vs 1%)

Tyrosine Kinase Inhibitors

Resistance to VEGF inhibition has been shown to be multi-factorial.[26] Receptor tyrosine kinase inhibitors (TKIs), many of which target several angiogenesis pathways, are a class of agents in clinical development for various malignancies. Many of the multi-targeted agents will theoretically inhibit several angiogenesis pathways and may specifically overcome resistance to VEGF inhibition. Several of these multi-targeted TKIs have been investigated for use in the treatment of NSCLC in clinical trials.

Sorafenib

Sorafenib is a multi-targeted TKI that inhibits VEGFR-2, VEGFR-3, platelet-derived growth factor (PDGF) receptor-β (PDGFR-β), v-raf1 murine leukemia viral oncogene homolog 1 (Raf), fms-like tyrosine kinase 3 (FLT-3), and stem cell factor receptor (c-KIT).[27] Sorafenib showed single-agent activity in several phase II trials in patients with previously treated advanced nonsquamous NSCLC,[28,29] but large randomized phase III trials have been disappointing.[30,31] A phase III trial (ESCAPE) of 926 patients with advanced nonsquamous and squamous cell NSCLC was halted due to lack of efficacy on interim analysis.[30] Patients with squamous histology receiving sorafenib had a shorter median OS (8.9 vs 13.7 months) compared with patients receiving chemotherapy alone. The 4 most common grade 3/4 AEs in the sorafenib arm were neutropenia (9%), rash/desquamation (8%), hand-foot skin reaction (8%), and fatigue (5%), while in the chemotherapy arm, these were neutropenia (6%), fatigue (3%), and diarrhea, sensory neuropathy, vomiting, and nausea (2% each). Four of the 6 fatal hemorrhagic/bleeding events observed in the study occurred in patients with squamous histology (2 in each arm).

A second phase III trial (NEXUS) excluded patients with squamous cell histology, subsequent to a protocol amendment.[31] This trial combined cisplatin/gemcitabine with or without sorafenib in 904 patients with advanced NSCLC, showing no difference in median OS with sorafenib versus placebo in nonsquamous disease (12.4 vs 12.5 months) but a statistically significant increase in median PFS (6.0 vs 5.5 months). Reported grade ≥3 AEs attributable to sorafenib included thrombocytopenia (10%), hand-foot skin reaction (9%), fatigue (7%), and rash (6%).

Sunitinib

Sunitinib is a multi-targeted TKI that inhibits VEGFR-2, PDGFR-β, rearranged during transfection (RET), c-KIT, and FLT-3.[32] Sunitinib has shown single-agent activity in phase II trials in previously treated NSCLC patients.[33,34] A phase III trial of sunitinib plus erlotinib versus erlotinib alone as second- or third-line therapy in 960 patients (90% with unknown *EGFR* mutational status) showed no significant difference between groups in the primary endpoint of OS (9.0 vs 8.5 months).[35] The most common grade 3/4 toxicities with sunitinib plus erlotinib were rash/dermatitis (17%), diarrhea (16%), and hypophosphatemia (13%), all higher than with erlotinib alone (10%, 3%, and 4%, respectively).

Nintedanib

Nintedanib (BIBF 1120) is a multi-targeted TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, fibroblast growth factor (FGF) receptor (FGFR)-1, FGFR-2, and FGFR-3; in addition, nintedanib has activity against FLT-3 and the v-src sarcoma viral oncogene homolog (src) family.[36] A phase II study of nintedanib dosed either at 250 mg twice daily or 150 mg twice daily in 73 patients with relapsed NSCLC showed mild activity.[37] A phase III study (LUME-Lung 1) in 1314 patients with advanced or metastatic squamous and non-squamous NSCLC that had progressed on first-line chemotherapy randomized patients to nintedanib or placebo in combination with docetaxel.[38] There was an improvement in median PFS (3.4 months vs 2.7 months), but not in median OS (10.1 months vs 9.1 months) in the nintedanib/docetaxel arm vs docetaxel/placebo arm.

Grade 3/4 AEs were similar in each arm, the most common included elevated ALT (8% vs 1%), and diarrhea (7% vs 3%). A separate phase III study (LUME-Lung 2) in patients with advanced or metastatic non-squamous NSCLC that had progressed on first-line chemotherapy comparing nintedanib or placebo in combination with pemetrexed was stopped early because of a signal for futility on an interim analysis.[39] The analysis of 713 enrolled patients (initially planned to enroll 1300 patients) showed an increase in median PFS (4.4 months vs 3.6 months) but no difference in RR (9% vs 9%) or median OS (HR 1.03). Reported grade 3/4 AEs included elevated ALT (23% vs 7%), elevated AST (12% vs 2%), and diarrhea (3% vs 1%).

Cediranib

Cediranib inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, FGFR-1, and c-KIT.[40] A phase II/III trial comparing carboplatin/paclitaxel with or without cediranib 30 mg in 296 patients with advanced NSCLC was halted early due to imbalances in the number of deaths observed in cediranib-treated patients.[41] The RR was 38%, median PFS was 5.6 months, and median OS was 10.5 months in the cediranib group compared with a RR of 16%, median PFS of 5.0 months, and median OS of 10.1 months in the placebo group. The 4 most common grade 3/4 AEs in the cediranib arm were neutropenia (49%), fatigue (29%), increased thyroid-stimulating hormone (TSH; 27%), and hypertension (19%). A phase II trial evaluating pemetrexed and cediranib in 2 cohorts of patients (a bevacizumab-naive group and a bevacizumab-pretreated group) has completed accrual of bevacizumab-naive patients.[42] Preliminary results in the bevacizumab-naive group showed a RR of 29%, median PFS of 5.6 months, and median OS of 11 months. The 4 most common grade 3/4 AEs in the bevacizumab-naive cohort were fatigue (22%), neutropenia (14%), diarrhea (14%), and infection (8%). Three treatment-related deaths have been reported.

Motesanib

Motesanib is a multi-targeted TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, and RET.[43] A phase II trial of motesanib in combination with doublet chemotherapy[44] as well as a phase III trial of carboplatin and paclitaxel with or without motesanib (MONET1) were performed. The phase III study was initially suspended due to a higher incidence of hemoptysis and mortality in patients with squamous cell histology. The trial resumed in patients with only nonsquamous histology and did not show a statistically significant improvement in median OS.[45] The RR was 40%, median PFS was 5.6 months, and median OS was 13.0 months in the motesanib arm versus 26%, 5.4 months, and 11.0 months, respectively, in the placebo arm. Grade ≥3 AEs with motesanib included neutropenia (22% vs 15% with placebo), diarrhea (9% vs 1%), hypertension (7% vs 1%), and cholecystitis (3% vs 0%). The incidence of grade 5 AEs was 14% with motesanib versus 9% with placebo.

Pazopanib

Pazopanib is a multi-targeted TKI that inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, FGFR-1, FGFR-3, and c-KIT,[46] and is currently being evaluated. In a phase II trial, 192 patients with advanced NSCLC who had failed 1 to 2 prior lines of therapy were randomized to pazopanib plus erlotinib versus placebo plus erlotinib.[47] There was a statistically

significant improvement in PFS in the combination arm (2.6 vs 1.8 months with erlotinib alone) but similar RR (6% vs 0%) and OS (6.8 vs 6.7 months) in the two arms. Severe nonhematologic toxicities in the combination group were fatigue (20%), diarrhea (19%), and proteinuria (5%).

Axitinib

Axitinib is a multi-targeted TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and c-KIT.[48] A phase II study of axitinib in 32 patients with NSCLC showed a RR of 9%, median PFS of 4.9 months, and median OS of 14.8 months.[49] Grade 3 hypertension (9%) and diarrhea and vomiting (3% each) were reported. In a randomized phase II study of 2 dosing schedules (continuous or intermittent) of axitinib with first-line pemetrexed/cisplatin in 170 patients with nonsquamous NSCLC, the axitinib arms were associated with higher RRs versus chemotherapy alone (45.5% in the continuous arm and 39.7% in the intermittent arm vs 26.3% in the chemotherapy alone arm) but with no significant prolongation of PFS (8.0, 7.9, and 7.1 months, respectively) or OS (16.6, 14.7, and 15.9 months, respectively).[50] The most common grade 3 AEs were hypertension (20%), neutropenia (18%), and nausea (16%) with continuous axitinib and hypertension (17%), fatigue (16%), and anemia (14%) with intermittent axitinib, with reports of grade 4 asthenia (1%) and pulmonary embolism (1%) with the latter schedule.

A phase II randomized study of axitinib or bevacizumab combined with paclitaxel/carboplatin as first-line therapy for patients with nonsquamous NSCLC failed to show an improvement with axitinib compared with bevacizumab in RR (29% vs 43%, respectively), PFS (5.7 vs 6.1 months), or OS (10.6 vs 13.3 months). The most common grade 3/4 AE in both arms was neutropenia, and there was a higher rate of treatment discontinuation due to AEs with axitinib than with bevacizumab (41% vs 31%, respectively).[51]

Vandetanib

Vandetanib is a TKI that inhibits VEGFR signaling, EGFR signaling to a lesser extent, and RET tyrosine kinases.[52] Vandetanib is no longer in development for the treatment of NSCLC. Several phase III trials failed to show a significant improvement in OS among previously treated patients with advanced NSCLC when vandetanib was combined with chemotherapy (ZEAL, ZODIAC),[53,54] given as a single-agent after failure of an EGFR TKI (ZEPHYR),[55] or compared with erlotinib (ZEST).[56]

Linifanib

Linifanib (ABT-869) is a multi-targeted TKI that is being evaluated in NSCLC. It inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, CSF-1R, and FLT-3.[57] Results from a phase II trial in 139 patients evaluating 2 doses of linifanib in chemo-refractory NSCLC showed a RR of 5.0%, median PFS of 3.6 months, and median OS of 9.0 months overall.[58] The incidence of grade 3/4 hypertension was 1.5% in the 0.1-mg/day group and 24.3% in the 0.25-mg/day group; no other grade 3/4 AEs were observed in >10% of patients overall.

Vascular Disrupting Agents

Ombrabulin

Ombrabulin (AVE8062) is a vascular disrupting agent and analog of combretastatin A4 that damages tumor vasculature.[59] The phase II DISRUPT trial randomized 176 patients with either squamous or nonsquamous histology to therapy with ombrabulin or placebo combined with a chemotherapy backbone of either cisplatin/docetaxel or carboplatin/paclitaxel for 6 cycles.[60] The RR was 32% in the ombrabulin arm versus 31% in the placebo group, PFS was 5.7 versus 5.5 months, and OS was 11.0 months in each arm. The safety profile was reported to be similar with 57% unspecified grade 3/4 AEs in the ombrabulin arm versus 52% in the placebo arm.

Vadimezan

Vadimezan (ASA404) is a vascular disrupting agent of the flavonoid class.[61] After promising results in a phase II trial in untreated patients,[62] it was tested in a phase III trial in advanced or metastatic NSCLC in combination with carboplatin/paclitaxel vs carboplatin/paclitaxel alone. 1299 patients were enrolled and the trial was stopped early due to futility. There was no statistical difference in OS (13.4 months vs 12.7 months), PFS (5.5 months vs 5.5 months), or RR (25% vs 25%) in the vadimezan arm vs chemotherapy alone.[63]

Lack of Predictive Biomarkers for Anti-Angiogenic Therapy in Lung Cancer

As summarized in this review, many anti-angiogenic agents have shown an increase in RR or PFS when compared to placebo, but in most cases this has not translated into an OS benefit. Predictive biomarkers are greatly needed to identify the subset of patients that may benefit from anti-angiogenic therapy or to identify patients likely to experience side effects, such as thrombosis and bleeding. A number of molecular signaling mediators of angiogenesis and inflammatory signaling have been investigated as potential biomarkers of anti-angiogenic therapy in lung cancer such as circulating VEGF[64], intercellular adhesion molecule (ICAM)[64], IL-2[65], IL-8[66], IL-12[65], and IL-16[65], but no biomarker has yet been prospectively validated to correlate with outcomes.

Conclusion

As the field of lung cancer moves further into the personalized medicine age, it will be imperative that we target the entire milieu surrounding the tumor environment and not merely the mutations within the cancer cell itself. Preclinical models and selected clinical trials have shown benefits for targeting angiogenesis in lung cancer. Currently, bevacizumab is the only anti-angiogenic agent recommended by the NCCN for use in the treatment of advanced NSCLC. There is a significant knowledge deficit in the understanding of the molecular basis of anti-angiogenic therapy and the AEs seen with these agents. A more thorough understanding of both the mechanisms of benefit and AEs is needed to better predict who will benefit from this treatment strategy. Predictive biomarkers are needed to help select patients who will benefit most or be least likely to suffer from the toxicities associated with these drugs.

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Abbreviations:

TKIs	tyrosine kinase inhibitors
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
FGFR	fibroblast growth factor receptor
PDGFR	platelet-derived growth factor receptor
c-KIT	stem cell factor receptor
FLT-3	fms-like tyrosine kinase 3
RET	rearranged during transfection
EGFR	epidermal growth factor receptor
PI3K	phosphatidylinositol-3-kinase
AKT	protein kinase B
SRC	v-src sarcoma viral oncogene homolog
RAS	retrovirus-associated DNA sequences
RAF	v-raf 1 murine leukemia viral oncogene homolog 1
MEK	mitogen activated protein kinase
ERK	extracellular signal-regulated kinase

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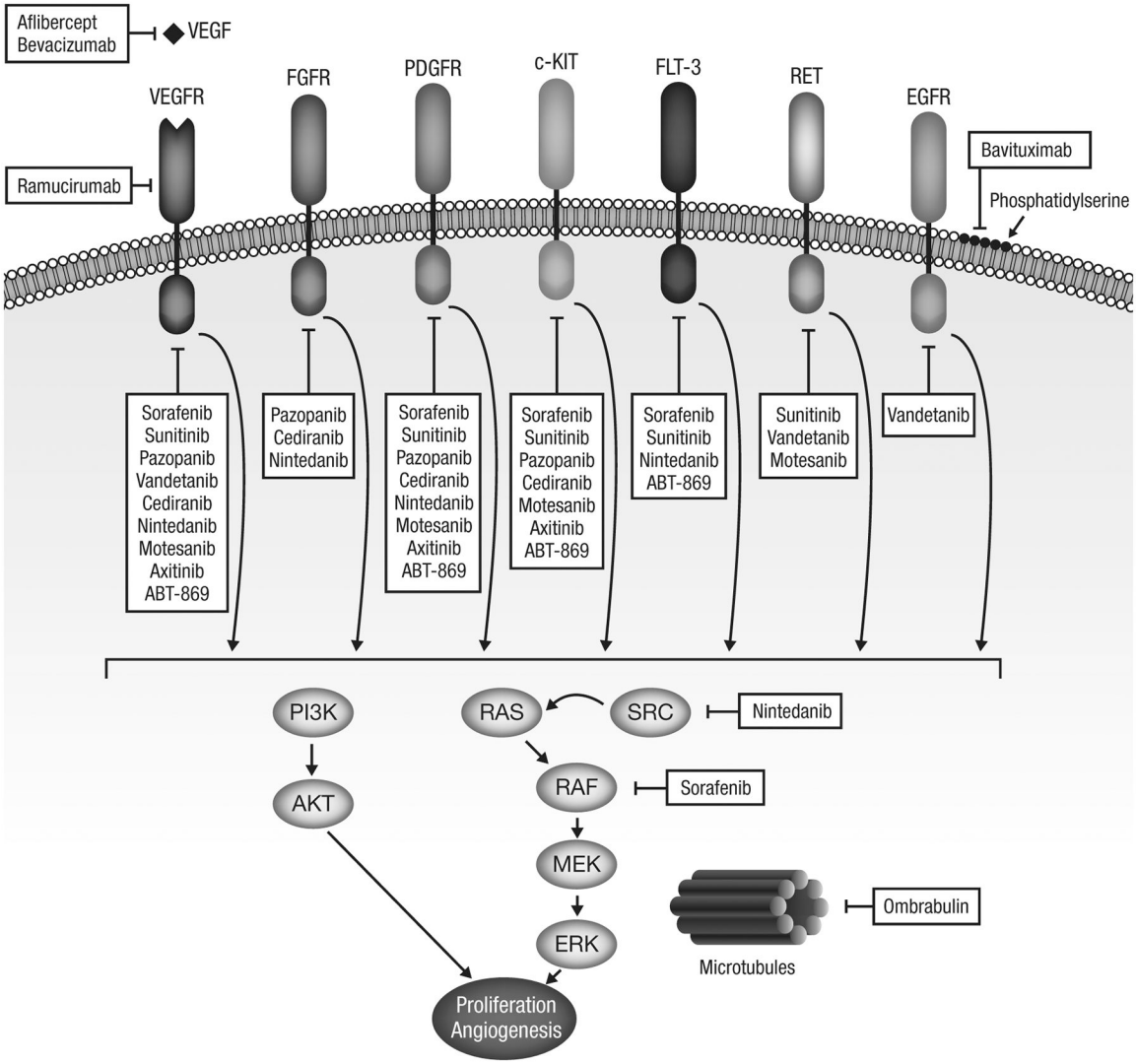

Figure 1. Targeting angiogenesis in lung cancer.

Receptors and downstream signaling pathways involved in angiogenesis and sites of action of anti-angiogenic antibody-based therapies and multi-targeted TKIs.

Table 1.

OS and RR Data Reported in Phase II and Phase III Trials of Anti-angiogenic Agents in SCLC and NSCLC

Study	Treatment	RR	OS
SCLC			
Bevacizumab: LS-SCLC			
LS-SCLC (N = 57)[8]	Carboplatin (AUC 5 D1) + irinotecan (50 mg/m^2 D1, D8) q 21 d × 2 cycles then q 28 d in 3rd/4th cycles + concurrent RT (61.2 Gy beginning with 3rd cycle) → BEV (10 mg/kg q 14 d × 10 doses)	80% (following concurrent CT + RT)	15 mo
LS-SCLC (N = 20)[9]	Carboplatin (AUC 4 D1) + irinotecan (60 mg/m^2 D1, D8) + BEV (10 mg/kg D1, D15) q 28 d + concurrent RT (61.2 Gy beginning with 3rd cycle) → BEV (10 mg/kg) q 28 d × 6 mo	78% (following concurrent CT + RT)	NR
Bevacizumab: ES-SCLC			
SALUTE: Previously untreated ES-SCLC (N = 102)[11]	Cisplatin (75 mg/m^2 D1) or carboplatin (AUC 5 D1) + etoposide (100 mg/m^2 D1–3) + BEV (15 mg/kg D1) q 21 d × 4 cycles → BEV (15 mg/kg) q 21 d vs cisplatin or carboplatin + etoposide + PBO q 21 d × 4 cycles → PBO q 21 d	58% vs 48%	9.4 vs 10.9 mo (HR, 1.16; 95% CI, 0.66–2.04)
ECOG 3501: Previously untreated ES-SCLC (N = 63)[10]	Cisplatin (60 mg/m^2 D1) + etoposide (120 mg/m^2 D1–3) + BEV (15 mg/kg D1) q 21 d × 4 cycles → BEV (15 mg/kg) q 21 d × 1 y	63.5%	10.9 mo
CALGB 30306: Previously untreated ES-SCLC (N = 72)[14]	Cisplatin (30 mg/m^2 D1) + irinotecan (65 mg/m^2 D1, D8) + BEV (15 mg/kg D1) q 21 d × 6 cycles	75%	11.6 mo
Previously untreated ES-SCLC (N = 51)[15]	Carboplatin (AUC 4 D1) + irinotecan (60 mg/m^2 D1, D8, D15) + BEV (10 mg/kg D1, D15) q 28 d × 4–6 cycles → BEV (10 mg/kg) q 14 d × 6 mo	84%	12.1 mo
Relapsed CT-sensitive SCLC (N = 34)[12]	Paclitaxel (90 mg/m^2 D1, D8, D15) + BEV (10 mg/kg D1, D15) q 28 d × 4–6 cycles → BEV (10 mg/kg D1, D15)	18%	7.1 mo
Aflibercept			
Platinum-treated ES-SCLC or LS-SCLC (N = 98)[17]	Topotecan (4 mg/m^2 weekly) + aflibercept (6 mg/kg q 3 wk) vs weekly topotecan	1% vs 0%	4.6 vs 3.9 mo (P = 0.25)
Sorafenib			
Platinum-treated ES-SCLC (N = 89)[20]	Sorafenib (400 mg BID) continuously on 28-d cycle	11% (platinum-sensitive); 2% (platinum-refractory)	6.7 mo (platinum-sensitive); 5.3 mo (platinum-refractory)
Previously untreated ES-SCLC (N = 28 [planned; accrual halted]; n = 12 evaluable for efficacy)[21]	Cisplatin (60 mg/m^2 D1) + etoposide (120 mg/m^2 D1–3) + sorafenib (200 mg BID continuous) q 21 d × 4 cycles → sorafenib (400 mg BID continuous) × 1 y	67%	7.4 mo
Sunitinib			
Previously untreated ES-SCLC (N = 34)[24]	Carboplatin (AUC 4 D1) + irinotecan (60 mg/m^2 D1, D8, D15) q 28 d × 6 cycles → sunitinib (25 mg daily)	59% (following CT)	Not reached

Study	Treatment	RR	OS
Post-induction ES-SCLC (N = 16)[25]	Cisplatin (75 mg/m^2 D1) or carboplatin (AUC 5 D1) + etoposide (100 mg/m^2 D1–3) q 21 d × 4 cycles → sunitinib (50 mg daily)	0% (following sunitinib)	8.2 mo
Cediranib			
Previously treated SCLC (N = 25)[29]	Cediranib (45 mg daily, decreased to 30 mg daily due to toxicity)	0%	6.0 mo
Vandetanib			
CT-responsive, both LS-SCLC and ES-SCLC (N = 107)[27]	Vandetanib (300 mg daily) vs PBO after completion of CT and RT	NR	10.6 vs 11.9 mo (HR, 1.43; 80% CI, 1.00–2.05; one-sided P = 0.9)
Pazopanib			
Previously treated SCLC (N = 30 [planned]; n = 21 evaluable for efficacy)[31]	Pazopanib (800 mg daily)	0%	NR
NSCLC			
Bevacizumab			
Previously untreated locally advanced or metastatic NSCLC (N = 99)[32]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) q 21 d × 6 cycles vs carboplatin/paclitaxel + BEV (7.5 or 15 mg/kg) → BEV (15 mg/kg) q 21 d	18.8% vs 28.1% (BEV 7.5 mg/kg); 31.5% (BEV 15 mg/kg)	14.9 vs 11.6 mo (BEV 7.5 mg/kg; P = 0.84 vs chemo alone); 17.7 mo (BEV 15 mg/kg; P = 0.63)
ECOG 4599: Recurrent or advanced nonsquamous NSCLC (N = 878)[33]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) q 21 d × 6 cycles vs carboplatin/paclitaxel + BEV (15 mg/kg D1) q 21 d × 6 cycles → BEV (15 mg/kg) q 21 d	15% vs 35%	10.3 vs 12.3 mo (HR, 0.79; 95% CI, 0.67–0.92; P = 0.003)
AVAiL: Recurrent or advanced nonsquamous NSCLC (N = 1,043)[36]	Cisplatin (80 mg/m^2 D1) + gemcitabine (1,250 mg/m^2 D1, D8) + BEV (15 mg/kg D1) q 21 d × 6 cycles → BEV (15 mg/kg) q 21 d vs cisplatin/gemcitabine + BEV (7.5 mg/kg D1) q 21 d × 6 cycles → BEV (7.5 mg/kg) q 21 d vs cisplatin/gemcitabine + PBO q 21 d × 6 cycles → PBO q 21 d	34.6% vs 37.8% vs 21.6%	13.4 mo (P = 0.42 vs PBO) vs13.6 mo (P = 0.76 vs PBO) vs13.1 mo
Previously untreated advanced nonsquamous NSCLC (N = 50)[37]	Pemetrexed (500 mg/m^2 D1) + carboplatin (AUC 6 D1) + BEV (15 mg/kg D1) q 21 d × 6 cycles → pemetrexed (500 mg/m^2) + BEV (15 mg/kg) q 21 d	55%	14.1 mo
Previously untreated advanced nonsquamous NSCLC (N = 38)[38]	Pemetrexed (500 mg/m^2 D1) + oxaliplatin (100 mg/m^2 D1) + BEV (7.5 mg/kg D1) q 21 d × 6 cycles → pemetrexed (500 mg/m^2) + BEV (7.5 mg/kg)	55.3%	14.6 mo
Previously untreated advanced nonsquamous NSCLC (N = 49)[39]	Cisplatin (80 mg/m^2 D1) + vinorelbine (25 mg/m^2 D1, D8) + BEV (15 mg/kg D1) q 21 d × 6 cycles → BEV (15 mg/kg)	29%	14.7 mo
Ramucirumab			
Previously untreated NSCLC (N = 31)[45]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) + ramucirumab (10 mg/kg D1) q 21 d × 6 cycles → ramucirumab (10 mg/kg) q 21 d	55%	NR
Aflibercept			

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Study	Treatment	RR	OS
Platinum and erlotinib resistant advanced or metastatic NSCLC (N = 98)[46]	Aflibercept (4 mg/kg) q 2 wk	2%	6.2 mo
VITAL: 1 prior platinum-based therapy (N = 913)[47]	Docetaxel (75 mg/m^2) + aflibercept (6 mg/kg) q 3 wk vs docetaxel + PBO q 3 wk	23.3% vs 8.9%	10.1 vs 10.4 mo (HR, 1.01; 95.1% CI, 0.87–1.17; *P* = 0.90)
Sorafenib			
Relapsed or refractory NSCLC (N = 54)[48]	Sorafenib (400 mg BID)	0%	6.7 mo
ESCAPE: CT-naive advanced NSCLC (N = 926)[50]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) + sorafenib (400 mg BID D2–19) × 6 cycles → sorafenib (400 mg BID) vs carboplatin/paclitaxel + PBO → PBO BID	27.4% vs 24.0%	10.7 vs 10.6 mo (HR, 1.15; 95% CI, 0.94–1.41; *P* = 0.92)
NEXUS: CT-naive advanced nonsquamous NSCLC (N = 904; n = 772 evaluable for efficacy)[51]	Cisplatin (75 mg/m^2 D1) + gemcitabine (1,250 mg/m^2 D1, D8) + sorafenib (400 mg BID D1–21) × 6 cycles → sorafenib (400 mg BID) vs cisplatin/gemcitabine + PBO → PBO BID	28% vs 26%	12.4 vs 12.5 mo (HR, 0.98; 95% CI, 0.83–1.16)
Sunitinib			
Previously treated NSCLC (N = 63)[52]	Sunitinib (50 mg daily × 4 wk followed by 2 wk no treatment)	11.1%	5.6 mo
Previously treated advanced NSCLC (N = 47)[53]	Sunitinib (37.5 mg daily)	2.1%	8.6 mo
Previously untreated advanced NSCLC (N = 960)[54]	Erlotinib (150 mg daily) + sunitinib (37.5 mg daily) vs erlotinib + PBO	10.6% vs 6.9%	9.0 vs 8.5 mo (HR, 0.92; 95% CI, 0.80–1.07; *P* = 0.14)
Nintedanib			
Previously treated advanced NSCLC (N = 73)[56]	Nintedanib (150 mg or 250 mg BID)	1.4%	5.2 mo
Cediranib			
NCIC BR24: CT-naive advanced NSCLC (N = 296)[57]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) + cediranib (either 45 or 30 mg daily) q 21 d × 6–8 cycles → cediranib (45 or 30 mg daily) vs carboplatin/paclitaxel + PBO × 6–8 cycles → PBO daily	38% vs 16%	10.5 vs 10.1 mo (HR, 0.78; 95% CI, 0.57–1.06; *P* = 0.11)
Previously treated NSCLC without prior BEV (N = 38)[58]	Pemetrexed (500 mg/m^2 D8) + cediranib (30 mg daily) q 21 d	29%	11 mo
Motesanib			
CT-naive advanced NSCLC (N = 186)[60]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) + motesanib (125 mg daily) q 21 d × 6 cycles → motesanib (125 mg daily) × 36 mo vs carboplatin/paclitaxel + motesanib (75 mg BID) q 21 d × 6 cycles → motesanib (75 mg BID) × 36 mo vs carboplatin/paclitaxel + BEV (15 mg/kg) q 21 days × 6 cycles → BEV (15 mg/kg) q 21 d × 36 mo	30% vs 23% vs 37%	14.0 mo (vs CT/BEV: HR, 1.05; 95% CI, 0.67–1.63) vs12.8 mo (vs CT/BEV: HR, 1.18; 95% CI, 0.76–1.83) vs14.0 mo
MONET-1: CT-naive advanced nonsquamous NSCLC (N = 1,090)[61]	Carboplatin (AUC 6 D1) + paclitaxel (200 mg/m^2 D1) + motesanib (125 mg daily) q 21 d × 6 cycles → motesanib (125 mg daily) vs carboplatin/paclitaxel + PBO daily q 21 d × 6 cycles → PBO daily	40% vs 26%	13.0 vs 11.0 mo (HR, 0.90; 95% CI, 0.78–1.04; *P* = 0.14)
Axitinib			

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Study	Treatment	RR	OS
CT-naive or previously treated NSCLC without prior angiogenic therapy (N = 32)[64]	Axitinib (5 mg BID)	9%	14.8 mo
Previously untreated nonsquamous NSCLC (N = 170)[65]	Cisplatin + pemetrexed + axitinib (5 mg BID [starting dose] continuous) q 21 d × 6 cycles vs cisplatin + pemetrexed + axitinib (5 mg BID [starting dose] D2–19) q 21 d × 6 cycles vs cisplatin/pemetrexed q 21 d × 6 cycles	45.5% vs 39.7% vs 26.3%	16.6 mo (vs CT alone: HR, 1.08; 95% CI, 0.66–1.76; P = 0.63) vs 14.7 mo (vs CT alone: HR, 1.39; 95% CI, 0.87–2.22; P = 0.89) vs 15.9 mo
Vandetanib			
ZEAL: Previously treated advanced NSCLC (N = 534)[66]	Pemetrexed (500 mg/m^2 D1) + vandetanib (100 mg daily) q 21 d × 6 cycles vs pemetrexed + PBO q 21 d × 6 cycles	19% vs 8%	10.5 vs 9.2 mo (HR, 0.86; 97.54% CI, 0.65–1.13; P = 0.22)
ZEST: Previously treated advanced NSCLC (N = 1,240)[69]	Erlotinib (150 mg daily) vs vandetanib (300 mg daily)	12% vs 12%	7.8 vs 6.9 mo (HR, 1.01; 95.08% CI, 0.89–1.16; P = 0.83)
ZODIAC: Previously treated locally advanced or metastatic NSCLC (N = 1,391)[67]	Docetaxel (75 mg/m^2) + vandetanib (100 mg daily) q 21 d × 6 cycles → vandetanib (100 mg daily) vs docetaxel + PBO daily q 21 d × 6 cycles → PBO daily	17% vs 10%	10.6 vs 10.0 mo. (HR, 0.91; 97.52% CI, 0.78–1.07; P = 0.20)
ZEPHYR: Previously treated locally advanced or metastatic NSCLC (N = 924)[68]	Vandetanib (300 mg daily) vs PBO daily	2.6% vs 0.7%	8.5 vs 7.8 mo (HR, 0.95; 95.2% CI, 0.81–1.11; P = 0.53)
Linifanib (ABT-869)			
Previously treated advanced or metastatic NSCLC (N = 139)[71]	Linifanib (0.10 mg/kg daily) vs linifanib (0.25 mg/kg daily)	3.1% vs 6.8%	9.0 mo (both doses combined)

OS, overall survival; RR, response rate; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; LS-SCLC, limited-stage small cell lung cancer; AUC, area under the curve; RT, radiation therapy; BEV, bevacizumab; CT, chemotherapy; NR, not reported; ES-SCLC, extensive-stage small cell lung cancer; PBO, placebo; HR, hazard ratio; CI, confidence interval; BID, twice daily.

Table 2.

Phase II and Phase III Trials of Approved[a] and Investigational Anti-angiogenic Agents in SCLC and NSCLC[b]

Trial	Phase	Description	Status[a]
Bevacizumab (SCLC)			
NCT00755157	II	Bevacizumab plus docetaxel as second-line treatment in patients with SCLC	Recruiting
Aflibercept (SCLC)			
NCT00828139	II	Aflibercept plus topotecan as second-line treatment in patients with ES-SCLC	Active, no longer recruiting
Sorafenib (SCLC)			
NCT00726986	II	Sorafenib plus cisplatin/etoposide followed by sorafenib maintenance in patients with ES-SCLC	Active, no longer recruiting
NCT01159327	II	Sorafenib maintenance in patients with ES-SCLC who responded to first-line chemotherapy	Recruiting
Sunitinib (SCLC)			
NCT00695292	II	Irinotecan/carboplatin followed by sunitinib maintenance as first-line treatment in patients with ES-SCLC	Active, no longer recruiting
NCT00616109	II	Sunitinib maintenance in patients with ES-SCLC who responded to first-line chemotherapy	Active, no longer recruiting
NCT00620347	II	Sunitinib as second-line treatment in patients with ES-SCLC	Active, no longer recruiting
NCT00953459	II	Sunitinib as first-line treatment in patients with ES-SCLC or second-line treatment in patients with recurrent SCLC	Active, no longer recruiting
NCT00453154	I/II	Cisplatin or carboplatin and etoposide followed by maintenance sunitinib as first-line treatment in patients with ES-SCLC	Recruiting
Vandetanib (SCLC)			
NCT00613626	II	Vandetanib plus cisplatin/etoposide as first-line treatment in patients with ES-SCLC	Recruiting
Bevacizumab (NSCLC)			
NCT01107626	III	Bevacizumab or pemetrexed or bevacizumab plus pemetrexed after at least stable disease after 4 cycles of induction therapy in patients with advanced nonsquamous NSCLC	Recruiting
NCT00762034	III	Carboplatin, pemetrexed, and bevacizumab followed by pemetrexed/bevacizumab maintenance therapy or carboplatin, paclitaxel, and bevacizumab followed by bevacizumab maintenance therapy in patients with advanced nonsquamous NSCLC	Recruiting
NCT00948675	III	Pemetrexed and carboplatin followed by pemetrexed maintenance therapy or paclitaxel, carboplatin and bevacizumab followed by bevacizumab maintenance therapy in patients with advanced nonsquamous NSCLC	Recruiting
NCT00946712	III	Carboplatin and paclitaxel with or without bevacizumab and/or cetuximab in patients with stage IV or recurrent NSCLC	Recruiting
NCT01364012	III	Bevacizumab or placebo in combination with paclitaxel/carboplatin as first-line therapy in patients with advanced or recurrent NSCLC	Recruiting
NCT01351415	III	Investigator’s choice of standard of care treatment with or without bevacizumab in patients with advanced nonsquamous NSCLC	Recruiting
NCT00324805	III	Chemotherapy (vinorelbine/cisplatin, docetaxel/cisplatin, gemcitabine/cisplatin, or pemetrexed/cisplatin) with or without bevacizumab in patients with stage IB, II, or IIIA after surgical resection	Recruiting
Ramucirumab (NSCLC)			
NCT01168973	III	Ramucirumab plus docetaxel as second-line treatment in patients with stage IV NSCLC	Recruiting

Trial	Phase	Description	Status[a]
NCT01160744	II	Ramucirumab plus paclitaxel/carboplatin as first-line treatment in patients with stage IV NSCLC	Recruiting
Sorafenib (NSCLC)			
NCT00863746	III	Sorafenib as third- or fourth-line treatment in patients with predominantly nonsquamous NSCLC	Active, no longer recruiting
NCT00600015	II	Sorafenib plus erlotinib or erlotinib alone in patients with previously treated advanced NSCLC	Active, no longer recruiting
NCT00609804	II	Sorafenib plus erlotinib or sorafenib alone in patients with advanced NSCLC after failure of erlotinib	Active, no longer recruiting
NCT00411671	II	Sorafenib in patients with previously treated advanced NSCLC (BATTLE)	Active, no longer recruiting
NCT00754923	II	Sorafenib in non-smokers or former light smokers with relapsed or refractory advanced NSCLC	Recruiting
Sunitinib (NSCLC)			
NCT00693992	III	Sunitinib maintenance in patients with advanced NSCLC after first-line combination chemotherapy	Recruiting
NCT00457392	III	Sunitinib plus erlotinib or erlotinib alone in patients with previously treated advanced NSCLC	Active, no longer recruiting
NCT00864721	II	Sunitinib as first-line treatment in patients over 70 years of age with NSCLC	Active, no longer recruiting
NCT01210053	II	Sunitinib maintenance in patients with advanced NSCLC	Recruiting
NCT00698815	II	Sunitinib plus pemetrexed or sunitinib monotherapy as second-line treatment in patients with advanced NSCLC	Recruiting
Nintedanib (NSCLC)			
NCT00805194	III	Nintedanib plus docetaxel as second-line treatment in patients with advanced NSCLC	Active, no longer recruiting
NCT00806819	III	Nintedanib plus pemetrexed as second-line treatment in patients with advanced NSCLC	Active, no longer recruiting
Cediranib (NSCLC)			
NCT00795340	III	Cediranib plus paclitaxel/carboplatin in patients with advanced NSCLC	Active, no longer recruiting
NCT00245154	II/III	Cediranib plus paclitaxel/carboplatin in patients with advanced NSCLC	Active, no longer recruiting
Pazopanib (NSCLC)			
NCT00775307	II/III	Pazopanib as adjuvant treatment in patients with stage I NSCLC after surgical resection	Recruiting
NCT01208064	II/III	Pazopanib maintenance in patients with advanced NSCLC after first-line chemotherapy	Recruiting
NCT00866528	II	Pazopanib plus paclitaxel as first-line treatment in patients with advanced NSCLC	Active, no longer recruiting
NCT01027598	II	Pazopanib plus erlotinib in patients with previously treated advanced NSCLC	Active, no longer recruiting
NCT01179269	II	Pazopanib plus paclitaxel as first-line treatment in patients with advanced NSCLC	Recruiting
NCT01313663	II	Pazopanib versus pemetrexed maintenance in patients with advanced NSCLC after first-line chemotherapy with carboplatin or cisplatin plus pemetrexed	Recruiting
NCT01262820	II	Pazopanib as second-line treatment in patients with advanced NSCLC after failure of bevacizumab	Recruiting
NCT01107652	II	Pazopanib plus pemetrexed or pazopanib alone as second-line treatment in patients with advanced NSCLC after failure of bevacizumab	Recruiting
Axitinib (NSCLC)			
NCT00600821	II	Carboplatin/paclitaxel plus either axitinib or bevacizumab as first-line treatment in patients with advanced NSCLC	Active, no longer recruiting

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Trial	Phase	Description	Status[a]
ABT-869 (NSCLC)			
NCT00517790	II	ABT-869 in patients with previously treated advanced NSCLC	Active, no longer recruiting

[a]Trials summarized of bevacizumab in NSCLC are limited to phase III.

[b]With trial status listed as “recruiting” or “active, no longer recruiting” based on ClinicalTrials.gov as of June 2012.

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ES-SCLC, extensive stage small cell lung cancer.

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