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REVIEW – CLINICAL ONCOLOGY

New advances in antiangiogenic combination therapeutic strategies for advanced non-small cell lung cancer

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Abstract

Purpose Tumor growth relies on the sufficient blood supply and continuously requires new blood vessels to maintain, which lead to vascular abnormalities (Folkman, N Engl J Med 285:1182–1186, 1971). Antiangiogenic therapy has emerged with the goal of normalizing vasculature and tumor microenvironment (TME). Some antiangiogenic therapies combined with chemotherapy, targeted therapy or immunotherapy have been approved for clinical application. In this review, we summarize the recent advances of antiangiogenic combination therapeutic strategies in advanced NSCLC.

Methods References of this review are searched through PubMed and EMBASE and the abstracts of cancer conferences. The ClinicalTrials.gov database was used for relative trials.

Results Based on different mechanisms, antiangiogenic agents can be divided into monoclonal antibodies (mAbs), which mainly include bevacizumab and ramucirumab, and multi-target antiangiogenic tyrosine kinase inhibitors (TKIs) which include sunitinib, sorafenib, nintedanib, apatinib, anlotinib, fruquintinib, etc. In recent years, a number of large clinical studies have shown that antiangiogenic agents have conferred a significant overall survival (OS) benefit to patients with advanced non-small cell lung cancer (NSCLC). More and more evidences confirm that the combination of antiangiogenic agents with chemotherapy, targeted therapy and immunotherapy can improve the effect and prolong the survival of NSCLC patients. However, many problems about the application of antiangiogenic agents on advanced NSCLC patients still need to be explored. For example, the combination therapy of multi-target antiangiogenic agents is just beginning, and the biomarkers are not clear.

Conclusions Antiangiogenic agents can achieve therapeutic benefit in advanced NSCLC patients and the combination of chemotherapy, targeted therapy or immunotherapy can lead to synergistic effect. However, exploring the best combination therapy and efficacy-related biomarkers needs further study.

Keywords Anti-angiogenesis · NSCLC · Chemotherapy · Targeted therapy · Immunotherapy

Abbreviations

TME	Tumor microenvironment
mAbs	Monoclonal antibodies
TKIs	Tyrosine kinase inhibitors
OS	Overall survival
NSCLC	Non-small cell lung cancer
VEGF	Vascular endothelial growth factor
PDGF	Platelet-derived growth factor
FGF	Fibroblast growth factor
Ang	Angiotensin
HGF	Hepatocyte growth factor
EGF	Epidermal growth factor
VEGFR	Vascular endothelial generated factor receptor
FDA	The Food and Drug Administration
VEGF-A	Vascular endothelial growth factor-A
ORR	Objective response rate
PFS	Progression-free survival
EGFR	Epidermal growth factor receptor
LUAD	Lung adenocarcinoma
PDGFR	Platelet-derived growth factor receptor
FGFR	Fibroblast growth factor receptor
DCR	Disease control rate

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CNS	Central nervous system
ALK	Anaplastic lymphoma kinase
KIT	Stem-cell factor receptor
FLT3	FMS-like tyrosine kinase 3
CSF1R	Colony-stimulating factor 1 receptor
RET	Rearranged during transfection
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein ligand 1
ICAM-1	Endothelial cell adhesion molecule-1
VCAM-1	Vascular cell adhesion molecule-1
Tregs	Regulatory T cells
DC	Dendritic cells
GM-CSF	Granulocyte macrophage colony-stimulating factor
ABCP	Atezolizumab plus bevacizumab and paclitaxel/carboplatin
BCP	Bevacizumab plus paclitaxel/carboplatin
G/GEJ	Gastric or gastroesophageal junction
UC	Urothelial carcinoma
TMB	Tumor mutation burden
MVD	Micro-vessel density
Teff	Effector T cell
CCL2	Chemokine ligand 2

Introduction

Globally, lung cancer is one of the most common malignant tumors and the leading cause of cancer death worldwide (Bray et al. 2018), of which NSCLC accounts for 80–85% by pathological type. The vast majority of NSCLC patients are first diagnosed with local progression or metastasis (Miller et al. 2016). Since Professor Jodah Folkman proposed antiangiogenic theory in 1971, scientists have recognized that angiogenesis is a potential target for inhibiting cancer progression. Angiogenesis, which refers to the formation of neovascularization on the basis of existing blood vessels, has become a promising therapeutic target in oncology (Folkman 1971,1972; Holleb and Folkman 1972; Wang et al. 2017). Vascular abnormalities are vital for the growth and metastasis of different solid tumors (Krzywinska et al. 2017). Tumor blood vessels are like a myriad of "grain tracts" that continuously supply oxygen and other nutrients to malignant cells. Encouragingly, many of the factors and related receptors associated with angiogenesis, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), angiotensin (Ang), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and the like. VEGF binds to vascular endothelial-generated factor receptor (VEGFR), inducing autophosphorylation of the carboxyl terminus of VEGFR and the insertion region of the phosphorylated kinase, facilitating downstream signaling cascades that leads to the vasodilation, distortion and changes in tumor vascular permeability (Tian et al. 2011). VEGFR includes VEGFR 1–3, of which VEGFR 1 has the highest affinity for VEGF, but VEGF–VEGFR2 signal transduction pathway plays a major role in tumor angiogenesis. Currently, antiangiogenic agents against the VEGF–VEGFR pathway have shown clinical benefit in certain settings, including bevacizumab, which binds to VEGF and a novel human IgG1 mAb, ramucirumab, which selectively inhibits VEGFR2. These two monoclonal antibodies exert the anti-tumor effect mainly by combination with other treatments (Table 1).

In addition, small molecule multi-target TKIs, such as sunitinib, sorafenib, nintedanib, fruquintinib, anlotinib and apatinib, the last two of which are self-developed by Chinese scientists, have become another major category of antiangiogenic agents (Fontanella et al. 2014). Small molecule TKIs can competitively bind to the intracellular tyrosine kinase domain, inhibit the intracellular tyrosine kinase domain's phosphorylation process, block the activation of downstream cell signaling pathways, and thereby inhibiting tumor angiogenesis (Hall et al. 2015). Typically, such small molecule agents block multiple targets, rather than selectively a specific target. In addition to VEGF/VEGFR, which is closely related to angiogenesis, PDGF/PDGFR, FGF/FGFR and c-Kit are also common targets for these agents. Due to the lack of significant selectivity, the adverse effects of these agents are generally more pronounced than that of single-target agents; thus, the dosage of these agents in clinical trials has been limited. Currently, most of the VEGFR TKI agents have failed to improve the OS in patients with advanced NSCLC using alone or in combination with cytotoxic agents in clinical studies, except for a few agents such as nintedanib and anlotinib (Table 2) (Han et al. 2018a,b).

Different from traditional chemotherapeutic agents and small molecule targeted agents, which mainly act on tumor cells, antiangiogenic agents can act on the TME to degenerate existing tumor blood vessels and inhibit tumor neovascularization. Clinical data show that antiangiogenic agents combined with other NSCLC systemic agents, including chemotherapy, small molecule targeted therapy, immunotherapy, can have a better anti-tumor effect and delay drug resistance. Therefore, antiangiogenic agents have gradually become one of the standard treatment options for advanced NSCLC in recent years. This article summarizes the combination therapy of existing anti-tumor angiogenesis agents in the field of NSCLC treatment.

Table 1 VEGF macromolecular monoclonal antibodies that have entered clinical stage of advanced NSCLC or have entered phase II/III clinical trials

Antiangiogenic agents	Targets	Phase/clinical studies	Treatment line	Plan/population	Main efficacy data	European and American approval of NSCLC indications
Bevacizumab	VEGF	Phase III/NCT01364012 (BEYOND)	First line	Combining with carboplatin and paclitaxel/Stage IIIB or IV non-squamous NSCLC	ORR 54.0%; PFS 9.2 months; OS 24.3 months	Europe: Combining with platinum-containing chemotherapy for first-line treatment of unresectable advanced, metastatic or recurrent non-squamous NSCLC patients; Combining with erlotinib for first-line treatment of EGFR mutation-positive unresectable advanced, metastatic or recurrent non-squamous NSCLC patients United States: Combining with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC
		Phase III/NCT00021060 (ECOG 4599)	First line	Combining with carboplatin and paclitaxel/Stage IIIB or IV non-squamous NSCLC	ORR 35.0%; PFS 6.2 months; OS 12.3 months	
		Phase III/NCT00806923 (AVAiL)	First line	Combining with cisplatin and gemcitabine/Stage IIIB or IV, or recurrent non-squamous NSCLC	BEV 7.5 mg/kg group: ORR 34.1%; PFS 6.7 months; OS 13.6 months BEV 15 mg/kg group: ORR 30.4%; PFS 6.5 months; OS 13.4 months	
		Phase III/NCT01107626 (ECOG-ACRIN 5508)	First line	Combining with pemetrexed/advanced non-squamous NSCLC, no prior systemic therapy, and ECOG performance status 0/1	PFS 7.5 months; OS 16.4 months	
		Phase II/ JapicCTI-111390 (JO25567)	First line	Combining with erlotinib/EGFR mutation-positive stage IIIB or IV non-squamous NSCLC	ORR 69%; PFS 16.4 months; OS 47.0 months	
		Phase III/NEJ026	First line	Combining with erlotinib/EGFR mutation-positive stage IIIB or IV non-squamous NSCLC	ORR 72.3%; PFS 16.9 months	
		Phase III/ NCT02366143 (IMpower 150)	First line	Combining with atezolizumab + chemotherapy/Stage IV or metastatic non-squamous NSCLC	PFS (wild type) 8.3 months; OS (wild type) 19.2 months	
Ramucirumab	VEGFR2	Phase III/NCT01168973 (REVEL)	Second line	Combining with docetaxel/Stage IV squamous and non-squamous NSCLC	ORR 23.0%; PFS 4.5 months; OS 10.5 months	Europe: Combining with docetaxel in advanced or metastatic NSCLC patients who have failed platinum-containing chemotherapy United States: Combining with docetaxel for second-line and above treatment of metastatic NSCLC patients who have failed platinum-containing chemotherapy
		Phase III/ NCT02411448(RELAY)	First line	Combining with erlotinib/Exon 19 deletion (del) or L858R and no CNS metastasis untreated metastatic NSCLC	ORR 76.3%; PFS 19.4 months	

VEGF vascular endothelial growth factor, *NSCLC* non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *PFS* progression-free survival, *OS* overall survival, *ORR* overall response rate, *CNS* central nervous system

Table 2 VEGF-TKI agents that have entered clinical stage of advanced NSCLC or have entered Phase II/III clinical trials

Antiangiogenic agents	Targets	Phase/clinical studies	Treatment line	Plan/population	Main efficacy data	European and American approval of NSCLC indications
Anlotinib	VEGFR-3/FGFR1-4/PDGFα,β/EGFR/c-Kit	Phase II/NCT01924195 (ALTER0302)	Third line and above	Single drug/Stage IIIB or IV NSCLC	ORR 10.0%; PFS 4.8 months; OS 9.3 months	Unapproved
		Phase III/NCT02388919 (ALTER0303)	Third line and above	Single drug/Stage IIIB or IV NSCLC	ORR 9.2%; PFS 5.4 months; OS 9.6 months	
Fruquintinib	VEGFR1-3	Phase II/NCT02590965	Third line	Single drug/advanced non-squamous NSCLC	ORR 13.1%; PFS 3.8 months; OS 7.7 months	Unapproved
Nintedanib	VEGFR1-3/PDGFα,β/RET/FLT3/Src	Phase III/NCT00805194 (LUME-Lung 1)	Second line	Combining with docetaxel/Stage IIIB or IV recurrent NSCLC	ORR 4.4%; PFS 3.4 months; OS 10.1 months	Europe: Combining with docetaxel for locally advanced, metastatic or locally recurrent LUAD patients who have failed previous chemotherapy United States: Unapproved
Sunitinib	VEGFR/PDGFR/c-Kit/FLT3	Phase III/NCT00693992 (CALGB 30607)	First line maintenance	Single drug/Stage IIIB or IV NSCLC	ORR 11.0%; PFS 4.3 months; OS 11.7 months	Unapproved
		Phase II/S Novello,2009	Second line	Single drug/Stage IIIB or IV NSCLC	ORR 2.1%; PFS 2.7 months; OS 8.6 months	
		Phase II/NCT00265317	Second line and above	Combining with erlotinib/Stage IIIB or IV NSCLC	ORR 4.6%; PFS 2.8 months; OS 8.2 months	
		Phase III/Scagliotti,2012	Second line and above	Combining with erlotinib/Stage IIIB or IV NSCLC	ORR 10.6%; PFS 3.6 months; OS 9.0 months	
Apatinib	VEGFR/PDGF/c-Kit/RET/Src	Phase II/NCT02515435	Second line and above	Single drug/Stage IIIB or IV NSCLC	ORR 13.2%; PFS 3.06 months; OS 7.69 months	Unapproved
		Phase I/II/NCT03083041	Second line and above	Combining with SHR-1210/EGFR and ALK negative NSCLC	≥2 prior lines:ORR 33.3%; mPFS 6.4 months bTMB-H:ORR 50.0%; mPFS 8.3 months bTMB-L:ORR 16.7%; mPFS 5.6 months	

VEGF-TKI vascular endothelial growth factor-tyrosine kinase inhibitor, *NSCLC* non-small cell lung cancer, *VEGFR* vascular endothelial growth factor receptor, *FGFR* fibroblast growth factor receptor, *PDGF* platelet-derived growth factor, *EGFR* epidermal growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *PFS* progression-free survival, *OS* overall survival, *ORR* overall response rate, *TMB* tumor mutation burden

Antiangiogenic agents combined with chemotherapy for advanced NSCLC

Bevacizumab combined with chemotherapy

Antiangiogenic agents can normalize tumor blood vessels before the blood vessels resolve by improving blood density, swelling and permeating. Hence, antiangiogenic agents enhance the penetration of chemotherapy agents and oxygen supply in a short period of time to increase the treatment sensitivity to chemotherapy (Lin and Sessa 2004). Bevacizumab is the first antiangiogenic agent approved by the Food and Drug Administration (FDA) for cancer treatment. It is a recombinant human mAb that binds vascular endothelial growth factor-A (VEGF-A) and inhibits VEGFR signaling. As the most widely prescribed antiangiogenic agent, it has been demonstrated to bring clinical benefits for patients with advanced NSCLC.

The phase III ECOG 4599 study showed that after adding bevacizumab, the OS in NSCLC patients was extended for more than 1 year for the first time (OS: 12.3 m vs 10.3 m). The risk of death was significantly reduced by 21%, while the objective response rate (ORR) more than doubled (35% vs 15%) (Sandler et al. 2006). Due to significant survival benefit and acceptable safety, bevacizumab combined with paclitaxel/carboplatin was proved by the US FDA in October 2006 for first-line treatment of locally unresectable advanced, recurrent or metastatic non-squamous NSCLC.

The efficacy and safety of bevacizumab combined with gemcitabine/cisplatin was studied in a large phase III trial, AVAiL, in Europe. Progression-free survival (PFS) was significantly prolonged in the bevacizumab group, and objective remission rate and remission time as the secondary end points were also significantly improved. The median OS in all treatment groups was more than 13 months, far exceeding the 1-year historical survival baseline (Reck et al. 2009,2010).

Meanwhile, combination of bevacizumab and platinum-containing agents showed better outcomes in Asians, especially Chinese patients with advanced non-squamous NSCLC in BEYOND study. PFS and OS in bevacizumab group significantly prolonged compared to those in the control group, which were 9.2 months compared to 6.5 months and 24.3 months compared to 17.7 months, respectively. A total of 40 patients with epidermal growth factor receptor (EGFR) mutation positive, 23 patients in the bevacizumab arm and 17 patients in the placebo arm, were enrolled in BEYOND study. However, the results showed that patients' PFS benefit from bevacizumab treatment was not related to EGFR status (Zhou et al. 2015).

Moreover, AVAPERL studies, published at the ASCO conference in 2011, showed that compared with bevacizumab alone, bevacizumab combined with pemetrexed as maintenance therapy can bring significant PFS benefits, but OS benefit is not significant (Barlesi et al. 2013). This year's ASCO conference again announced two studies involving maintenance therapy with bevacizumab. ECOG-ACRIN 5508 showed that compared with pemetrexed maintenance alone or bevacizumab maintenance alone, the combined treatment could prolong PFS, but the OS extension was not significant. The median PFS and OS in the combined group were 7.5 and 16.4 months, respectively, yet in the controlled group using pemetrexed alone the PFS and OS were 5.1 months and 15.9 months, while in that of using bevacizumab alone, the PFS and OS were 3.2 months and 14.4 months (Ramalingam et al. 2019). Another study, WJOG5610L, which analyzed bevacizumab combined with pemetrexed as maintenance therapy, was also published at ASCO in 2019. The results showed that bevacizumab combined with pemetrexed significantly prolonged PFS compared with PFS of using bevacizumab alone. Moreover, OS results showed that the OS in the combined group (23.3 months) was longer than that in the bevacizumab group (19.6 months), but there was no statistical difference (HR = 0.87, 95% CI: 0.72–1.04). On the other hand, in the wild-type NSCLC population of EGFR, the OS difference between the two groups was statistically significant (HR = 0.82, 95% CI: 0.68–0.99) (Seto et al. 2019). In the field of cross-line treatment of bevacizumab, some retrospective studies and phase II randomized controlled WJOG 5910L studies have shown that cross-line treatment of bevacizumab could benefit PFS in non-squamous NSCLC patients, but the newly published phase III study AvaALL showed that cross-line treatment of bevacizumab in NSCLC patients was negative. This study included advanced NSCLC patients using bevacizumab as the first-line treatment and standard therapy combined with or without bevacizumab as second-line treatment. After the second and third progression, patients receiving bevacizumab continued to receive standard therapy combined with bevacizumab, while the patients in the standard treatment group only received standard treatment. The results showed that there was no significant difference in OS between bevacizumab group and standard treatment group (11.9 months vs 10.2 months, HR = 0.84, $P = 0.104$). In subgroup analysis, according to the dosage of bevacizumab, there was no significant difference in the median OS in patients. The OS of bevacizumab 7.5 mg/kg group was 11.4 vs 10.2 months, HR 0.86, and that of bevacizumab 15 mg/kg group was 12.6 vs 10.2 months, HR 0.84 (Gridelli et al. 2018).

Ramucirumab combined with chemotherapy

The ramucirumab is another agent that has been approved for use in locally advanced or metastatic NSCLC. Ramucirumab is a human IgG1 mAb that specifically binds to the VEGFR2 extracellular domain. It has a high affinity to VEGFR2, preventing all combination of VEGF ligands and activation of receptors. In a multicenter, double-blind, randomized, phase III REVEL study, 1253 patients with stage IV NSCLC who had progressed during or after platinum-containing chemotherapy were included. 628 patients received ramucirumab plus docetaxel, with the median OS of 10.5 months and 625 patients received placebo plus docetaxel, with the OS of 9.1 months (HR = 0.857, 95%CI 0.751–0.979, $P = 0.0235$). The median PFS in the two groups were 4.5 and 3.0 months, respectively (HR = 0.762, 95%CI 0.677–0.859, $P < 0.0001$). The most common grade 3 or worse adverse event was neutropenia (49% in the ramucirumab group vs 40% in the control group) (Garon et al. 2014). Based on the results of this study, the US FDA approved ramucirumab plus docetaxel as second-line treatment for advanced NSCLC in December 2014.

A phase II study in 2015 evaluated ramucirumab combined with pemetrexed and platinum-based chemotherapy as the first-line treatment for advanced metastatic NSCLC patients. Compared to the control group, the ramucirumab combination treatment group neither met primary end point for PFS, nor did the ORR show a significant improvement (Doebele et al. 2015).

Multi-target TKIs combined with chemotherapy

Initial phase II and III clinical trials of multi-target TKIs showed that these agents did not bring survival benefits to NSCLC patients. For example, in ESCAPE (Scagliotti et al. 2010), NExUX (Paz-Ares et al. 2012) and ZEAL (Boer et al. 2011), sorafenib and vandetanib combined with chemotherapy as the first-line treatment failed to help patients by comparing to the patients using chemotherapy; NCCTG N0626 showed that sorafenib combined with pemetrexed as second-line treatment did not prolong their OS (Molina et al. 2011).

However, LUME-Lung 1 has changed the bottleneck of multi-target TKI in recent 10 years. This study included advanced NSCLC patients with first-line treatment failure. The results showed that compared with placebo group, combining nintedanib and docetaxel significantly prolonged PFS (3.4 months and 2.7 months, respectively). Although there was no significant difference in OS between the two NSCLC groups, in the lung adenocarcinoma (LUAD) population, combining nintedanib with docetaxel prolonged OS by 2.3 months compared with docetaxel combined with placebo (Reck et al. 2014). In November 2014, the European Union approved nintedanib in combination with docetaxel for the second-line treatment of advanced or metastatic LUAD. Furthermore, the CALGB 30607 study assessed the efficacy of sunitinib as maintenance therapy after first-line chemotherapy in stage IIIB/IV NSCLC. The results showed that the median PFS in patients treated by sunitinib was 4.3 months yet PFS in patients taking placebo was 2.6 months (HR = 0.62, $P = 0.0006$), but there was no significant difference in OS between the two groups (11.7 months for sunitinib OS, 12.1 months for HR = 0.98, $P = 0.89$) (Baggstrom et al. 2017).

Besides the agents mentioned above, anlotinib is a small molecule multi-target TKI developed independently in China. It can effectively inhibit VEGFR, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), c-kit and other targets, and has dual effects of anti-tumor angiogenesis and tumor growth inhibition. The main research results of ALTER0303 make it be approved for the third-line treatment of NSCLC (Han et al. 2018b). The exploratory study of first-line treatment of EGFR/ALK/ROS1 negative advanced NSCLC with anlotinib combined with chemotherapy showed that ORR and disease control rate (DCR) were up to 60% and 96.7%, respectively. The incidence of grade 3–4 adverse events was low and the most common ones were thrombocytopenia (grade 3 10% and grade 4 10%) and hypertriglyceridemia (grade 3 10%) (Han et al. 2019).

Antiangiogenic agents combined with EGFR-TKI for advanced NSCLC

VEGF and EGFR share many overlapping and parallel downstream pathways (Perdrizet and Leighl 2019). Several angiogenic growth factors increased through EGFR signaling regulation, including VEGF, interleukin-8 (IL-8), and basic fibroblast growth factor (bFGF) (Luca et al. 2008). In turn, VEGF up-regulation contributes to resistance to EGFR inhibition. The biological rationale suggests that inhibiting both pathways could improve the efficacy of antitumor and remove the resistance of EGFR inhibition (Fig. 1) (Tabernero 2007). Besides, preclinical researches have shown the similar results. In a gastric cancer mouse model, the combination of DC101 (VEGFR2 antibody) and C225 (EGFR antibody) significantly inhibited the tumor cell proliferation by decreasing tumor vascularity and increasing endothelial cell apoptosis (Jung et al. 2002). In an EGFR-mutated NSCLC xenograft model, VEGF was evidently reduced in the erlotinib-sensitive phase and conversely increased in the erlotinib-refractory phase by erlotinib, demonstrating that erlotinib plus bevacizumab would show synergistic efficacy after erlotinib resistance (Masuda et al. 2017). Based on these, a number of prospective studies have confirmed that

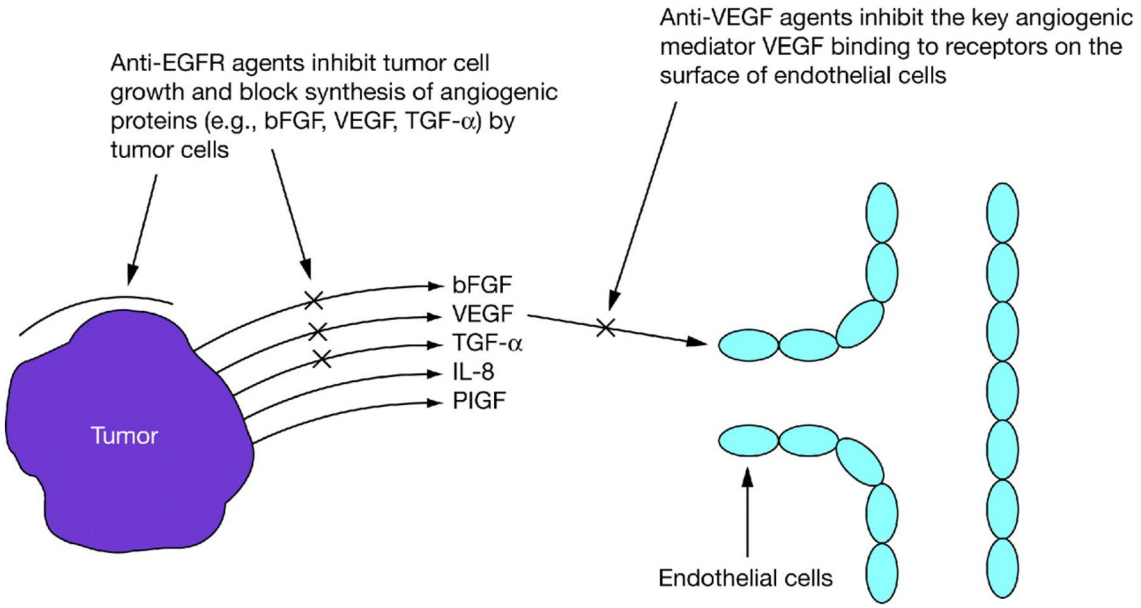

Fig.1 Dual inhibition of EGFR and VEGF signaling pathways could improve the antitumor effects (Tabernero 2007). *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor, *bFGF* basic fibroblast growth factor, *TGF-α* transforming growth factor-A, *IL-8* interleukin-8, *PIGF* placenta growth factor

VEGF inhibitors in combination with EGFR-TKI significantly prolong patients' survival.

Monoclonal antibodies (mAbs) combined with EGFR-TKI

BeTa study in 2011 showed that comparing to erlotinib in non-EGFR subjects, the combination of bevacizumab and erlotinib increased the PFS of the second-line treatment (3.4 months vs 1.7 months), but OS did not prolong (9.3 months vs 9.2 months) (Herbst et al. 2011). A phase II one-arm study (1001 study) in 2015 was designed to verify the efficacy and safety of gefitinib plus bevacizumab in the first-line treatment for advanced NSCLC patients who were positive for EGFR mutations. This study provided evidence that the first-line treatment of bevacizumab in combination with gefitinib conferred clinical benefits and good tolerance in advanced NSCLC patients with EGFR mutation, of whom patients with exon 19 deletion benefited more (Ichihara et al. 2015).

The JO25567 study was the first prospective randomized controlled phase II clinical study to evaluate the first-line treatment of erlotinib plus bevacizumab for advanced NSCLC patients with EGFR mutations. The study showed that the median PFS of the treatment group and the control group were 16.0 and 9.7 months, respectively, confirming that the combination of the two agents can significantly prolong the PFS of the patients (Seto et al. 2014); therefore, bevacizumab plus erlotinib were approved by the European Union for first-line treatment to advanced non-squamous NSCLC EGFR-mutated patients in June 2016. At the ASCO meeting in 2018, Dr. Noboru Yamamoto reported the follow-up survival results of the JO25567 study. The median OS of advanced EGFR mutation-positive non-squamous NSCLC patients, who received first-line treatment of bevacizumab plus erlotinib, are nearly 5 years. However, there is no significant difference in terms of the OS between the treatment group and the control group (Yamamoto et al. 2018). Whether bevacizumab plus erlotinib can extend the OS requires further phase III clinical studies to be confirmed since the lost rate of follow-up was up to 16% in this study.

Based on the results of JO25567, the first phase III multicenter randomized double-blind controlled clinical study, NEJ026, was conducted in Japan. The treatment group and the control group each included 107 patients. The study confirmed the PFS benefit of bevacizumab plus erlotinib treatment, which reached 16.9 months, extending 3.6 months compared to the erlotinib group (Furuya et al. 2018). However, longer follow-up, and OS and quality-of-life data are required to further assess this combination in this setting (Saito et al. 2019).

Beyond that, the ARTEMIS study was reported at the ESMO conference this year, which is the first phase III clinical trial of bevacizumab combined with erlotinib for the treatment of advanced EGFR-mutated NSCLC in Chinese population. The results confirmed that the combination therapy significantly prolonged the PFS (BIRC: 18.0 m vs 11.3 m, HR = 0.55). There was an absolute benefit of

nearly 7 months compared to the control group. In the subgroup analysis, we found that the PFS benefit of patients with 21L858R mutation was more significant, reaching 19.5 months, which was nearly 10 months longer than that of the control group (19.5 vs 9.7 months, HR = 0.51). This may be the longest PFS data for patients with 21L858R, including any other chemotherapy or one to three generations of single-agent TKI protocol. TKI single agent has limited benefits for patients with 21L858R mutation, "A + T" can just make up for the clinical needs of these patients. Second, in the ARTEMIS study, nearly 30% of patients with baseline brain metastases were enrolled, and PFS HR was 0.42, suggesting that the combined model may have better benefits. All patients' adverse reactions are tolerable. However, the probability of grade 3 or greater adverse events during treatment doubled in the bevacizumab group. The common ≥ grade 3 adverse events in the combination group include hypertension (18.5%), proteinuria (8.3%) and rash (5.1%) (Zhou et al. 2019b).

There are no positive results in the study of monoclonal antiangiogenic agents used as the maintenance treatment of advanced NSCLC. In the phase IIIB ATLAS study, bevacizumab combined with erlotinib as maintenance treatment improved median PFS statistically (4.8 months vs 3.7 months) but not OS compared to using bevacizumab alone as maintenance treatment. Patients with EGFR mutation-positive or KRAS wild-type NSCLC received a greater PFS (Johnson et al. 2013; Kabbinavar et al. 2014).

Additionally, many clinical studies of antiangiogenic agents combined with different EGFR-TKIs are ongoing.

Afatinib, a second-generation EGFR-TKI, is an irreversible ErbB family blocker that exhibits a high anti-tumor effect by covalently attaching to the tyrosine kinase domain of EGFR and irreversibly inhibiting phosphorylation. Phase I clinical study of bevacizumab in combination with afatinib did not show dose-limiting toxicity, and using afatinib 30 mg/d + bevacizumab 15 mg/kg was recommended as the dose selection for the phase II clinical trial. Phase II study published in 2019 mainly compared the efficacy of afatinib plus bevacizumab with only afatinib in the first-line treatment of EGFR mutation-positive non-squamous NSCLC. The results showed that the combination therapy was more effective in NSCLC patients with EGFR mutant. Therefore, the combination of bevacizumab and second-generation EGFR-TKI afatinib as the first-line treatment of NSCLC is also expected (Ninomiya et al. 2019).

Moreover, there are also studies of combining the third-generation EGFR-TKI and bevacizumab to treat advanced EGFR-mutated NSCLC. Osimertinib is a third-generation EGFR-TKI that not only has a potential inhibition on mutant tyrosine kinases which are sensitive to first- and second-generation EGFR-TKIs, but also on T790M mutant EGFR tyrosine kinases (Uchino et al. 2018). The preliminary results of phase I/II study of osimertinib combined with bevacizumab were also presented at the ASCO conference in 2019. The results showed that the first-line combination of osimertinib and bevacizumab was safe and controllable with an ORR rate of 80%, even though 71% of patients with brain metastasis were included in the study. The median PFS is 18.4 months (Yu et al. 2019).

In addition to that, in the RELAY study published at the ASCO conference in 2019, advanced NSCLC patients with EGFR mutation (19del/21L858R) and without central nervous system (CNS) metastasis were randomized (1:1) into either erlotinib plus ramucirumab group or erlotinib plus placebo group. The results showed that erlotinib plus ramucirumab significantly prolonged PFS (19.4 m vs.12.4 m, $P < 0.0001$). In terms of ≥ grade 3 adverse events, ramucirumab plus erlotinib group had a higher incidence of hypertension (52% vs 12%) and proteinuria (6% vs 0%) compared with the placebo group (Nakagawa et al. 2019). Another study, TORG1833 which mainly evaluates osimertinib plus ramucirumab comparing with osimertinib for NSCLC with EGFR gene mutation, is currently in progress (Nakahara et al. 2019).

Clinical studies on combination of antiangiogenetic monoclonal antibodies with anaplastic lymphoma kinase (ALK) inhibitors have not yet been published. Phase I/II clinical trials of alectinib combined with bevacizumab in the treatment of ALK gene-positive NSCLC are currently being recruited (NCT02521051).

Multi-target TKIs combined with EGFR-TKI

There are also many studies on the combination of multi-target antiangiogenic agents with EGFR-TKI. Sunitinib, a small molecule multi-target inhibitor, acts on VEGFR-1/2/3, PDGFR-a/b, stem-cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF1R) and rearranged during transfection (RET). Phase III trials included NSCLC patients (no EGFR gene test) with previous treatment failures. The combination of sunitinib and erlotinib significantly increased PFS (3.6 months vs 2.0 months) and RR (10.6% vs 6.9%) compared with erlotinib alone, but there was no major difference in OS (9.0 months vs 8.5 months) (Scagliotti et al. 2012).

A one-arm, open multicenter clinical study on fruquintinib plus gefitinib was published at the 2017 WCLC. The results of the study showed that using 4 mg fruquintinib plus 250 mg gefitinib was safe and effective. Among the 17 patients who were able to observe the effect, the ORR was 76.5% and the clinical benefit rate was 100%. Fruquintinib plus gefitinib shows good therapeutic potential and it is expected that subsequent studies will further confirm the efficacy of this combination (Lu et al. 2017).

Apatinib is a highly selective VEGFR2 inhibitor with antiangiogenic and anti-tumor activity. The ongoing Ahead-L303 study is under way for the first-line treatment of EGFR mutations with apatinib and gefitinib in advanced non-squamous NSCLC patients, and the final results are expected (Table 3).

For untreated EGFR mutation-positive advanced NSCLC patients, the combination of anlotinib and erlotinib has been studied. Based on the current clinical data of 27 patients, ORR was 92.6% and DCR was up to 100%. The incidence of grade 3 adverse events was high in rash (17.24%) and oral mucositis (10.34%). One case of grade 4 hypertension was observed among all patients (Han et al. 2019). PFS time is still in follow-up (Han et al. 2019).

Antiangiogenic therapy combined with immunological checkpoint inhibitors for advanced NSCLC

In recent years, significant progress has been made in the immunotherapy which mainly reflected in better efficacy, sustained response and manageable toxicity, among which blocking either of programmed cell death protein 1 (PD-1) or programmed cell death protein ligand 1 (PD-L1) has been developed successfully for NSCLC (Wang et al. 2017). VEGF, a cytokine that promotes angiogenesis, induces tumor-associated immunodeficiency and plays an important regulatory role in the immunosuppressive microenvironment in which tumor cells evade immune surveillance. On the one hand, VEGF inhibits the adhesion of lymphocytes to activate endothelial cells and is associated with the accumulation deficiency of endothelial cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells. VEGF affects the transport of lymphocytes through the endothelial cells into the tumor, thereby blocking T cell infiltration (Bouzin et al. 2007). VEGF also prevents T cell mobilization and trafficking by acting on Fas ligands (Motz et al. 2014). On the other hand, VEGF plays the role of immunosuppression through several mechanisms including induction and proliferation of regulatory T cells (Tregs) (Finke et al. 2008; Terme et al. 2013), and suppression of dendritic cell (DC) maturation (Gabrilovich et al. 1998,1996). Antiangiogenic agents can reduce the compactness of tumors to relieve vascular pressure, normalize the abnormal tumor vasculature, increase the infiltration of immune effector cells, and convert the intrinsically immunosuppressive tumor microenvironment to an immuno-supported one; thus, the perfusion and oxygenation of the TME can be improved (Fig. 2) (Manegold et al. 2017; Fukumura et al. 2018).

Multiple preclinical evidence supported that antiangiogenic agents combined with immunological checkpoint inhibitors may play a synergistic role in improving the outcomes of patients. In two murine tumor models of the B16 melanoma and the CT26 colon carcinoma, VEGF blockade combined with granulocyte macrophage colony-stimulating factor (GM-CSF)-secreting tumor cell immunotherapy significantly increased the survival of the animals and provided enhanced antitumor responses (Li et al. 2006). Combined bevacizumab and CIK cell therapy in the treatment of LUAD-bearing murine models had synergistic inhibition effects for advanced NSCLC (Tao et al. 2014). Additionally, in Colon-26 adenocarcinoma model in vivo, simultaneous treatment of blocking PD-1 and VEGFR2 mAbs inhibited tumor growth without overt toxicity (Yasuda et al. 2013). In

Table 3 Ongoing trials on antiangiogenic combination therapy in advanced non-small cell lung cancer

Study	Design	Interventions	Status
NCT01454102	Phase I	Nivolumab; bevacizumab; platinum-based doublet chemotherapy; erlotinib; ipilimumab	Active, not recruiting
NCT02443324	Phase I	Ramucirumab; pembrolizumab	Active, not recruiting
NCT02521051	Phase I/II	Alectinib; bevacizumab	Recruiting
NCT03201146	Phase I/II	Apatinib; pemetrexed; carboplatin; cisplatin	Recruiting
NCT03416231	Phase II	Apatinib; docetaxel	Recruiting
NCT03527108	Phase II	Nivolumab; ramucirumab	Not yet recruiting
NCT03713944	Phase II	Atezolizumab; bevacizumab; carboplatin; pemetrexed	Recruiting
NCT03836066	Phase II	Atezolizumab; bevacizumab	Recruiting
NCT03909334	Phase II	Ramucirumab; osimertinib	Recruiting
NCT02824458	Phase III	Apatinib; gefitinib	Recruiting
NCT03829319	Phase III	Lenvatinib; pembrolizumab; pemetrexed; carboplatin; cisplatin	Recruiting
NCT02954172	Phase III	Bevacizumab; paclitaxel; carboplatin	Active, not recruiting
NCT02759614	Phase III	Bevacizumab; erlotinib	Active, not recruiting
NCT03799601	Phase IV	Anlotinib; docetaxel; carboplatin	Not yet recruiting

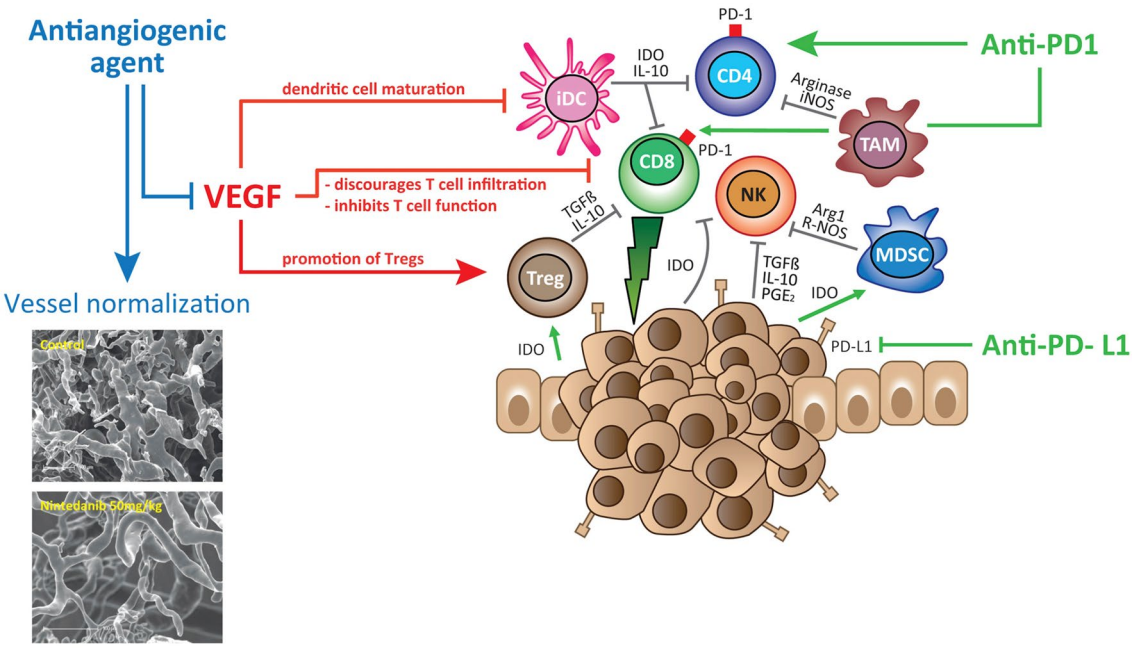

Fig. 2 Combined inhibition of tumor angiogenesis and the immune checkpoint (Manegold et al. 2017). *Arg1* arginase1, *CD4* cluster of differentiation 4, *CD8* cluster of differentiation 8, *iDC* immature dendritic cell, *IDO* indole amine 2, 3-dioxygenase, *IL-10* interleukin-10, *iNOS* inducible nitric oxide synthase, *MDSC* myeloid-derived suppressor cell, *NK* natural killer, *PD-L1* programmed death ligand 1, *PGE2* prostaglandin E2, *TAM* Tyro3 Axl and Mer, *R-NOS* reactive nitrogen oxide species, *TGFβ* transforming growth factor β, *Treg* T-regulatory cell, *VEGF* vascular endothelial growth factor

view of its good toxicity characteristics, the combination of agents has important clinical application value (Manegold et al. 2017).

In 2015, a newly developed anti-PD-1 inhibitor, nivolumab, mainly blocks the binding of PD-1 receptor and PD-L1 ligand to promote T-cell activation, activates T cells to infiltrate the tumor and directly attacks tumor cells. In patients with advanced NSCLC but no progression by treating with first-line platinum chemotherapy, Rizvi evaluated the efficacy and safety of nivolumab monotherapy and that of nivolumab in combination with bevacizumab. The nivolumab monotherapy group included both squamous and non-squamous NSCLC patients, while the nivolumab plus bevacizumab group included only non-squamous NSCLC patients. The results showed that neither group has reached the median OS. In the nivolumab plus bevacizumab group, the median PFS is 37.1 weeks, whereas in the nivolumab monotherapy group, the median PFS is 16 weeks in patients with squamous cell NSCLC, and the median PFS was 21.4 weeks in patients with non-squamous cell NSCLC. ORR of the combined group (8%) and the nivolumab monotherapy group (10%) are similar. Additionally, nivolumab plus bevacizumab has a tolerable safety characteristic (Rizvi et al. 2014).

The IMpower150 study is a successful model of antiangiogenic agents plus immunotherapy. Atezolizumab (Tecentriq), a human IgG anti-PD-L1 mAb, prevents the binding of PD-1 receptor and PD-L1 by blocking PD-L1 ligand thus promotes T-cell proliferation which plays an important role in treating NSCLC patients with high expression of PD-L1. This is a phase III multicenter randomized controlled clinical trial about the treatment of bevacizumab in combination with atezolizumab for advanced non-squamous NSCLC. The results showed that the median PFS of the atezolizumab plus bevacizumab and paclitaxel/carboplatin (ABCP) group is 8.3 months, and the risk of progression decreases 41% (HR = 0.59, 95% CI 0.50–0.70, $P < 0.0001$). At the same time, the median OS is 19.2 months, and the 2-year survival rate is as high as 43%. Furthermore, it was also observed that ABCP treatment achieved greater PFS benefit than bevacizumab plus paclitaxel/carboplatin (BCP) regimen on patients with EGFR or ALK mutation (median PFS: ABCP group 9.7 months vs BCP group 6.1 months, HR 0.59, 95% CI 0.37 ~ 0.94) as well as patients with liver metastasis (median PFS: ABCP group 7.4 months vs BCP group 4.9 months, HR 0.59, 95% CI 0.26 ~ 0.66) (Socinski et al. 2018a; Reck et al. 2019). Based on this study, FDA approved ABCP as first-line treatment of metastatic non-squamous NSCLC patients on December 6, 2018. However, ABCP was not approved as the treatment for patients with EGFR/ALK mutations (Socinski et al. 2018b).

JVDF is a multi-cohort, non-randomized, open-label, phase 1a/b trial to study ramucirumab combined with pembrolizumab for advanced NSCLC, gastric or gastroesophageal junction (G/GEJ) adenocarcinoma, or urothelial carcinoma (UC). The results of phase 1a study indicated that no additional dose-limiting toxicities occurred. The following phase 1b study showed that median PFS of all patients was 9.3 months and the common ≥ grade 3 treatment-related adverse events were hypertension (15.4%) and myocardial infarction (7.7%). The better efficacy was correlated to the higher expression of PD-L1. The clinical benefit of patients with PD-L1 ≥ 50% is more obvious (Herbst et al. 2019a,b).

The WJOG 11218L APPLE study was designed to evaluate whether bevacizumab, based on immunotherapy plus chemotherapy, can improve survival in patients with non-squamous NSCLC. This study is from Japan and is ongoing (Shiraishi et al. 2019).

Compared with mAb, small molecule multi-target antiangiogenic agents combined with immunotherapy is on the rise. According to the preliminary data, the curative effect seems to be better than that of mAb combined immunotherapy. In a study presented at ASCO in 2019, Chinese developed monoclonal antibody, SHR-1210, combined with apatinib was used in first-line treatment but failed in NSCLC population. ORR and DCR were 29.7% and 81.3%, respectively (Zhou et al. 2019a).

The result of combining sintilimab and anlotinib as the first-line treatment, which was one arm from a multi-cohort phase Ib trail, was reported at 2019 WCLC. According to the current small sample data, ORR (72.7%) has reached the primary end point and DCR was 100%. In terms of safety, the most common adverse event was hypertension and the incidence of ≥ grade 3 treatment-related adverse events was 27.3%. In all patients, the expression of PD-L1 was detected in 21 cases and tumor mutation burden (TMB) was detected in 18 cases. The results showed that patients with different levels of PD-L1 expression could all benefit from the treatment (Han et al. 2019).

This year also saw a phase III study in newly enrolled cases that evaluated the combination of immunotherapy and the multi-target agent lenvatinib (FGF1-4, PDGFa, c-kit and RET on VEGFR 1-3). This study included patients with advanced non-squamous NSCLC.

All the other ongoing researches on anti-neoplastic vascular combined immunotherapy are presented in the table (Table 3).

Biomarkers

Antiangiogenic agents have been proved to be effective in many clinical trials of NSCLC. To further improve the effectiveness of antiangiogenic treatment and determine the beneficiaries, searching for reliable biomarkers will be the main basis for screening. Due to the complexity of tumor occurrence and development and the heterogeneity of patients, although some biomarkers may be related to the effectiveness of anti-vascular therapy in NSCLC, the predictive effect of these biomarkers on the effectiveness has not been verified. This paper mainly discusses the combination therapy of antiangiogenic agents, as the biomarkers of the combination therapy will be more complicated.

First of all, results for biomarkers associated with the efficacy of bevacizumab were inconsistent. For example, in an open-label, randomized phase II clinical trial Abigail, the results showed that the initial level of VEGF-A in plasma was related to the efficacy of bevacizumab combined chemotherapy. When treating with bevacizumab combined with chemotherapy and comparing with patients having high level of VEGF-A, patients with low level of VEGF-A treated with bevacizumab combined chemotherapy had longer PFS (6.1 and 7.4 months, $P = 0.002$), and longer OS (11.1 and 9.8 months, $P = 0.004$) (Mok et al. 2014). However, some studies have shown that the level of VEGF-A in NSCLC patients with TP53 mutation is higher, and bevacizumab is more effective to these kind of patients (Schwaederle et al. 2015). The results seem to contradict the studies of Mok et al. (2011). Therefore, whether the level of VEGF-A is related to the efficacy of bevacizumab or not needs further verification.

There are few biomarkers that can predict the efficacy of bevacizumab in NSCLC patients. Some studies have shown that the undifferentiated micro-vessel density (MVD) in tumor may be a biomarker to predict the effect of chemotherapy combined with bevacizumab in the treatment of NSCLC. The higher MVD value, the better the treatment responses (Zhao et al. 2012). It has also been shown that a large number of circulating neutrophils and monocytes, and a high ratio of neutrophils to lymphocytes at the initial diagnosis are related to the shorter PFS and OS in patients who were treated with bevacizumab (Mok et al. 2014). However, further studies are needed to verify the predictive role of these indicators in the treatment of NSCLC with bevacizumab.

For the biomarkers of antiangiogenetic agents combined with immunotherapy, Impower150 study showed that patients could benefit from bevacizumab combined with immunotherapy and chemotherapy, regardless of the expression of PD-L1 and effector T cell (Teff), yet the higher the expression, the more benefits the patients could gain (Reck et al. 2019). However, phase Ib study of the combination of ramucirumab and pembrolizumab showed that patients with the expression of PD-L1 more than 50% benefited significantly (Herbst et al. 2019a,b). Therefore, the expression of PD-L1 is the main biomarker in the combination of mAb and immunotherapy so far.

The combination therapy of multi-target antiangiogenic agents has just started, and the research on biomarkers is insufficient. Lu J's article demonstrated an important anti-angiogenesis mechanism of anlotinib via chemokine ligand 2 (CCL2) blockade in LUAD and the changes in serum CCL2 levels, which could be used to monitor and predict clinical benefit in anlotinib-administered refractory advanced NSCLC patients (Lu et al. 2019). However, in combination therapy, the correlation between PD-L1 expression, TMB level and efficacy seems to be insignificant in the study combining sintilimab with anlotinib (Han et al. 2019). The value of CCL2 also needs to be confirmed by prospective large sample study.

Therefore, there is still a long way to go to explore the biomarkers of antiangiogenic agents in the efficacy of NSCLC. Thus, more clinical trials are needed to verify whether the biomarkers (such as VEGF-A level and tumor MVD) are related to the efficacy. Furthermore, more studies are needed to explore new biomarkers that may relate to the efficacy of antiangiogenic treatment, so as to maximize the benefits of patients.

Conclusions

From the traditional platinum-based doublet chemotherapy to molecular targeted therapy that has been used in the past 10 years, and to the tumor immunotherapy that has emerged in the past 4 years, the treatment concept of advanced NSCLC is constantly changing. Since the US FDA approved the antiangiogenic agent, bevacizumab, for the first-line treatment of advanced NSCLC in 2006, this type of agents has always held an important position in the clinical management of advanced NSCLC patients based on a large number of clinical data and actual clinical application. Tumor angiogenesis is closely related to the occurrence and progression of solid tumors including NSCLC, and is throughout the whole process of tumor progression. Hence, antiangiogenic agents can achieve therapeutic benefit in a wide range of advanced NSCLC patients. As a result, the combination of antiangiogenic agents and the main treatments of NSCLC including chemotherapy, targeted therapy and immunotherapy can lead to synergistic effect.

There are still many problems about the application of antiangiogenic agents on advanced NSCLC patients and those problems need to be further studied in the future. First of all, exploring the best combination therapy is an important direction for further research. Based on the current research results, antiangiogenic agents combined with new-type targeted agents or emerging tumor immunotherapy may both become important strategies for future clinical treatment of advanced NSCLC. Second, the optimal mode of administration of antiangiogenic agents in advanced NSCLC patients remains to be determined, especially the most appropriate dose and the order of administration in combination therapy. Last but not the least, the efficacy-related biomarkers are the prerequisite for selecting superior population and achieving precise antiangiogenic therapy. However, the exploration of biomarkers relating to the efficacy of antiangiogenic agents in NSCLC is still in its infancy. Additionally, biomarkers are more complicated from the perspective of combination therapy. Therefore, how to screen the dominant population is the key to antiangiogenic factor combination therapy.

To sum up, anti-angiogenesis therapy is an important and promising method of advanced non-small cell lung cancer treatment, no matter in the era of chemotherapy, targeted therapy or now immunotherapy, but there are still many questions that need more research to explore further.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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