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REVIEW ARTICLE

# Anti-angiogenesis therapy for lung cancer: the shore and the other shore*

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## Abstract

Angiogenesis is known to be an important event in tumor growth. In preclinical and clinical researches, anti-angiogenesis therapy has made great progress, but there are still many problems for future anti-angiogenesis therapy. Here, we review recently completed clinical trials of emerging antiangiogenic agents in patients with non-small cell lung cancer (NSCLC) and discuss the challenges of anti-angiogenic therapy.

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In 1971, Folkman [1] proposed that tumor growth and metastasis depended on tumor angiogenesis; thus, blocking tumor angiogenesis is an effective strategy to control tumor growth. Later, Senger *et al* [2] found that a cytokine secreted by tumor cells could increase vessel permeability, which was then named "vascular permeability factor (VPF)." The VPF antibody could inhibit the tumor-induced accumulation of ascites, which suggests that the antibody could be used in the treatment of tumors. In 1989, Ferrara *et al* [3–4] reported that VPF induced the growth of vascular endothelial cells and angiogenesis, and named it "vascular endothelial growth factor (VEGF)." Bevacizumab, a monoclonal antibody directed against the VEGF ligand, is the first anti-angiogenesis drug approved by the US Food and Drug Administration for the treatment of patients with metastatic colorectal cancer in 2004 and those with advanced-stage, non-squamous, non-small cell lung cancer (NSCLC) in 2006, which started the era of anti-angiogenesis therapy for NSCLC.

Angiogenesis is a complicated process that involves multitudinous regulatory factors, including angiogenesis activators [3, 5] such as VEGF, matrix metalloproteinases, placenta growth factor, fibroblast growth factor, hepatocyte growth factor, interleukin-8, and angiogenesis inhibitors [6–7], including thrombospondins, endostatin, angiostatin, and interleukin 12. Under physiological conditions, angiogenesis activators and inhibitors are balanced. When a tumor develops, the balance shifts to promote physiological processes to a pathological condition [8]. VEGF is a key angiogenesis activator involved in various processes, including the initial activation phase of endothelial cells, degradation of the basement membrane, endothelial cell migration, endothelial cell proliferation and differentiation, formation of new vascular vessels, maintenance vasculature stability, and maturation [9]. Approaches that target angiogenesis act against not only the VEGF signal system (ligand, receptors, and intracellular downstream pathways) but also the signal components of other angiogenic factors. Bevacizumab is a humanized monoclonal antibody with a high binding affinity for circulating VEGF-A. Aflibercept, a soluble hybrid receptor composed of vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR2 fragments, binds and neutralizes free VEGF. Small molecular tyrosine kinase inhibitors (TKIs), including motesanib, sorafenib, sunitinib, pazopanib, vandetanib, regorafenib, and cabozantinib, inhibit the kinase activity of VEGFR. Endostar, a novel modified recombinant human endostatin, inhibits the proliferation and migration of endothelial cells by blocking angiogenesis. Vascular-disrupting agents target the existing vasculature of tumors and cause rapid vascular shutdown, and lead to cell death and central necrosis.

## The shore of the anti-angiogenesis therapy for lung cancer

The efficacy of bevacizumab has been studied exten-

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sively in NSCLC. In Eastern Cooperative Oncology Group 4599, bevacizumab plus chemotherapy broke the platform of chemotherapy for the first time, and this regimen demonstrated prolongation of the median overall survival (OS) over 1 year. A number of clinical studies, such as the AVAiL, SAiL, AVAPER, and BEYOND, expand our understanding of the efficacy, safety, and application of bevacizumab. A meta-analysis [10] of data from 33 randomized controlled trials was conducted to investigate the efficacy and safety of angiogenesis inhibitors in 17,396 patients with advanced NSCLC treated with antibodies that targeted VEGF or VEGFR, VEGFR-TKIs, or angiogenesis inhibitors. A significant improvement was observed in the progression-free survival [PFS; hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.76–0.85; $P < 0.001$] and OS (HR, 0.95; 95% CI, 0.92–0.98; $P = 0.004$) of patients treated with these antibodies compared with those treated with the non-angiogenesis inhibitors.

Preclinical studies [11] have shown a synergistic activity of the combination of anti-epidermal growth factor receptor (EGFR) and anti-angiogenesis drugs. The ATLAS and BeTa studies used the combination therapy of bevacizumab and erlotinib as maintenance treatment and first-line treatment of non-selective NSCLC, respectively. The ATLAS study [12] found that maintenance treatment with bevacizumab/erlotinib improved PFS (4.76 vs. 3.71 months, $P < 0.001$). In particular, patients who were harboring an activating EGFR mutation ($n = 52$) had a greater improvement in PFS when treated with bevacizumab/erlotinib ($n = 27$) than with bevacizumab/placebo ($n = 25$; HR, 0.44; 95% CI, 0.22–0.86). In the BeTa study [13], the combination therapy did not improve the survival of patients with recurrent or refractory NSCLC, but showed favorable outcomes in patients with EGFR mutation status in a subgroup analysis (HR, 0.44; 95% CI, 0.11–1.67).

Basing on the results of the three 2-phase studies, an open-label, randomized, multicenter, phase 2 study (JO25567) [13] was conducted to compare the efficacy and safety of the combination of erlotinib and bevacizumab ($n = 75$) in comparison with those of erlotinib alone ($n = 77$) among patients with advanced non-squamous NSCLC who were harboring EGFR mutations. The median PFS was 16.0 months (95% CI, 13.9–18.1) when treated with erlotinib plus bevacizumab and 9.7 months (95% CI, 5.7–11.1) when treated with erlotinib alone (HR, 0.54; 95% CI, 0.36–0.79; log-rank test, $P = 0.0015$). Analysis of PFS in patients with mutation showed that the median PFS was significantly longer in the patients with exon 19 deletion who were treated with erlotinib plus bevacizumab ($n = 40$) than in those treated with erlotinib alone ($n = 40$; 18.0 months vs. 10.3 months; $P = 0.0011$). The median PFS in patients with Leu858Arg mutation did not significantly differ ($P = 0.1653$) between those treated with erlotinib plus bevacizumab and those treated with erlotinib alone (13.9 months vs. 7.1 months, respectively). OS data are lacking at present. As for adverse events (AEs), 68 patients (91%) in the erlotinib plus bevacizumab group and 41 (53%) in the erlotinib group had grade 3 or 4 AEs. Serious AEs were reported in 18 patients (24%) in the erlotinib plus bevacizumab group and in 19 (25%) in the erlotinib group. JO25567 is known as the first prospective randomized study to investigate the combination of erlotinib and bevacizumab as fist-line treatment and showed that the combination therapy can significantly prolong the PFS in patients with non-squamous, EGFR mutation-positive NSCLC, without new safety signals. Although the OS with the treatment needs to be validated, the study provided new insights that suggest the efficacy and safety of the combination of more than two drugs that target different signal pathways. Nevertheless, AEs and high expenses could not be avoided in combination treatment.

VEGF (also known as VEGF-A) stimulates angiogenesis through VEGFR-2 [14–15]. Ramucirumab [16] is a fully humanized monoclonal antibody directed against the extracellular domain of VEGFR-2. A multicenter, double-blind, randomized phase 3 trial (REVEL) [17] assessed the efficacy and safety of docetaxel plus ramucirumab in comparison with a placebo as a second-line treatment for 1253 patients with stage IV NSCLC who had undergone platinum-based therapy. The primary end-point was OS. The secondary end-points included PFS and objective response rate. The median OS and PFS improved in patients treated with docetaxel plus ramucirumab compared with placebo plus docetaxel (10.5 months vs. 9.1 months and 4.5 months vs. 3.0 months, respectively). In a subgroup analysis, patients with non-squamous and squamous NSCLC who received docetaxel plus ramucirumab had longer OS than those who received placebo plus docetaxel (11.1 months vs. 9.7 months and 9.5 months vs. 8.2 months, respectively). The most common grade 3/4 AEs were neutrocytopenia (49% vs. 40%), febrile neutropenia fatigue (14% vs. 10%), leukocytopenia (14% vs. 12%), and hypertension (6% vs. 2%). However, benefits from the clinical trial need to be verified in terms of survival, quality of life, and treatment cost in a larger patient population.

Nintedanib [18] is a potent, oral angiokinase inhibitor that targets proangiogenic pathways mediated by VEGFR1–3, fibroblast growth factor receptors 1–3, and platelet-derived growth factor receptors α and β, as well as receptor kinases RET, FLT3, and Src family. Nintedanib can sustain blockade of VEGFR2 *in vitro* and delay tumor growth in xenograft models [19]. A phase 1/2 clinical trial [20–21] reported that nintedanib showed a manageable safety profile and antitumor activity in patients with solid tumors, including NSCLC, and limited drug–drug interactions [22]. As the efficacy of nintedanib is not affected by CYP450 enzymes, it can be combined with cytotoxic

drugs such as docetaxel or pemetrexed [23]. The LUME-Lung 1 [24] phase 3 trial assessed the efficacy and safety of the combination of nintedanib and docetaxel in patients with advanced NSCLC progressing after first-line chemotherapy. An increase was observed in the median PFS (3.4 months vs. 2.7 months), but not in the median OS (10.1 months vs. 9.1 months), in the 1314 patients, especially those with adenocarcinoma, treated with nintedanib/docetaxel compared with those treated with docetaxel/placebo. Grade 3 or higher AEs, including diarrhea (6.6% vs. 2.6%), reversible increases in alanine aminotransferase level (7.8% vs. 0.9%), and reversible increases in aspartate aminotransferase level (3.4% vs. 0.5%) were more common with nintedanib and docetaxel. Nintedanib in combination with docetaxel is an effective second-line treatment option for patients with advanced NSCLC, especially those with adenocarcinoma, who had been treated with platinum-based therapy as first-line treatment. The trial led to the approval of nintedanib as a second-line treatment of advanced non-squamous NSCLC by the European Medicines Agency.

## The other shore of the anti-angiogenesis therapy for lung cancer

Preclinical and clinical research studies on the application of anti-angiogenesis therapy have made great progress, but many challenges remain to be resolved in the future.

### Judicious application of anti-angiogenesis agents

Tumor growth and metastasis depend on tumor blood vessels for oxygen and nutrient supply. Anti-angiogenesis indirectly inhibits tumor growth by reducing blood supply and interfering with nutrition delivery. Clinical studies showed that anti-angiogenesis monotherapy produced modest objective responses only, but not long-term survival benefits, whereas combination anti-angiogenesis therapy, and chemotherapy or radiotherapy showed greater therapeutic effects [25]. However, excessive impairment of vasculature reduces tumor blood supply, affects nutrition delivery, and produces hypoxia, thereby weakening the efficacy of antitumor therapies [26], which seems paradoxical. To resolve these issues, in 2001, Jain RK [27] proposed a hypothesis of "normalization" of tumor blood vessels by administration of anti-angiogenesis agents. He suggested that the judicious application of anti-angiogenesis agents can normalize abnormal tumor vasculature to enhance the efficiency of drug and oxygen deliveries to the targeted cancer cells. Abnormal tumor vasculature creates a hypoxic tumor microenvironment and leads to an immunosuppressive status of immunocytes and inflammatory cells in the microenvironment [28]. Anti-angiogenesis treatment reprograms the tumor microenvironment, induces normalization of tumor vasculature, generates a homogeneous distribution of perfused tumor vessels, and facilitates the infiltration of T-effector cells while reducing the accumulation of myeloid-derived suppressor cells. In addition, it polarizes tumor-associated macrophages to an immune-stimulatory M1-like phenotype. Thus, vascular normalization could be an effective strategy to alleviate the immunosuppressive tumor microenvironment and enhance cancer immunotherapy [28]. Anti-angiogenesis agents should be applied within the normalization window (about 1 month for humans [29] and 5 days for mice [30]), but not when the administration time is shorter or longer than the normalization window. The difference in normalization window between humans and mice suggests that more preclinical and clinical research studies are needed to identify the normalization window for individualized anti-angiogenesis agents, tumor types, and specific patient characteristics. In the future, the combination of anti-angiogenesis therapy and immunotherapy may be a new direction.

### Evaluation of responses to anti-angiogenesis agents

Because anti-angiogenesis agents suppress tumor growth indirectly, as it targets each angiogenesis stage and not tumor cells directly, the volumetric change of tumors might not occur timely. The conventional criteria for assessing tumor response to therapies, including those of the World Health Organization and the Response Evaluation Criteria in Solid Tumors, mainly assess changes in tumor volume, and not change in tumor vasculature, after angiogenesis therapy. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [31] has emerged as a noninvasive imaging modality for examining tumor vascularity *in vivo*, and it has been verified in preclinical models. Furthermore, it has been used as a pharmacodynamic measure or predictor of tumor response in clinical solid tumors treated with angiogenesis and anti-angiogenesis therapies. A study [32] assessed the predictive value of DCE-MRI for survival benefits of anti-angiogenesis treatment with bevacizumab and erlotinib in patients with advanced NSCLC. The study showed in 28 patients who underwent DCE-MRI at baseline and after 3 weeks that an increase in $K^{trans}$SD by 15% was predictive of treatment failure. The quantitative parameter of DCE-MRI might be useful in the evaluation of the effect of anti-angiogenesis therapy but needs to be validated in a larger cohort.

### Biomarkers for anti-angiogenesis therapy for cancer

Anti-angiogenesis therapy has become an anti-tumor pattern with diverse outcomes. Some cancer patients (including those with colorectal cancer, renal cancer, and

NSCLC) benefit from the therapy, but others do not (including those with prostatic cancer, breast cancer, pancreatic carcinoma) [33]. Some patients respond to anti-angiogenesis treatment well, but other patients show no response. Anti-angiogenesis agents may induce significant AEs and are relatively costly [33]. One potential solution to solve this problem might depend on identifying reliable biomarkers and optimizing the effects of anti-angiogenesis therapies accordingly. Several novel biomarker candidates have been identified for this type of cancer therapy, including plasma biomarkers (EGF-A, short VEGF-A isoforms, and VEGFR1), circulating endothelial progenitor cells, single-nucleotide polymorphism, tissue-based biomarkers, and hypertension [33–35]. However, the data on angiogenesis-specific biomarkers are controversial. Thus far, no particularly effective predictive biomarkers for anti-angiogenesis-based therapy have been discovered.

### Mechanisms of resistance to anti-angiogenesis therapies

Anti-angiogenesis therapy indirectly targets tumor cells by acting on tumor blood vessels. Thus, mechanisms of resistance to anti-angiogenesis therapy have become a prominent issue, and tumor response and drug resistance are likely to stem from a complex interaction between tumor cells and stroma. To our knowledge, the mechanisms include [36] alternative pathway activation, initiation of a tumor self-protection mechanism through autophagy/tumor dormancy, and increased hypoxia-tolerant expression of cancer stem cells in terms of prevalence and frequency.

Anti-angiogenesis therapy that targets VEGFR is still attractive. With further understanding of profound mechanisms involved in tumor angiogenesis, anti-angiogenesis drug targets, and predictive markers of efficacy of anti-angiogenesis therapy, anti-angiogenesis agents can be judiciously applied to treat patients. Currently, although novel drugs have emerged and therapeutic targets are becoming clearer, more effort is still need to elucidate appropriate strategies for applying anti-angiogenesis agents, whole-period disease management methods, and methods of rationally distributing various therapeutic agents for advanced NSCLC.

### Conflicts of interest

The authors indicated no potential conflicts of interest.

## References


1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971, 285: 1182–1186.
2. Senger DR, Galli SJ, Dvorak AM, *et al.* Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science, 1983, 219: 983–985.
3. Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochem Biophys Res Commun, 1989, 161: 851–858
4. Leung DW, Cachianes G, Kuang WJ, *et al.* Vascular endothelial growth factor is a secreted angiogenic mitogen. Science, 1989, 246: 1306–1309.
5. Khoury CC, Ziyadeh FN. Angiogenic factors. Contrib Nephrol, 2011, 170: 83–92.
6. Taraboletti G, Rusnati M, Ragona L, *et al.* Targeting tumor angiogenesis with TSP-1-based compounds: rational design of antiangiogenic mimetics of endogenous inhibitors. Oncotarget, 2010, 1: 662–673.
7. Dass CR, Tran TM, Choong PF. Angiogenesis inhibitors and the need for anti-angiogenic therapeutics. J Dent Res, 2007, 86: 927–936.
8. Bouck N. Angiogenesis: a mechanism by which oncogenes and tumor suppressor genes regulate tumorigenesis. Cancer Treat Res, 1992, 63: 359–371.
9. Gacche RN, Meshram RJ. Targeting tumor micro-environment for design and development of novel anti-angiogenic agents arresting tumor growth. Prog Biophys Mol Biol, 2013, 113: 333–354.
10. Hong S, Tan M, Wang S, *et al*. Efficacy and safety of angiogenesis inhibitors in advanced non-small cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014 Nov 6. [Epub ahead of print]
11. Schicher N, Paulitschke V, Swoboda A, *et al.* Erlotinib and bevacizumab have synergistic activity against melanoma. Clin Cancer Res, 2009, 15: 3495–3502.
12. Johnson BE, Kabbinavar F, Fehrenbacher L, *et al*. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol, 2013, 31: 3926–3934.
13. Herbst RS, Ansari R, Bustin F, *et al.* Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. Lancet, 2011, 377: 1846–1854.
14. Seto T, Kato T, Nishio M, *et al.* Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol, 2014, 15: 1236–1244.
15. Ferrara N. VEGF-A: a critical regulator of blood vessel growth. Eur Cytokine Netw, 2009, 20: 158–163.
16. Nagy JA, Dvorak AM, Dvorak HF. VEGF-A and the induction of pathological angiogenesis. Annu Rev Pathol, 2007, 2: 251–275.
17. Aprile G, Bonotto M, Ongaro E, *et al.* Critical appraisal of ramucirumab (IMC-1121B) for cancer treatment: from benchside to clinical use. Drugs, 2013, 73: 2003–2015.
18. Garon EB, Ciuleanu TE, Arrieta O, *et al.* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet, 2014, 384: 665–673.
19. Hilberg F, Roth GJ, Krssak M, *et al*. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res, 2008, 68: 4774–4782.
20. Mross K, Stefanic M, Gmehling D, *et al*. Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors. Clin Cancer Res, 2010, 16: 311–319.
21. Reck M, Kaiser R, Eschbach C, *et al.* A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell

lung cancer. Ann Oncol, 2011, 22: 1374–1381.
22. Bousquet G, Alexandre J, Le Tourneau C, *et al*. Phase I study of BIBF 1120 with docetaxel and prednisone in metastatic chemo-naive hormone-refractory prostate cancer patients. Br J Cancer, 2011, 105: 1640–1645.
23. Ellis PM, Kaiser R, Zhao Y, *et al.* Phase I open-label study of continuous treatment with BIBF 1120, a triple angiokinase inhibitor, and pemetrexed in pretreated non-small cell lung cancer patients. Clin Cancer Res, 2010, 16: 2881–2889.
24. Reck M, Kaiser R, Mellemgaard A, *et al*. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol, 2014, 15: 143–155.
25. Teicher BA. A systems approach to cancer therapy. (Antioncogenics + standard cytotoxics-->mechanism(s) of interaction). Cancer Metastasis Rev, 1996, 15: 247–272.
26. Ma J, Pulfer S, Li S, *et al.* Pharmacodynamic-mediated reduction of temozolomide tumor concentrations by the angiogenesis inhibitor TNP-470. Cancer Res, 2001, 61: 5491–5498.
27. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med, 2001, 7: 987–989.
28. Huang Y, Goel S, Duda DG, *et al*. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res, 2013, 73: 2943–2948.
29. Winkler F, Kozin SV, Tong RT, *et al.* Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Cancer Cell, 2004, 6: 553–563.
30. Batchelor TT, Sorensen AG, di Tomaso E, *et al.* AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell, 2007, 11: 83–95.
31. Chang YC, Yu CJ, Chen CM, *et al.* Dynamic contrast-enhanced MRI in advanced nonsmall-cell lung cancer patients treated with first-line bevacizumab, gemcitabine, and cisplatin. J Magn Reson Imaging, 2012, 36: 387–396.
32. de Langen AJ, van den Boogaart V, Lubberink M, *et al*. Monitoring response to antiangiogenic therapy in non-small cell lung cancer using imaging markers derived from PET and dynamic contrast-enhanced MRI. J Nucl Med, 2011, 52: 48–55.
33. Duda DG. Molecular biomarkers of response to antiangiogenic therapy for cancer. ISRN Cell Biol, 2012, 2012: pii: 587259.
34. Lambrechts D, Lenz HJ, de Haas S, *et al.* Markers of response for the antiangiogenic agent bevacizumab. J Clin Oncol, 2013, 31: 1219–1230.
35. Kim R, Toge T. Changes in therapy for solid tumors: potential for overcoming drug resistance in vivo with molecular targeting agents. Surg Today, 2004, 34: 293–303.
36. Giuliano S, Pagès G. Mechanisms of resistance to anti-angiogenesis therapies. Biochimie, 2013, 95: 1110–1119.

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