Targeting Angiogenesis in Advanced Non–Small Cell Lung Cancer

Philip E. Lammers, MD, MSCI, and Leora Horn, MD, MSc

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 antiangiogenic agent currently recommended by NCCN for the treatment of advanced NSCLC. However, several antibody-based therapies and multitargeted tyrosine kinase inhibitors are currently under investigation for the treatment of patients with NSCLC. This article summarizes the available clinical trial data on the efficacy and safety of these agents in patients with advanced lung cancer. (JNCCN 2013;11:1235–1247)

Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 228,190 new cases and 159,480 deaths in 2013. More than two-thirds of patients with lung cancer will present with advanced disease. 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. Approximately 60% of patients with stage IIIB/IV adenocarcinoma have a molecular mutation thought to drive tumor growth. However, only patients with epidermal growth factor receptor (EGFR) mutations (approximately 10%–15%) or anaplastic lymphoma kinase (ALK) rearrangements (approximately 5%) have an FDA-approved therapy available. Other potential targets have been identified, such as c-ros oncogene 1 (ROS1) gene fusions and BRAF mutations, and clinical trials using targeted agents are ongoing. Alternative targets continue to be investigated, one of which is angiogenesis, a necessary process in the growth and metastasis of solid tumors. Bevacizumab is the only antiangiogenic therapy FDA-approved for NSCLC, but other agents have been tested in advanced NSCLC. Currently, NCCN recommends that bevacizumab be considered 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 antiangiogenic agents is a rational approach to treating lung cancer, but must 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 antiangiogenic inhibitors may be most beneficial. The current data for antiangiogenic agents vary widely among the studied drugs, and safety data are especially limited for many of the agents studied. This review summarizes the available efficacy and safety/tolerability data from clinical trials of antiangiogenic agents in advanced NSCLC. (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, progression-free and overall survivals have been rounded to the nearest tenth, and hazard ratio, confidence interval, and P values have been rounded to 2 decimal places.)
Efficacy and Safety of Antiangiogenic Agents for NSCLC

Antibody-Based Therapeutics

Bevacizumab: Bevacizumab is a humanized monoclonal antibody with a high affinity for vascular endothelial growth factor (VEGF). 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 antiangiogenic agents described in this article 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 antihypertensive therapies.

Bevacizumab is the most studied antiangiogenic agent in advanced NSCLC (Tables 1 and 2). After promising results from a phase II study, ECOG 4599 was conducted as a randomized phase III trial comparing carboplatin/paclitaxel with or without bevacizumab in 878 patients with recurrent or advanced nonsquamous NSCLC. Improvements in median overall survival (OS), median progression-free survival (PFS), and response rate (RR) occurred in patients treated with bevacizumab compared with those in 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).

Figure 1  Targeting angiogenesis in lung cancer. Receptors and downstream signaling pathways involved in angiogenesis and sites of action of antiangiogenic antibody-based therapies and multitargeted tyrosine kinase inhibitors. Abbreviations: AKT, protein kinase B; c-KIT, stem cell factor receptor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; FLT-3, fms-like tyrosine kinase 3; MEK, mitogen-activated protein kinase; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol-3-kinase; RAF, v-raf 1 murine leukemia viral oncogene homolog 1; RAS, retrovirus-associated DNA sequences; RET, rearranged during transfection; SRC, v-src sarcoma viral oncogene homolog; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Table 1 Overall Survival and Response Rate Data Reported in Selected Phase II and III Trials of Antiangiogenic Agents in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Response Rate</th>
<th>Overall Survival</th>
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<tr>
<td><strong>Bevacizumab</strong></td>
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<tr>
<td>Previously untreated locally advanced or metastatic NSCLC (N=99)</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m² day 1) q21d x 6 cycles vs carboplatin/paclitaxel + BEV (15 mg/kg) → BEV (15 mg/kg) q21d</td>
<td>18.8% vs 28.1% (BEV, 7.5 mg/kg); 31.5% (BEV, 15 mg/kg)</td>
<td>14.9 vs 11.6 mo (BEV, 7.5 mg/kg; P=.84 vs CT alone); 17.7 mo (BEV, 15 mg/kg; P=.63)</td>
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<td>ECOG 4599: recurrent or advanced nonsquamous NSCLC (N=878)</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m² day 1) q21d x 6 cycles vs carboplatin/paclitaxel + BEV (15 mg/kg) q21d x 6 cycles → BEV (15 mg/kg) q21d</td>
<td>15% vs 35%</td>
<td>10.3 vs 12.3 mo (HR, 0.79; 95% CI, 0.67–0.92; P=.003)</td>
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<td>AVAiL: recurrent or advanced nonsquamous NSCLC (N=1043)</td>
<td>Cisplatin (80 mg/m² day 1) + gemcitabine (1250 mg/m² day 1, day 8) + BEV (15 mg/kg day 1) q21d x 6 cycles → BEV (15 mg/kg) q21d vs cisplatin/ gemcitabine + BEV (7.5 mg/kg day 1) q21d x 6 cycles → BEV (7.5 mg/kg) q21d vs cisplatin/ gemcitabine + PBO q21d x 6 cycles → PBO q21d</td>
<td>34.6% vs 37.8% vs 21.6%</td>
<td>13.4 mo (P=.42 vs PBO) vs 13.6 mo (P=.76 vs PBO) vs 13.1 mo</td>
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<td>Previously untreated advanced nonsquamous NSCLC (N=50)</td>
<td>Pemetrexed (500 mg/m² day 1) + carboplatin (AUC 6 day 1) + BEV (15 mg/kg) day 1) q21d x 6 cycles → pemetrexed (500 mg/m²) + BEV (15 mg/kg) q21d</td>
<td>55%</td>
<td>14.1 mo</td>
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<tr>
<td>Previously untreated advanced nonsquamous NSCLC (N=939)</td>
<td>Pemetrexed (500 mg/m²) + carboplatin (AUC 6) + BEV (15 mg/kg) q21d x 4 cycles → pemetrexed (500 mg/m²) + BEV (15 mg/kg) q21d vs paclitaxel (200 mg/m²) + carboplatin (AUC 6) + BEV (15 mg/kg) q21d x 4 cycles → BEV (15 mg/kg) q21d</td>
<td>34.1% vs 33.0%</td>
<td>12.6 vs 13.4 mo (HR, 1.00; P=.949)</td>
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<td>Advanced nonsquamous NSCLC and asymptomatic, untreated brain metastases (N=91)</td>
<td>Carboplatin (AUC 6) + paclitaxel (200 mg/m²) + BEV (15 mg/kg) q21d x 6 cycles → BEV (15 mg/kg) q21d (first-line) or BEV (15 mg/kg) q21d + erlotinib (150 mg qd) (second-line)</td>
<td>63% or 13%</td>
<td>16.0 or 12.0 mo</td>
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<td><strong>Ramucirumab</strong></td>
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<td>Previously untreated advanced NSCLC (N=40)</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m² day 1) + ramucirumab (10 mg/kg day 1) q21d x 6 cycles → ramucirumab (10 mg/kg) q21d</td>
<td>55%</td>
<td>NR</td>
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<td>Previously untreated advanced nonsquamous NSCLC (N=140)</td>
<td>Ramucirumab + pemetrexed + either carboplatin or cisplatin vs pemetrexed + either carboplatin or cisplatin</td>
<td>44% vs 37%</td>
<td>NR</td>
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<td><strong>Bavituximab</strong></td>
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<td>Previously untreated advanced or metastatic nonsquamous NSCLC (N=86)</td>
<td>Bavituximab (3 mg/kg) q7d + carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d x 6 cycles vs carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d x 6 cycles</td>
<td>32% vs 31%</td>
<td>NR</td>
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<td><strong>Afiblercept</strong></td>
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<td>Platinum and erlotinib resistant advanced or metastatic NSCLC (N=98)</td>
<td>Afiblercept (4 mg/kg) q2wk</td>
<td>2%</td>
<td>6.2 mo</td>
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<td>VITAL: 1 prior platinum-based therapy (N=913)</td>
<td>Docetaxel (75 mg/m²) + afiblercept (6 mg/kg) q3wk vs docetaxel + PBO q3wk</td>
<td>23.3% vs 8.9%</td>
<td>10.1 vs 10.4 mo (HR, 1.01; 95.1% CI, 0.87–1.17; P=.90)</td>
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Abbreviations: AUC, area under the curve; BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio; NR, not reported; NSCLC, non–small cell lung cancer; PBO, placebo.
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<td><strong>Sorafenib</strong></td>
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<tr>
<td>Relapsed or refractory NSCLC (N=54)$^{38}$</td>
<td>Sorafenib (400 mg bid)</td>
<td>0%</td>
<td>6.7 mo</td>
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<td>ESCAPE: CT-naive advanced NSCLC (N=926)$^{39}$</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m$^2$ day 1) + sorafenib (400 mg bid days 2–19) x 6 cycles $\rightarrow$ sorafenib (400 mg bid) vs carboplatin/paclitaxel + PBO $\rightarrow$ PBO bid</td>
<td>27.4% vs 24.0%</td>
<td>10.7 vs 10.6 mo (HR, 1.15; 95% CI, 0.94–1.41; $P=.92$)</td>
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<td>NEXUS: CT-naive advanced nonsquamous NSCLC (N=904; n=772 evaluable for efficacy)$^{40}$</td>
<td>Cisplatin (75 mg/m$^2$ day 1) + gemcitabine (1250 mg/m$^2$ days 1, 8) + sorafenib (400 mg bid days 1–21) x 6 cycles $\rightarrow$ sorafenib (400 mg bid) vs cisplatin/gemcitabine + PBO $\rightarrow$ PBO bid</td>
<td>27% vs 26%</td>
<td>12.4 vs 12.5 mo (HR, 0.98; 95% CI, 0.83–1.16)</td>
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<td><strong>Sunitinib</strong></td>
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<tr>
<td>Previously treated NSCLC (N=63)$^{41}$</td>
<td>Sunitinib (50 mg daily x 4 wk followed by 2 wk no treatment)</td>
<td>11.1%</td>
<td>5.6 mo</td>
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<td>Previously treated advanced NSCLC (N=47)$^{42}$</td>
<td>Sunitinib (37.5 mg daily)</td>
<td>2.1%</td>
<td>8.6 mo</td>
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<td>Previously untreated advanced NSCLC (N=960)$^{43}$</td>
<td>Erlotinib (150 mg daily) + sunitinib (37.5 mg daily) vs erlotinib + PBO</td>
<td>10.6% vs 6.9%</td>
<td>9.0 vs 8.5 mo (HR, 0.92; 95% CI, 0.80–1.07; $P=.14$)</td>
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<td><strong>Nintedanib</strong></td>
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<tr>
<td>Previously treated advanced NSCLC (N=73)$^{44}$</td>
<td>Nintedanib (150 or 250 mg bid)</td>
<td>1.4%</td>
<td>5.2 mo</td>
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<td>LUME-Lung 1: previously treated advanced NSCLC (N=1314)$^{45}$</td>
<td>Nintedanib (200 mg bid) + docetaxel, 75 mg/m$^2$ q21d vs docetaxel + PBO</td>
<td>5% vs 3%</td>
<td>10.1 vs 9.1 mo (HR, 0.94; $P=.272$)</td>
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<td>LUME-Lung 2: previously treated advanced nonsquamous NSCLC (N=713)$^{46}$</td>
<td>Nintedanib (200 mg bid) + pemetrexed, 500 mg/m$^2$ q21d vs pemetrexed + PBO</td>
<td>9% vs 9%</td>
<td>NR (HR, 1.03; $P=NR$)</td>
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<td><strong>Cediranib</strong></td>
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<td>NCIC BR24: CT-naive advanced NSCLC (N=296)$^{47}$</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m$^2$ day 1) + cediranib (either 45 or 30 mg daily) q21d x 6–8 cycles $\rightarrow$ cediranib (45 or 30 mg daily) vs carboplatin/paclitaxel + PBO x 6–8 cycles $\rightarrow$ PBO daily</td>
<td>38% vs 16%</td>
<td>10.5 vs 10.1 mo (HR, 0.78; 95% CI, 0.57–1.06; $P=.11$)</td>
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<td>Previously treated NSCLC without prior BEV (N=38)$^{48}$</td>
<td>Pemetrexed (500 mg/m$^2$ day 8) + cediranib (30 mg daily) q21d</td>
<td>29%</td>
<td>11 mo</td>
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<td><strong>Motesanib</strong></td>
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<td>CT-naive advanced NSCLC (N=186)$^{49}$</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m$^2$ day 1) + motesanib (125 mg daily) q21d x 6 cycles $\rightarrow$ motesanib (125 mg daily) x 36 mo vs carboplatin/paclitaxel + motesanib (75 mg bid) q21d x 6 cycles $\rightarrow$ motesanib (75 mg bid) x 36 mo vs carboplatin/paclitaxel + BEV (15 mg/kg) q21d x 6 cycles $\rightarrow$ BEV (15 mg/kg) q21d x 36 mo</td>
<td>30% vs 23% vs 37%</td>
<td>14.0 mo (vs CT/BEV; HR, 1.05; 95% CI, 0.67–1.63) vs 12.8 mo (vs CT/BEV; HR, 1.18; 95% CI, 0.76–1.83) vs 14.0 mo</td>
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<tr>
<td>MONET-1: CT-naive advanced nonsquamous NSCLC (N=1090)$^{50}$</td>
<td>Carboplatin (AUC 6 day 1) + paclitaxel (200 mg/m$^2$ day 1) + motesanib (125 mg daily) q21d x 6 cycles $\rightarrow$ motesanib (125 mg daily) x 36 mo vs carboplatin/paclitaxel + PBO daily q21d x 6 cycles $\rightarrow$ PBO daily</td>
<td>40% vs 26%</td>
<td>13.0 vs 11.0 mo (HR, 0.90; 95% CI, 0.78–1.04; $P=.14$)</td>
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Abbreviations: AUC, area under the curve; BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio; NR, not reported; NSCLC, non–small cell lung cancer; PBO, placebo.
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<td><strong>Pazopanib</strong>&lt;br&gt;Previously treated advanced NSCLC (N=192)⁷</td>
<td>Pazopanib (600 mg qd) + erlotinib (150 mg qd) vs PBO + erlotinib (150 mg qd)</td>
<td>6% vs 0%</td>
<td>6.8 vs 6.7 mo (HR, 1.1; 95% CI, 0.77–1.55; P=.61)</td>
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<tr>
<td><strong>Axitinib</strong>&lt;br&gt;CT-naïve or previously treated NSCLC without prior angiogenic therapy (N=32)¹¹</td>
<td>Axitinib (5 mg bid)</td>
<td>9%</td>
<td>14.8 mo</td>
</tr>
<tr>
<td>Previously untreated nonsquamous NSCLC (N=170)¹⁰</td>
<td>Cisplatin + pemetrexed + axitinib (5 mg bid [starting dose] continuous) q21d x 6 cycles vs cisplatin + pemetrexed + axitinib (5 mg bid [starting dose] days 2–19) q21d x 6 cycles vs cisplatin/pemetrexed q21d x 6 cycles</td>
<td>45.5% vs 39.7% vs 26.3%</td>
<td>16.6 mo (vs CT alone: HR, 1.08; 95% CI, 0.66–1.76; P=.63) vs 14.7 mo (vs CT alone: HR, 1.39; 95% CI, 0.87–2.22; P=.89) vs 15.9 mo</td>
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<tr>
<td>Previously untreated advanced nonsquamous NSCLC (N=118)</td>
<td>Axitinib (5 mg bid) + carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d vs bevacizumab (15 mg/kg) + carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d</td>
<td>29.3% vs 43.3%</td>
<td>10.6 vs 13.3 mo (HR, 1.12; 95% CI, 0.74–1.69; P=.70)</td>
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<td><strong>Vandetanib</strong>&lt;br&gt;ZEAL: previously treated advanced NSCLC (N=534)¹³</td>
<td>Pemetrexed (500 mg/m² day 1) + vandetanib (100 mg daily) q21d x 6 cycles vs pemetrexed + PBO q21d x 6 cycles</td>
<td>19% vs 8%</td>
<td>10.5 vs 9.2 mo (HR, 0.86; 95.74% CI, 0.65–1.13; P=.22)</td>
</tr>
<tr>
<td>ZEST: previously treated advanced NSCLC (N=1240)¹⁰</td>
<td>Erlotinib (150 mg daily) vs vandetanib (300 mg daily)</td>
<td>12% vs 12%</td>
<td>7.8 vs 6.9 mo (HR, 1.01; 95.08% CI, 0.89–1.16; P=.83)</td>
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<tr>
<td>ZODIAC: previously treated locally advanced or metastatic NSCLC (N=1391)¹⁴</td>
<td>Docetaxel (75 mg/m²) + vandetanib (100 mg daily) q21d x 6 cycles → vandetanib (100 mg daily) vs docetaxel + PBO daily q21d x 6 cycles → PBO daily</td>
<td>17% vs 10%</td>
<td>10.6 vs 10.0 mo (HR, 0.91; 95.72% CI, 0.78–1.07; P=.20)</td>
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<tr>
<td>ZEPHIR: previously treated locally advanced or metastatic NSCLC (N=924)¹⁵</td>
<td>Vandetanib (300 mg daily) vs PBO daily</td>
<td>2.6% vs 0.7%</td>
<td>8.5 vs 7.8 mo (HR, 0.95; 95.2% CI, 0.81–1.11; P=.53)</td>
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<td><strong>Linifanib (ABT-869)</strong>&lt;br&gt;Previously treated advanced or metastatic NSCLC (N=139)²⁰</td>
<td>Linifanib (0.10 mg/kg daily) vs linifanib (0.25 mg/kg daily)</td>
<td>3.1% vs 6.8%</td>
<td>9.0 mo (both doses combined)</td>
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<td><strong>Ombrabulin (AVE8062)</strong>&lt;br&gt;Previously untreated metastatic NSCLC (N=176)¹⁰</td>
<td>Ombrabulin (35 mg/m² day 1) + docetaxel (75 mg/m²)/cisplatin (75 mg/m²) day 2 or paclitaxel (200 mg/m²)/carboplatin (AUC 6) day 2 q21d vs PBO day 1 + docetaxel (75 mg/m²)/cisplatin (75 mg/m²) day 2 or paclitaxel (200 mg/m²)/carboplatin (AUC 6) day 2 q21d</td>
<td>32% vs 31%</td>
<td>11.0 vs 11.0 mo (HR, 0.96; 60% CI, 0.76–1.21; P=NR)</td>
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<td><strong>Vadimezan (ASA404)</strong>&lt;br&gt;Previously untreated advanced or metastatic NSCLC (N=1204)¹⁵</td>
<td>Vadimezan (1800 mg/m²) + carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d x 6 cycles vs PBO + carboplatin (AUC 6)/paclitaxel (200 mg/m²) q21d x 6 cycles → PBO q21d</td>
<td>25% vs 25%</td>
<td>13.4 vs 12.7 mo (HR, 1.01; 95% CI, 0.85–1.19; P=.54)</td>
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Abbreviations: AUC, area under the curve; BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio; NR, not reported; NSCLC, non–small cell lung cancer; PBO, placebo.
analysis, elderly patients (age ≥70 years) had improved median PFS and RR but no improvement in median OS. The most common grade 3 or higher AEs in the bevacizumab arm were neutropenia (26%), hypertension (7%), febrile neutropenia (5%), and bleeding events (4%). Compared with chemotherapy alone, bevacizumab plus chemotherapy was associated with higher rates of grade 4 neutropenia (26% vs 17%) and 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 15.0 mg/kg) in 1043 patients with advanced or recurrent nonsquamous NSCLC. Median PFS (6.7 months in the bevacizumab, 7.5-mg/kg arm and 6.5 months in the bevacizumab, 15.0-mg/kg arm vs 6.1 months in the placebo arm) and RR (38% in the bevacizumab, 7.5-mg/kg arm and 35% in the bevacizumab, 15.0-mg/kg arm vs 22% in the 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, 13.4, and 13.1 months, respectively). Grade 3/4 AEs in the bevacizumab, 15.0-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, 15.0-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 and led investigators to conduct a large randomized phase III trial of 939 patients to evaluate for superiority of pemetrexed/carboplatin/bevacizumab followed by single-agent bevacizumab maintenance. 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; more grade 3/4 thrombocytopenia (23.3% vs 5.6%), anemia (14.5% vs 2.7%), and fatigue (10.9% vs 5.0%) were seen in the pemetrexed group, whereas more grade 3/4 neutropenia (40.6% vs 25.8%), febrile neutropenia (4.1% vs 1.4%), and sensory neuropathy (4.1% vs 0%) were seen 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. 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 or higher 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.

**Ramucirumab:** Ramucirumab (IM-1121B), a human monoclonal anti-VEGFR-2 antibody, is currently being evaluated in patients with diverse histologic 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 an RR of 55% and a median PFS of 7.9 months. 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 carboplatin or cisplatin versus single-agent pemetrexed in combination with carboplatin or cisplatin. An interim analysis showed an RR of 44% and aPFS of 6.3 months in the ramucirumab arm versus an RR of 37% and a 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

\(^{a}\)Trials of bevacizumab listed are limited to phase III.

\(^{b}\)Based on information on ClinicalTrials.gov as of June 2013.

### Table 2 Ongoing Phase II and Phase III Trials in the United States of Approved© and Investigational Antiangiogenic Agents in Advanced or Metastatic NSCLC©

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>III</td>
<td>Bevacizumab or pemetrexed or bevacizumab plus pemetrexed after at least stable disease after 4 cycles of induction therapy in patients with advanced nonsquamous NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01107626</td>
<td>III</td>
<td>Pemetrexed and carboplatin followed by pemetrexed maintenance therapy or paclitaxel, carboplatin, and bevacizumab followed by bevacizumab maintenance therapy in patients with advanced nonsquamous NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT00946712</td>
<td>III</td>
<td>Carboplatin and paclitaxel with or without bevacizumab and/or cetuximab in patients with stage IV or recurrent NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01351415</td>
<td>III</td>
<td>Investigator’s choice of standard of care treatment with or without bevacizumab in patients with advanced nonsquamous NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>III</td>
<td>Ramucirumab plus docetaxel as second-line treatment in patients with stage IV NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT01168973</td>
<td>II</td>
<td>Ramucirumab plus cisplatin or carboplatin with paclitaxel or gemcitabine as first-line treatment in patients with stage IV NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01160601</td>
<td>II</td>
<td>Carboplatin and paclitaxel with or without bavituximab in patients with previously untreated advanced nonsquamous NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>II</td>
<td>Sorafenib plus erlotinib or sorafenib alone in patients with advanced NSCLC after failure of erlotinib</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT00609804</td>
<td>II</td>
<td>Sunitinib maintenance in patients with advanced NSCLC after first-line combination chemotherapy</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00693992</td>
<td>III</td>
<td>Sunitinib plus pemetrexed or sunitinib monotherapy as second-line treatment in patients with advanced NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT01351415</td>
<td>III</td>
<td>Cediranib plus paclitaxel/carboplatin in patients with advanced NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT00410904</td>
<td>II</td>
<td>Cediranib plus pemetrexed in patients with previously treated NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>II</td>
<td>Pazopanib plus erlotinib in patients with previously treated advanced NSCLC</td>
<td>Active, no longer recruiting</td>
</tr>
<tr>
<td>NCT01268220</td>
<td>II</td>
<td>Pazopanib plus paclitaxel as first-line treatment in patients with advanced NSCLC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01179269</td>
<td>II</td>
<td>Pazopanib as second-line treatment in patients with advanced NSCLC after failure of bevacizumab</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

Abbreviation: NSCLC, non–small cell lung cancer.

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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.

A phase II trial, aflibercept was administered to 98
patients with platinum- and erlotinib-resistant lung
adenocarcinoma, and results showed an RR of 2%,
a median PFS of 2.7 months, and a median OS of
6.2 months.24 The 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 versus docetaxel alone
as second-line therapy in advanced NSCLC showed
an improvement in RR (23% vs 9%) and median
PFS (5.2 vs 4.1 months), but OS was not improved
(10.1 vs 10.4 months).25 The most common grade
3/4 AEs were neutropenia (28% in the aflibercept
arm vs 21% in the chemotherapy-alone arm), fatigue
(11% vs 4%), and stomatitis (9% vs 1%).

**Tyrosine Kinase Inhibitors**

Resistance to VEGF inhibition has been shown to be
multifactorial.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 multitargeted
agents will theoretically inhibit several angiogen-
esis pathways and may specifically overcome resis-
tance 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 multitargeted TKI that in-
hibits VEGFR-2, VEGFR-3, platelet-derived growth
factor receptor-β (PDGFR-β), v-raf1 murine leuke-
mia viral oncogene homolog 1 (Raf), fms-like tyro-
sine 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
studied advanced nonsquamous NSCLC,28,29 but
large randomized phase III trials have been disap-
pointing.30,31 A phase III trial (ESCAPE) of 926 pa-

tients with advanced nonsquamous and squamous
cell NSCLC was halted because of lack of efficacy on
interim analysis.32 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%), whereas in the chemothera-
py 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 pa-

tients with squamous cell histology, subsequent to
a protocol amendment.31 This trial combined cis-
plat/in/gemcitabine with or without sorafenib in 904
patients with advanced NSCLC, showing no differ-
ence 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 or higher AEs at-
tributable to sorafenib included thrombocytopenia
(10%), hand-foot skin reaction (9%), fatigue (7%),
and rash (6%).

**Sunitinib:** Sunitinib is a multitargeted 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 patients with previously treated NSCLC.33,34 A
phase III trial of sunitinib plus erlotinib versus er-
lotinib alone as second- or third-line therapy in 960
patients (90% with unknown EGFR mutational sta-
tus) showed no significant differences in the primary
end point of OS (9.0 vs 8.5 months).35 The most
common grade 3/4 toxicities with sunitinib plus er-
lotinib 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 receptor (FGFR)-1, FGFR-2, and
FGFR-3. In addition, nintedanib has activity
against FLT-3 and the v-src sarcoma viral onco-
gene homolog (src) family.36 A phase II study of
nintedanib dosed at either 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) randomized 1314 patients with
advanced or metastatic squamous and nonsqua-
mous NSCLC that had progressed on first-line

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chemotherapy to either nintedanib or placebo in combination with docetaxel. An improvement was seen in median PFS (3.4 vs 2.7 months) but not in median OS (10.1 vs 9.1 months) in the nintedanib/docetaxel arm versus the docetaxel/placebo arm. Grade 3/4 AEs were similar in each arm, the most common included elevated alanine aminotransferase (ALT) (8% vs 1%) and diarrhea (7% vs 3%). A separate phase III study (LUME-Lung 2) comparing nintedanib or placebo in combination with pemetrexed in patients with advanced or metastatic nonsquamous NSCLC that had progressed on first-line chemotherapy was stopped early because of a signal for futility on an interim analysis. The analysis of 713 enrolled patients (initial enrollment planned for 1300 patients) showed an increase in median PFS (4.4 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 aspartate aminotransferase (12% vs 2%), and diarrhea (3% vs 1%).

**Cediranib:** Cediranib inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, FGFR-1, FGFR-3, and c-KIT. A phase II/III trial comparing carboplatin/paclitaxel with or without cediranib, 30 mg, in 296 patients with advanced NSCLC was halted early because of imbalances in the number of deaths observed in cediranib-treated patients. The RR was 38%, median PFS was 5.6 months, and median OS was 10.1 months in the placebo group. The 4 most common grade 3 AEs in the cediranib arm were fatigue (20%), diarrhea (19%), and proteinuria (5%). A phase II trial of cediranib in 2 cohorts of patients (a bevacizumab-naïve group and a bevacizumab-pretreated group) has completed accrual of bevacizumab-naïve patients. Preliminary results in the bevacizumab-naïve group showed an 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-naïve cohort were fatigue (22%), neutropenia (14%), diarrhea (14%), and infection (8%). Three treatment-related deaths have been reported.

**Motesanib:** Motesanib is a multitargeted TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, c-KIT, and RET. A phase II trial of motesanib in combination with doublet chemotherapy and a phase III trial of carboplatin and paclitaxel with or without motesanib (MONET1) were performed. The phase III study was initially suspended because of 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. 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 or higher 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 multitargeted TKI that inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, FGFR-1, FGFR-3, and c-KIT, and is currently being evaluated. In a phase II trial, 192 patients with advanced NSCLC for whom 1 to 2 prior lines of therapy failed were randomized to pazopanib plus erlotinib versus placebo plus erlotinib. A statistically significant improvement in PFS was seen in the combination arm (2.6 vs 1.8 months with erlotinib alone), but both arms showed similar RR (6% vs 0%) and OS (6.8 vs 6.7 months). Severe nonhematologic toxicities in the combination group were fatigue (20%), diarrhea (19%), and proteinuria (5%).

**Axitinib:** Axitinib is a multitargeted TKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and c-KIT. A phase II study of axitinib in 32 patients with NSCLC showed an RR of 9%, a median PFS of 4.9 months, and a median OS of 14.8 months. 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). The most common grade 3 AEs were hypertension (20%), neutropenia (18%), and nau-
sea (16%) with continuous axitinib, and hypertension (17%), fatigue (16%), and anemia (14%) with intermittent axitinib, and grade 4 asthenia (1%) and pulmonary embolism (1%) were also reported 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 in RR (29% vs 43%, respectively), PFS (5.7 vs 6.1 months), or OS (10.6 vs 13.3 months) for axitinib versus bevacizumab. The most common grade 3/4 AE in both arms was neutropenia, and axitinib was associated with a higher rate of treatment discontinuation because of AEs compared 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 (ZEPHIR),55 or compared with erlotinib (ZEST).56

**Linifanib:** Linifanib (ABT-869) is a multitargeted 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 evaluating 2 doses of linifanib (0.10 mg/d and 0.25 mg/d) in 139 patients with chemorefractory NSCLC showed an 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 0.10-mg/d group and 24.3% in the 0.25-mg/d group; no other grade 3/4 AEs were observed in more than 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 either 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 a 57% incidence of 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 versus carboplatin/paclitaxel alone. A total of 1299 patients were enrolled and the trial was stopped early because of futility. No statistical differences in OS (13.4 vs 12.7 months), PFS (5.5 vs 5.5 months), or RR (25% vs 25%) were seen in the vadimezan arm versus the chemotherapy-alone arm.63

**Lack of Predictive Biomarkers for Antiangiogenic Therapy in Lung Cancer**

Many antiangiogenic agents have shown an increase in RR or PFS when compared with placebo, but in most cases this has not translated into an OS benefit. Predictive biomarkers are greatly needed to identify the subset of patients who may benefit from antiangiogenic therapy or those likely to experience side effects, such as thrombosis and bleeding. Several molecular mediators of angiogenesis and inflammatory signaling have been investigated as potential biomarkers of antiangiogenic therapy in lung cancer, such as circulating VEGF64 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.

**Conclusions**

As the field of lung cancer moves further into the age of personalized medicine, it will be imperative to 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 antiangiogenic agent recommended by the NCCN for use in the treatment of advanced NSCLC. A significant knowledge deficit exists in the understanding of the molecular basis of antiangiogenic therapy and the AEs seen with these agents. A more thorough understanding of 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 from or be least likely to experience the toxicities associated with these drugs.

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