Antiangiogenic Agents in Lung Cancer: Lost Cause or Flicker of Hope?

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Abstract

Novel insights into the critical role that angiogenesis plays in non-small cell lung cancer (NSCLC) have led to the development of multiple antiangiogenic strategies. These agents target the vascular endothelial growth factor (VEGF)/VEGF receptor pathway, a key mediator of tumor survival, migration, and mobilization, and broadly fall into 2 categories: neutralizing monoclonal antibodies and small-molecule tyrosine kinase inhibitors. This article reviews the clinical experience with these agents in advanced NSCLC, and discusses future implications and strategies of such an approach.

Key words: Angiogenesis, vascular endothelial growth factor, bevacizumab, ramucirumab, tyrosine kinase inhibitors

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide.[1] Over the past decade, the development of molecularly targeted therapies coupled with the emergence of immunotherapy has reshaped our approach to the treatment of advanced non-small cell lung cancer (NSCLC). In addition, novel insights into the critical role of angiogenesis in NSCLC development and progression have led to the development of multiple antiangiogenic strategies. These include agents targeting the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway, a key mediator of both normal and pathologic angiogenesis implicated in tumor survival, migration, and mobilization.[2-6] This review focuses on the recent developments of antiangiogenic therapies in NSCLC, which fall broadly into 2 categories: neutralizing monoclonal antibodies (mAbs) and small-molecule tyrosine kinase inhibitors (TKIs).

Monoclonal Antibodies

Bevacizumab: Patients With Treatment-Naïve NSCLC

Several mAbs targeting VEGF and VEGFR have been clinically evaluated, including bevacizumab, and more recently, ramucirumab. Bevacizumab, a humanized mAb to VEGF, interferes with VEGF binding to VEGFR.[7] It is the most extensively evaluated agent in advanced lung cancer and is currently FDA-approved for use in combination with chemotherapy for patients with advanced nonsquamous NSCLC. Although reviewing all studies evaluating bevacizumab in NSCLC is outside the scope of this review, several important phase III studies warrant discussion (**Table 1**).

Two phase III studies, Eastern Cooperative Oncology Group (ECOG) 4599[8] and the AVAiL trial,[9] evaluated the addition of bevacizumab to platinum-based chemotherapy versus platinum-based chemotherapy alone. The ECOG 4599 study evaluated the addition of bevacizumab to platinum chemotherapy followed by maintenance bevacizumab. In this trial, the addition of bevacizumab (15 mg/kg) to carboplatin/paclitaxel improved response rate (RR; 35% vs 15%; P <.001), progression-free survival (PFS; 6.2 vs 4.5 months; P <.01), and overall survival (OS; 12.3 vs 10.3 months; hazard ratio [HR], 0.79; P <.01) compared with carboplatin/paclitaxel alone.[8] A post-hoc subset analysis of the 602 patients with adenocarcinoma from this trial demonstrated a more pronounced survival advantage with bevacizumab (14.2 vs 10.3 months; HR, 0.69; 95% CI, 0.58-0.83).[10] Grade 3-5 adverse events (AEs) that were more pronounced in the bevacizumab arm included hemorrhage (4.7% vs 1.1%), hypertension (7.7% vs 0.7%), and proteinuria (3.1% vs 0%). There also were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including 5 from pulmonary hemorrhage, versus 2 treatment-related deaths in the chemotherapy-alone group.

Following the ECOG 4599 study, the European AVAiL trial[9] evaluated the addition of bevacizumab at 2 dosages (7.5 mg/kg or 15 mg/kg) to cisplatin/gemcitabine versus cisplatin/gemcitabine alone. Whereas this study did demonstrate an improvement in PFS for both the low-dose bevacizumab group (6.1 vs 6.7 months; HR, 0.75; P = .003) and the high-dose group (6.1 vs 6.5 months; HR, 0.82; P = .03), there was no improvement in OS with either low-dose or high-dose bevacizumab (13.1, 13.4, and 13.6 months for the placebo, high-dose bevacizumab, and low dose-bevacizumab groups, respectively; HR, 1.03; P = .761).

TABLE 1. Selected Clinical Trials Evaluating Bevacizumab in NSCLC

Study	Setting	Treatment Arms	N	RR (%)	PFS (mo)	OS
Bevacizumab						
ECOG 4599[8]	1st line	Carboplatin/paclitaxel Carboplatin/paclitaxel/bevacizumab	444 434	15 35[a]	4.5 6.2[a] HR, 0.66	10.3 12.3[a] HR, 0.79
AVAiL[9]	1st line	Cisplatin/gemcitabine/placebo Cisplatin/gemcitabine/bevacizumab[b] Cisplatin/gemcitabine/bevacizumab[c]	347 345 351	20.1 34.1[a] 30.4[a]	6.1 6.7[a] HR, 0.75 6.5[a] HR, 0.85	13.1 13.6 HR, 0.9 13.4 HR, 1.0
PointBreak[11]	1st line	Carboplatin/paclitaxel/bevacizumab Carboplatin/pemetrexed/bevacizumab	467 472	33.0 34.1	5.6 6[a] HR, 0.83	13.4 12.6 HR, 1.0
PRONOUNCE[12]	1st line	Carboplatin/paclitaxel/bevacizumab Carboplatin/pemetrexed	182 179	27.4 23.6	2.9[d] 3.9[d] HR, 0.85	11.7 10.5 HR,1.1
Seto et al[15]	1st line	Erlotinib Erlotinib/bevacizumab	77 77	63.6 69.3	9.7 16 HR, 0.54	NR NR
AVAPERL[49,50]	Maintenance[e]	Bevacizumab Bevacizumab/erlotinib	125 128	50.0[g] 55.5[g]	3.7 7.4[a] HR, 0.45	12.8 NR HR, 0.75
ATLAS[51]	Maintenance[f]	Bevacizumab Bevacizumab/pemetrexed	373 370	NR NR	3.7 4.8[a] HR, 0.7	13.3 14.4 HR, 0.92
BeTA[13]	2nd line	Erlotinib/placebo Erlotinib/bevacizumab	317 319	6 13	1.7 3.4 HR, 0.64	9.2 9.3 HR, 0.97
Ramucirumab						
Camidge et al[21]	1st line	Carboplatin/paclitaxel + ramucirumab	40	55	7.9	16.9
Doebele et al[22]	1st line	Platinum/pemetrexed Platinum/pemetrexed + ramucirumab	71 69	38 49.3	5.6 7.2 HR, 0.75	10.5 13.9 HR, 1.03
REVEL[20]	2nd line	Docetaxel/placebo Docetaxel/ramucirumab	625 628	14 23[a]	3 4.5[a] HR, 0.76	9.1 10.5[a] HR, 0.86

HR indicates hazard ratio; Mo, months; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate.

[a] P <.05. HR designates hazard ratio;

[b] Bevacizumab 7.5 mg/kg.

[c] Bevacizumab 15 mg/kg.

[d] PFS without grade 4 toxicity (G4PFS).

[e] Maintenance after induction cisplatin/pemetrexed/bevacizumab.

[f] Maintenance after induction chemotherapy/bevacizumab.

[g] During both induction and maintenance.

mo, months; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate.

Grade 3-5 AEs that were more prevalent in the bevacizumab arms included bleeding (4% in both the low- and high-dose arms vs 2% in the placebo arm), hypertension (6% and 9% in the low- and high-dose arms, respectively, vs 2% in the placebo arm), and hemoptysis (7% and 9.7% in the low- and high-dose arms, respectively, vs 5.2% in the placebo arm).

Several trials evaluating bevacizumab in combination with platinum/pemetrexed for patients with nonsquamous NSCLC have also been completed. Two of these studies, PointBreak[11] and PRONOUNCE,[12] directly compared pemetrexed-containing

TABLE 2. Selected Clinical Trials Evaluating Bevacizumab in NSCLC

Study	Setting	Treatment Arms	N	RR (%)	PFS (mo)	OS
Nintedanib						
LUME-Lung 1[28]	2nd line	Docetaxel/placebo Docetaxel/nintedanib	659 655	2.7 3.4[a]	3.3 4.4 HR, 0.79	9.1 10.1 HR, 0.94
LUME-Lung 2[43]	2nd line	Pemetrexed/placebo Pemetrexed/nintedanib	360 353	8.3 9.1	3.6 4.4 HR, 0.83	12.7 12.2 HR, 1.03
Vandetanib						
Heymach et al[34]	1st line	Carboplatin/paclitaxel Carboplatin/paclitaxel/vandetanib Vandetanib	52 56 73	25 32 7[a]	5.6 6.0 HR, 0.76 2.9	12.6 10.2 HR, 1.15 10.2
ZEAL[33]	2nd line	Pemetrexed/placebo Pemetrexed/vandetanib	278 256	8 19[a]	3.0 4.4 HR, 0.86	9.2 10.5 HR, 0.86
ZODIAC[30]	2nd line	Docetaxel/placebo Docetaxel/vandetanib	697 694	10 17[a]	3.2 4.0 HR, 0.79	9.9 10.3 HR, 0.91
ZEST[31]	2nd/3rd line	Erlotinib Vandetanib	617 623	12 12	2.0 2.6 HR, 0.98	7.8 6.9 HR, 1.0
ZEPHYR[32]	2nd line/prior TKI	Placebo Vandetanib	307 617	0.7 2.6	1.8 1.9 HR, 0.63	7.8 8.5 HR, 0.95
Sorafenib						
ESCAPE[24]	1st line	Carboplatin/paclitaxel/placebo Carboplatin/paclitaxel/sorafenib	462 464	24 28	5.4 4.6 HR, 0.99	10.6 10.7 HR, 1.15
NexUS[44]	1st line	Cisplatin/gemcitabine/placebo Cisplatin/gemcitabine/sorafenib	387 385	26 28	5.5 6.0[a] HR, 0.83	12.5 12.4 HR, 0.98
MISSION[45]	3rd/4th lines	Placebo Sorafenib	353 350	0.9 4.9[a]	1.4 2.8[a] HR, 0.61	8.4 8.3 HR, 0.99
Sunitinib						
CALGB 30607[26]	Switch maintenance	Placebo Sunitinib	104 106	5.8 11	2.8 4.3[a] HR, 0.59	11.2 11.2 HR, 1.05
Scagliotti et al[27]	2nd/3rd lines	Erlotinib/placebo Erlotinib/sunitinib	480 480	6.9 10.6[a]	2.0 3.6[a] HR, 0.81	8.5 9.0 HR, 0.92
Pazopanib						
Spigel et al[42]	2nd/3rd lines	Erlotinib/placebo Erlotinib/pazopanib	65 127	5 10	1.8 2.6[a]	6.7 6.8

[a] $P < .05$.

BID, twice daily; HR indicates hazard ratio; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.

TABLE 2. Selected Clinical Trials Evaluating Bevacizumab in NSCLC (continued)

Study	Setting	Treatment Arms	N	RR (%)	PFS (mo)	OS
Axitinib						
Belani et al[41]	1st line	Cisplatin/pemetrexed Cisplatin/pemetrexed/daily axitinib Cisplatin/pemetrexed/axitinib (days 2-19 only)	57 55 58	26.3 45.5 39.7	7.1 8.0 HR, 0.89 7.9 HR, 1.02	15.9 17 HR, 1.05 14.7 HR, 1.45
Twelves et al[35]	1st line	Carboplatin/paclitaxel/placebo Carboplatin/paclitaxel/axitinib	60 58	43.3 29.3	6.1 5.7 HR, 1.09	13.3 10.6 HR, 1.12
Cediranib						
Goss et al (BR24)[29]	1st line	Carboplatin/paclitaxel/placebo Carboplatin/paclitaxel/cediranib	125 126	16 38[a]	5.0 5.6 HR, 0.77	10.1 10.5 HR, 0.78
MONET1[37]	1st line	Carboplatin/paclitaxel/placebo Carboplatin/paclitaxel/motesanib	549 541	26 40[a]	5.4 5.6[a] HR, 0.79	11 13 HR, 0.90
Motesanib						
Bleumenshein et al[38]	1st line	Carboplatin/paclitaxel/bevacizumab Carboplatin/paclitaxel/motesanib (125 mg daily) Carboplatin/paclitaxel/motesanib (75 mg BID)	63 61 62	37 30 23	8.3 7.7 HR, 1.14 5.8 HR, 1.22	14 14 HR, 1.05 12.8 HR, 1.18

[a] $P < .05$.

BID, twice daily; HR, hazard ratio; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.

regimens to the ECOG 4599 reference regimen of carboplatin/paclitaxel/bevacizumab. The PointBreak study randomized patients to either induction carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab or to carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab.[11] Maintenance was delivered for those patients with nonprogressive disease after induction therapy. Unfortunately, this study failed to demonstrate a survival advantage with the carboplatin/pemetrexed/bevacizumab (12.6 vs 13.4 months; HR, 1.0; $P = .949$). Both regimens were well tolerated but resulted in different toxicity profiles, with more grade 3-4 anemia (14.5% vs 2.7%), thrombocytopenia (23.3% vs 5.6%), and fatigue (10.9% vs 5.0%) in the pemetrexed arm and more grade 3 or 4 neutropenia (40.6% vs 25.8%), febrile neutropenia (4.1% vs 1.4%), neuropathy (4.1% vs 0%), and alopecia (grade 1 or 2; 36.8% vs 6.6%) in the paclitaxel-containing arm.

The PRONOUNCE study randomized patients to either carboplatin/paclitaxel/bevacizumab induction followed by maintenance bevacizumab (CbPacBev) or to carboplatin/pemetrexed followed by maintenance pemetrexed (CbPem).[12] Similar to the PointBreak study, maintenance was given only in the absence of progressive disease in the induction regimen. The primary endpoint of PFS without grade 4 toxicity (G4PFS) was not met (3.91 for CbPem and 2.86 for CbPacBev; HR, 0.85; 90% CI, 0.7-1.04; $P = .176$). Although this study was not powered for OS, there also was no difference in survival between the 2 regimens, suggesting that a non-bevacizumab, pemetrexed-containing regimen may be as efficacious as the ECOG 4599 regimen.

In the second-line setting, the BeTa trial[13] compared the addition of bevacizumab to erlotinib versus erlotinib plus placebo in unselected patients who had progressed on frontline therapy. Although there was an improvement in RR (13% vs 6%) and PFS (3.4 vs 1.7 months; HR, 0.62; 95% CI, 0.52-0.75) in favor of the bevacizumab arm, there was no significant survival benefit (9.3 vs 9.2 months; HR, 0.97; $P = .76$). Interestingly, a post-study biomarker analysis showed that the addition of bevacizumab to erlotinib had a more pronounced effect in the subgroup of patients who harbored *EGFR* mutations.[14]

Given the potential predictive utility of *EGFR* mutations for bevacizumab treatment, a recent Japanese study was conducted to address the role of bevacizumab in combination with erlotinib in patients with advanced-stage, treatment-naïve disease with activating *EGFR* mutations.[15] This randomized phase II study demonstrated that the addition of bevacizumab to erlotinib significantly improved PFS compared with erlotinib alone (16 vs 9.6 months, respectively; HR, 0.54; *P* = .0015). At the time of publication, OS data were immature and had not been reported. The randomized phase II study evaluating this combination regimen in patients with *EGFR*-mutant lung cancer is being conducted in the United States.[16]

Ramucirumab

Ramucirumab is the fully humanized mAb that targets VEGFR2, which binds to the VEGF ligand. VEGFR2 is considered to be the most important receptor of the VEGFR family and mediates the majority of VEGF downstream signaling effects.[17-19] Ramucirumab has been evaluated in both treatment-naïve and refractory NSCLC.

The phase III REVEL study[20] evaluated the addition of ramucirumab to docetaxel in patients with NSCLC who had progressed after platinum-based frontline therapy. A total of 1253 patients were randomized 1:1 to docetaxel plus ramucirumab or docetaxel plus placebo. Of note, all histologies (squamous and nonsquamous) and patients with prior bevacizumab exposure were included. Similar to ECOG 4599, this study demonstrated an improvement in RR (23% vs 14%; *P* <.0001), PFS (4.5 vs 3.0 months; HR, 0.76; *P* <.0001), and OS (10.5 vs 9.1 months; HR, 0.86; *P* = .023) with the addition of an antiangiogenic drug to cytotoxic chemotherapy. Although not powered for subgroup analysis, improved survival was witnessed in most subsets, including patients with squamous cell histology (9.5 vs 8.2 months; HR, 0.88; 95% CI, 0.69-1.13) and responders to first-line therapy (11.2 vs 10.3 months; HR, 0.84; 95% CI, 0.71-0.99). The most common grade ≥3 AEs were neutropenia (49% in the ramucirumab group vs 40% in the placebo group), febrile neutropenia (16% vs 10%), and fatigue (14% vs 10%). Interestingly, the incidence of all-grade hypertension and grade >3 bleeding events were notably low in the ramucirumab arm (6% and 2%, respectively).

Two phase II studies have also evaluated the addition of ramucirumab to platinum doublet chemotherapy in the first-line setting.[21,22] In a single-arm study, ramucirumab was combined with carboplatin/paclitaxel followed by ramucirumab maintenance.[21] The RR and 6-month PFS were 55% and 59%, respectively. Median PFS was 7.9 months and OS was 17.9 months. Another phase II study randomizing patients to either platinum/pemetrexed or platinum/pemetrexed/ramucirumab demonstrated no significant difference in PFS (5.6 vs 7.2 months, respectively; HR, 0.75; *P* = .132).[22] Currently, other clinical trials with ramucirumab in combination with first-line chemotherapy are ongoing, including cisplatin and gemcitabine for squamous histology and cisplatin and pemetrexed in nonsquamous NSCLC.[23]

Tyrosine Kinase Inhibitors

The practice-changing results from mAbs have led to the development of other antiangiogenic agents, including small-molecule TKIs targeting VEGFR. To date, several phase II and III clinical trials have been conducted evaluating multitargeted TKIs, with activity mainly directed at VEGFR2. These drugs, including vandetanib, sorafenib, sunitinib, pazopanib, nintedanib, axitinib, cediranib, and motesanib (**Table 2**), have been evaluated as single agents and in combination with chemotherapy or erlotinib.[24-45] Although many of these studies have demonstrated modest improvements in RR and PFS, none have translated into significant survival advantages. One agent, nintedanib, warrants further discussion due to more promising activity.

Nintedanib

The LUME-Lung 1 study[28] was a multinational, randomized, phase III clinical trial that assessed the addition of nintedanib (200 mg twice daily) to docetaxel (75 mg/m^2) in patients with advanced NSCLC with any histology who had progressed after frontline therapy. A total of 1314 patients were randomized to docetaxel plus nintedanib versus docetaxel plus placebo. The primary endpoint, PFS, was significantly improved in the docetaxel/nintedanib arm compared with docetaxel alone (3.4 vs 2.7 months; HR, 0.79; *P* = .0019). While no significant improvement in OS was seen in the intent-to-treat population (10.1 vs 9.1 months; HR, 0.94; *P* = .2720), there was statistically significant improvement in OS for patients with adenocarcinoma histology (12.6 vs 10.3 months, respectively; HR, 0.83; *P* = .0359). Grade ≥3 AEs that were more common in the combination arm included diarrhea (6.6% vs 2.6%) and reversible transaminitis (3.5% vs 0.5%).[28] Based on the subset analysis of patients with adenocarcinoma from LUME-Lung 1, the randomized, phase III LUME Columbus trial[46] is evaluating the efficacy of docetaxel in combination with nintedanib in patients with adenocarcinoma histology who have progressed on first-line therapy.

Cost-Effectiveness of Antiangiogenic Drugs in NSCLC

Drug costs and the definition of "value" have become important considerations when treating all cancers, including NSCLC. The cost-effectiveness of antiangiogenic drugs such as bevacizumab should be factored in when making treatment decisions. Several cost-effective analyses of bevacizumab have demonstrated the use of this drug in NSCLC to be associated with a cost of $350,000 per life-year gained.[47,48]

Conclusion

Over the past decade, recognition of the VEGF/VEGFR path-

way as a crucial mediator of tumor survival and growth has sparked interest in the development of antiangiogenic agents for NSCLC. Several strategies have been exploited, only 2 drugs, bevacizumab and ramucirumab, have demonstrated survival advantages in patients with treatment-naïve and refractory NSCLC, respectively. Moving forward, several questions remain regarding future trials and the routine clinical use of these agents. First, the utility of additional clinical trials evaluating TKIs in unselected patient populations is unclear, given that none of these agents have demonstrated improvements in survival, thus far. The exception to this has been nintedanib, which demonstrated a survival advantage in the subset of patients with adenocarcinoma in LUME-Lung 1.

Second, no clear predictive biomarkers have been identified to guide therapy selection for this class of drugs. Because of the genomic heterogeneity of NSCLC, molecular enrichment strategies have become paramount in identifying patients eligible for targeted therapies. Given the cost and potential toxicity of these drugs, further studies to identify serum and tissue biomarkers are urgently needed. The recently reported results from the Japanese study and the ongoing US phase II ACCRU study evaluating bevacizumab in combination with erlotinib in *EGFR*-positive patients may define a molecular niche for this agent.

Third, it remains unclear whether bevacizumab and ramucirumab should be combined with any nontaxane cytotoxic chemotherapy. Although bevacizumab added to carboplatin/paclitaxel demonstrated a survival advantage, this agent added no survival benefit when combined with cisplatin/gemcitabine and has never been evaluated combined with platinum/pemetrexed compared with platinum/pemetrexed alone. Finally, the cost-effectiveness of antiangiogenic drugs should be factored in when making treatment decisions.

We look forward to future studies evaluating novel agents exploiting the VEGF pathway, and hope that further efforts will help better define which patients are more likely to benefit from such strategies.

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