

Prospect of immunotherapy combined with anti-angiogenic agents in patients with advanced non-small cell lung cancer

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Abstract: In the latest years, some drugs have been approved by European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA) for the treatment of patients with advanced non-small cell lung cancer (NSCLC), particularly for the treatment of those who have no targeted gene mutations or who have progressed on previously targeted therapy or platinum-containing dual-agent chemotherapy. In general, these drugs fall into two categories: anti-angiogenic agents and immune checkpoint inhibitors (ICIs). Anti-angiogenic agents currently approved by the FDA and/or EMA for advanced NSCLC treatment include bevacizumab, nintedanib, and ramucirumab. Anlotinib has been approved in advanced NSCLC by Chinese Food and Drug Administration (CFDA). These anti-angiogenic agents can induce anti-angiogenesis by targeting vascular endothelial growth factor (VEGF)/VEGF2 or inhibiting multiple small molecules involved in angiogenic and proliferative pathways such as platelet-derived growth factor receptors (PDGFRs) and fibroblast growth factor receptors (FGFRs). Although these drugs show significant therapeutic efficacy, most patients inevitably experience disease progression resulting in death. ICIs approved by the FDA and/or EMA for advanced NSCLC treatment include nivolumab, pembrolizumab, and atezolizumab. These ICIs can significantly improve efficacy compared with standard chemotherapy by targeting programmed cell death protein 1 (PD-1) receptor or PD-2 receptor with longer response duration and acceptable toxicity. However, the response rate of ICIs is suboptimal, and only a few patients ultimately benefit from immunotherapy. So current efforts have focused on exploring new potential combinatorial strategies with synergistic antitumor activity. Here, we summarized the theoretical basis, current clinical data, and potential future perspective of immunotherapy combined with anti-angiogenic agents for advanced NSCLC.

Keywords: non-small cell lung cancer, immunotherapy, anti-angiogenic agents

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. It is often diagnosed at a late stage and has a poor prognosis.¹ The ability to induce angiogenesis is a key point in the development of cancer. The formation of new blood vessels can prevent tumors from being deprived of oxygen and nutrients, which is a typical feature of cancer cells.²⁻⁴ Hypoxia-driven vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis, which can stimulate the proangiogenic signaling pathway by binding to the VEGF receptor 2 (VEGFR2).⁵⁻⁷ Various drugs targeting this pathway have been developed for advanced NSCLC. In general, there are two types: monoclonal antibodies (mAbs) targeting VEGF (bevacizumab) or VEGFR

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(ramucirumab) or small molecule tyrosine kinase inhibitor (TKI) inhibiting multiple angiogenesis and proliferative pathway (nintedanib and erlotinib). Table 1 summarizes the results of landmark phase III trial of antiangiogenic agents in NSCLC. Immunotherapy targeting the T cell immune checkpoint receptor programmed cell death protein (PD-1) or its ligand PD-L1 has been approved by US Food and Drug Administration (FDA)/European Medicines Agency (EMA) for the treatment of patients with advanced NSCLC.^{8–18} The homeostasis of the immune response was based on the physiologic balance between costimulatory and inhibitory molecules, which are present on antigen-presenting cells and tumor cells and can interact with specific receptors on immune cells.¹⁹ The PD-1 pathway is a T cell inhibition pathway induced by PD-1 receptor on the T cell membrane binding on PD-L1 on tumor cells. Tumor cells can control this pathway by up-regulating PD-L1 expression and preventing T cell-mediated tumor destruction. Thus, PD-1/PD-L1 antagonist antibodies can activate antitumor T cells and eventually kill tumor cells. Currently, a variety of PD-1/PD-L1 mAbs are approved for the treatment of advanced NSCLC, including nivolumab, pembrolizumab, and atezolizumab. Table 2 summarizes the results of landmark phase III trial of ICIs in NSCLC. Immunotherapy has an improved efficacy, longer duration of response, and controlled toxicity compared with standard chemotherapy and has become one of the major new treatment options for patients with advanced NSCLC. However, only a few patients can benefit from this treatment; this is related to the restriction of useful biomarkers and the complexity and dynamic nature of the tumor microenvironment (TME).^{13,20}

Recently, the investigators are focused on the use of immunotherapy as a basic therapy in combination with other treatment strategies (such as radiotherapy, chemotherapy, and targeted drugs), which have been thought to increase tumor-related immunogenicity by inducing tumor cell death and new antigen release.^{21,22} Some evidence suggests that angiogenesis may be associated with immunosuppression in the TME, thereby enhancing the immune escape of tumor cells.²³ In this review, we outline the current data, ongoing trials, and challenges of immunotherapy plus antiangiogenic agents for the treatment of patients with advanced NSCLC.

Antiangiogenic agents

Bevacizumab

Bevacizumab is a fully humanized mAb and can block the interaction of VEGFR1 and VEGFR2, the major receptors

involved in endothelial cell proliferation and migration, by binding to VEGF-A and prevents interactions with VEGFR1 and VEGFR2, which are the major receptors involved in endothelial cell proliferation and migration.^{24–27} Phase III clinical trials (ECOG 4599) evaluated the efficacy of bevacizumab (Bev) in combination with carboplatin (C) and paclitaxel (P) as first-line treatment in patients with metastatic or recurrent NSCLC. The results showed that, in comparison with CP chemotherapy alone, the Bev + CP group significantly prolonged the progression-free survival (PFS) (6.2 months vs 4.5 months; hazards ratio [HR] 0.66; $P < 0.001$) and overall survival (OS) (12.3 months vs 10.3 months; HR 0.79; $P = 0.003$).^{27,28} In 2006, the US Food and Drug Administration (FDA) approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. The POINTBREAK trial compared the efficacy and safety of pemetrexed (Pem) plus carboplatin (C) plus bevacizumab (Bev) followed by pemetrexed plus bevacizumab (PemCBev) in patients with advanced NSCLC. Results showed that, compared with paclitaxel (Pac) plus carboplatin (C) plus bevacizumab (Bev) followed by bevacizumab (PacBev), PemCBev had superior median PFS (6.0 months vs 5.6 months; $P = 0.012$) but did not prove OS (12.6 months vs 13.4 months; $P = 0.949$) advantage.²⁹ The phase III AVAPERL trial evaluated the safety and efficacy of cisplatin plus pemetrexed plus bevacizumab followed by bevacizumab maintenance with or without pemetrexed in nonsquamous NSCLC. The results showed that patients allocated to BevPem maintenance had significantly improved PFS (7.4 months vs 3.7 months; HR 0.57; 95% confidence interval (CI) 0.44–0.75; $P < 0.0001$), whereas OS did not benefit from double-agent maintenance (17.1 months vs 13.2 months; HR 0.87; 95% CI 0.63–1.21; $P = 0.29$).³⁰ The phase III BEYOND trial³¹ confirmed the efficacy of first-line bevacizumab plus carboplatin/paclitaxel (PacC) in Chinese patients with advanced or recurrent non-squamous NSCLC who have not received previous chemotherapy. It is reported that both PFS (9.2 months vs 6.5 months; HR, 0.40; 95% CI, 0.29–0.54; $P < 0.001$) and OS (24.3 months vs 17.7 month; HR, 0.68; 95% CI 0.50–0.93; $P = 0.0154$) was prolonged with PacC + Bev versus PacC + Placebo. In summary, in the advanced non-squamous NSCLC, bevacizumab combined with CP can improve the therapeutic effect. Compared with paclitaxel, pemetrexed combined with platinum and bevacizumab did not demonstrate superior OS, and the combination with pemetrexed does not appear to improve the efficacy of bevacizumab maintenance therapy.

Table 1 Results of landmark phase III trials evaluating anti-angiogenic agents in metastatic non-small-cell lung cancer

Clinical Trial/ Phase	Patients	Treatment	No. of pts	ORR (%)	Median PFS (months)	HR (95% CI); P	Median OS (months)	HR (95% CI); P
ECOG4599	Previously untreated advanced, metastatic or recurrent NSCLC	CP+BeV CP and CP+BeV	434 444	35 15	6.2 4.5	HR=0.66 (0.57–0.77) P<0.001	12.3 10.3	HR=0.79 (0.67–0.92) P=0.003
NCT00762034 (POINTBREAK)	Previously untreated IIIB or IV nonsq-uamous NSCLC	PemCBev PacCBev	472 467	34 33	5 5.6	HR=0.83 (0.71–0.96) P=0.012	12.6 13.4	HR=1.0 (0.86–1.16) P=0.949
NCT00961415 (AVAPERL I)	inoperable, LA, metastatic or recurrent nonsquamous NSCLC	PemCisBev→PemBev PemCisBev→Bev	128 125	–	7.4 3.7	HR=0.57 (0.44–0.75) P<0.0001	17.1 13.3	HR=0.87 (0.63–1.21) P=0.29
NCT01364012 (BEYOND)	Previously Naive-palliative chemotherapy recurrent or advanced nonsquamous NSCLC	PacC+Bev PacC+Placebo	138 138	54 26	9.2 6.5	HR=0.40 (0.29–0.54) P<0.001	24.3 17.7	HR=0.68 (0.50–0.93) P=0.0154
NCT01168973 (REVEL)	stage IV NSCLC after platinum-based therapy	Doc+Ram Doc+Placebo	628 625	23 14	4.5 3.0	HR=0.76 (0.68–0.86) P<0.0001	10.5 9.1	HR=0.86 (0.75–0.98) P<0.023
NCT00805194 (LUME-lung 1)	advanced NSCLC previously treated with one line of platinum-based therapy	Doc+Nintedanib Doc	655 659	4.9 1.5	3.4 2.7	HR=0.79 (0.68–0.92) P=0.0019	10.1 9.1	HR=0.94 (0.83–1.05) P=0.2720
NCT00806819 (LUME-lung2)	Stage IIIB/IV or Recurrent NSCLC After failure of First Line Chemotherapy	Pem+Nintedanib Pem+Placebo	353 360	9.1 8.3	4.4 3.6	HR=0.83 (0.70–0.99) P=0.0435	12.0 12.7	HR=1.01 (0.85–1.21) P=0.8940
NCT02388919 (ALTER)	Stage IIIB/IV NSCLC after failure of at least two systematic chemotherapy	Anlotinib Placebo	296 143	9.2 0.7	5.4 1.4	HR=0.25 (0.19–0.31) P<0.001	9.6 6.3	HR=0.68 (0.54–0.87) P=0.002

Abbreviations: LA, locally advanced; pts, patients; CP, carboplatin and paclitaxel; BeV, bevacizumab; PemCBev, pemetrexed plus carboplatin plus bevacizumab followed by pemetrexed plus bevacizumab; PacC, paclitaxel plus carboplatin; PacCBev, paclitaxel plus carboplatin plus bevacizumab followed by bevacizumab; PemCisBev, pemetrexed plus cisplatin plus bevacizumab; PemBev, pemetrexed plus bevacizumab; Doc, Docetaxel; Ram, ramucicirumab.

Table 2 Results of landmark phase III trials evaluating Immune Checkpoint Inhibitors in metastatic non-small-cell lung cancer

Clinical Trial/ Phase	Patients	Line of treatment	Treatment	No. of pts	ORR (%)	Median PFS (months)	HR (95% CI); P	Median OS (months)	HR (95% CI); P
NCT01642004 (Checkmate017)	Metastatic squamous NSCLC	Second line	Nivolumab	135	20.0	3.5	HR=0.62 (0.47–0.81) P<0.001	9.2	HR=0.59 (0.43–0.81) P<0.001
			Docetaxel	137	8.8	2.8		6.0	
NCT01673867 (Checkmate057)	Metastatic nonsquamous NSCLC	Second or third line	Nivolumab	292	19.2	2.3	HR=0.92 (0.77–1.11) P=0.3932	12.2	HR=0.73 (0.59–0.89) P=0.002
			Docetaxel	290	12.4	4.2		9.4	
NCT 01905657 (KEYNOTE010)	Metastatic NSCLC with PD-L1 positive	More than second line	Pembrolizumab	344	18.0	3.9	HR=0.88 (0.73–1.04) P=0.06758;	10.4	HR=0.71 (0.58–0.88) P<0.001
			(2 mg/kg)	346	18.5	4.0		12.7	
			Pembrolizumab (10 mg/kg)	343	9.3	4.0	HR=0.79 (0.66–0.94) P<0.001;	8.5	HR=0.61 (0.49–0.75) P=0.00462
NCT 02142738 (KEYNOTE024)	Metastatic NSCLC with PD-L1 ≥50%	First line	Pembrolizumab	154	44.8	–	–	30.0	HR=0.63 (0.47–0.86) P=0.002
			SOC Chemotherapy	151	27.8		14.2		
NCT 02220894 (KEYNOTE042)	PD-L1 positive advanced or metastatic NSCLC	First line	Pembrolizumab ^a	299	39.5	7.1	HR=0.81 (0.67–0.99) P=0.0170;	20.0	HR=0.69 (0.56–0.85) P=0.0003
			SOC treatment ^a	300	32.0	6.4		12.2	
			Pembrolizumab ^b	413	33.4	6.2	HR=0.94 (0.80–1.11) P=0.2331;	17.7	HR=0.77 (0.64–0.92) P=0.0020
			SOC treatment ^b	405	28.9	6.6		13.0	
			Pembrolizumab ^c	637	27.3	5.4	HR=1.07 (0.94–1.21) P=0.8445;	16.7	HR=0.81 (0.71–0.93) P=0.0018
NCT 02775435 (KEYNOTE407)	Metastatic squamous NSCLC	First line	Pembrolizumab	278	57.9	6.4	HR=0.56 (0.45–0.70) P<0.001;	15.9 [#]	HR=0.64 (0.49–0.85) P=0.0008
			+PC PC	281	38.4	4.8		11.3	
NCT 02578680 (KEYNOTE189)	Metastatic non-squamous NSCLC	First line	Pembro+AC/AP	410	47.6	8.8	HR=0.52 (0.43–0.64) P<0.001	NA	HR=0.49 (0.38–0.64) P<0.001
			Placebo+AC/AP	206	18.9	4.9		11.3	
NCT 02008227 (OAK)	Pre-treated LA or metastatic NSCLC	Second or third line	Atezolizumab	612	13.6	2.8	HR=0.93 (0.81–1.08) P=0.3596	13.8	HR=0.73 (0.62–0.86) P<0.001
			Docetaxel	613	13.4	4.0		9.6	
NCT 02366143 (Ipower150)	Stage IV NSCLC	First line	ACP ^d	402	40.6	6.7	HR=0.91 (0.78–1.06) HR=0.59 (0.50–0.69)	19.4	HR=0.85 (0.71–1.03) HR=0.76 (0.63–0.93)
			ABC ^d	400	56.4	8.4		19.8	
			BCP ^d	400	40.2	6.8		14.9	

(Continued)

Table 2 (Continued).

Clinical Trial/ Phase	Patients	Line of treatment	Treatment	No. of pts	ORR (%)	Median PFS (months)	HR (95% CI); P	Median OS (months)	HR (95% CI); P
NCT 02367781 (Ipower130)	Metastatic non-squamous NSCLC	First line	Atezo+Nab- PacC Nab-PacC	483 240	-	7.0 5.5	HR=0.64 (0.54–0.77) P<0.001	18.6 13.9	HR=0.79 (0.64–0.98) P=0.0331
NCT 02367794 (Ipower131)	Stage IV squamous NSCLC	First line	Atezo+PacC Atezo+Nab- PacC Nab-PacC	338 343 340	-32 16	NR 6.3 5.6	HR=0.72 (0.60–0.85) P=0.0001	-14.0 13.9	HR=0.96 (0.78–1.18) P=0.6931
NCT 02657434 (Ipower132)	Stage IV non-squamous NSCLC	First line	Atezo+Cis/Car +Pem Cis/Car+Pem	292 286	47 32	7.6 5.2	HR=0.60 (0.49–0.72) P<0.0001	18.1 13.6	HR=0.81 (0.64–1.03) P=0.0797

Notes: #OS upper limit not reached; ^aPatients with PD-L1 Tumor Proportion Score \geq 50%; ^bPatients with Tumor Proportion Score \geq 20%; ^cPatients with Tumor Proportion Score \geq 1%; ^dIntention-to-treat population.

Abbreviations: SOC, standard of care; NA, median OS not reached; LA, locally advanced; ACP, Atezolizumab + Carboplatin + Paclitaxel; ABCP, Atezolizumab + Carboplatin + Paclitaxel; BCP, Bevacizumab + Carboplatin + Paclitaxel; PC, nab-paclitaxel or paclitaxel + carboplatin; Cis/Car, Cisplatin or Carboplatin; NR, not reached.

Ramucirumab

Ramucirumab is a human IgG1 mAb targeting VEGFR2. Phase III REVEL trial evaluated the efficacy and safety of docetaxel plus ramucirumab combination or docetaxel alone as a second-line treatment for patients with stage IV NSCLC. The results showed that the docetaxel plus ramucirumab combination slightly but statistically prolonged PFS (4.5 months vs 3.0 months; HR 0.76; 95% CI 0.68–0.86; $P<0.0001$) and OS (10.5 months vs 9.1 months; HR 0.86; 95% CI 0.75–0.98; $P=0.023$) compared with docetaxel alone. The treatment-related adverse event (AE) rate of the ramucirumab group and the control group was 98% (613/627) and 95% (594/618), respectively. There were no significant increase in thromboembolic events in the ramucirumab group, and hypertension and bleeding was generally mild.³² Based on this result, the FDA approved the use of ramucirumab in combination with docetaxel for patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy.

Nintedanib

Nintedanib is a triple vascular kinase inhibitor targeting VEGFR, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). The phase III LUME-Lung 1 trial assessed the efficacy and safety of docetaxel plus nintedanib as a second-line therapy for patients with advanced NSCLC previously treated with one line of platinum-based therapy. Results showed that docetaxel plus nintedanib significantly improved PFS (median 3.4 months vs 2.7 months; HR 0.79; 95% CI 0.68–0.92; $P=0.0019$) compared with the docetaxel plus placebo group, whereas it did not demonstrate OS advantage (median 10.1 months vs 9.1 months; HR 0.94; 95% CI 0.83–1.05; $P=0.2720$). However, OS was statistically improved in patients with all adenocarcinoma histology NSCLC (median 12.6 months vs 10.3 months; HR 0.83; 95% CI 0.70–0.99; $P=0.0359$) and with adenocarcinoma histology that progressed within 9 months after the start of first-line treatment (median 10.9 months vs 7.9 months; HR 0.75; 95% CI 0.60–0.92; $P=0.0073$) in the docetaxel plus nintedanib group.^{33,34} Phase III LUME-Lung 2 trial investigated the efficacy and safety of nintedanib plus pemetrexed in patients with pretreated nonsquamous NSCLC. Results suggested that nintedanib plus pemetrexed significantly improved PFS over pemetrexed alone (median 4.4 months vs 3.6 months; HR 0.83; 95% CI 0.70–0.99; $P=0.0435$), but there was no OS difference

between the two groups (median 12.0 months vs 12.7 months; HR 1.01; 95% CI 0.85–1.21; $P=0.8940$). The nintedanib plus pemetrexed group had a higher incidence of grade ≥ 3 elevated alanine aminotransferase, elevated aspartate aminotransferase, and diarrhea compared to the control group, but there was no difference in hypertension, bleeding, or thrombosis.³⁵ Based on these results, Europe approved nintedanib for the second-line treatment of NSCLC.

Anlotinib

Anlotinib is a novel multitarget TKI targeting receptor tyrosine kinases VEGF receptors 1 to 3, epidermal growth factor receptor (EGFR), FGFR 1 to 4, PDGFR α and β , and stem cell factor receptor.^{36–38} Phase III ALTER 0303 trial evaluated the efficacy and safety of anlotinib in patients with advanced NSCLC. Results showed that anlotinib can significantly prolong the OS (9.6 months vs 6.3 months; HR 0.68; 95% CI 0.54–0.87; $P=0.002$) and PFS (5.4 months vs 1.4 months; HR 0.25; 95% CI 0.19–0.31; $P<0.001$) over placebo, and it is well tolerated.³⁹ Based on these results, the CFDA approved anlotinib for the third-line treatment of advanced NSCLC.

Immune checkpoint inhibitors

Nivolumab

Nivolumab is a fully human IgG4 PD-1 ICI antibody that may restore antitumor immunity by affecting PD-1-mediated signaling.^{40–42} Checkmate 017 trial demonstrated that nivolumab statistically improved PFS (3.5 months vs 2.8 months; HR 0.62; 95% CI 0.47–0.81; $P<0.001$) and OS (9.2 months vs 6.0 months; HR 0.59; 95% CI 0.43–0.81; $P<0.001$) compared with docetaxel in previously treated advanced or metastatic squamous NSCLC.⁸ The checkmate 057 trial assessed the efficacy of nivolumab among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, and the results suggested that OS was longer with nivolumab than with docetaxel (12.2 months vs 9.4 months; HR 0.73; 95% CI 0.59–0.89; $P=0.002$) despite its failure to demonstrate PFS advantage (2.3 months vs 4.2 months; HR 0.92; 95% CI 0.77–1.11; $P=0.3932$).⁹ Based on the data of these two trials, the FDA and EMA have approved nivolumab as subsequent therapy for patients with metastatic squamous/nonsquamous cell NSCLC. The checkmate 078 trial evaluated the efficacy and safety of nivolumab for treatment in

previously treated advanced NSCLC in a predominantly East Asian population and demonstrated superior PFS (2.8 months vs 2.8 months; HR 0.77; 95% CI 0.62–0.95; $P=0.0147$) and OS (12.0 months vs 9.6 months; HR 0.68; 95% CI 0.52–0.90; $P=0.0006$) in the nivolumab group over the docetaxel group, which was consistent with checkmate 017 and checkmate 057 trials.¹¹

Pembrolizumab

Pembrolizumab is a human IgG4 mAb against PD-1. Keynote 010 assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced NSCLC. The results showed that pembrolizumab 2 mg/kg significantly improved OS compared with docetaxel (10.4 months vs 8.5 months; HR 0.71; 95% CI 0.58–0.88; $P=0.0008$), although it did not demonstrate any PFS difference (3.9 months vs 4.0 months; HR 0.88; 95% CI 0.74–1.05; $P=0.07$). Pembrolizumab 10 mg/kg statistically improved both OS (12.7 months vs 8.5 months; HR 0.61; 95% CI 0.49–0.75; $P<0.0001$) and PFS (4.0 months vs 4.0 months; HR 0.79; 95% CI 0.66–0.94; $P=0.004$). Grades 3–5 treatment-related AEs were less common in the pembrolizumab group than in the control group.¹² Keynote 024 found that in patients with advanced NSCLC with PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer PFS (10.3 months vs 6.0 months; HR 0.50; 95% CI 0.37–0.68; $P<0.001$) and longer OS (not reached in either group; HR 0.60; 95% CI 0.41–0.89; $P=0.005$) over platinum-based chemotherapy.¹³ Keynote 189 demonstrated that the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug significantly prolonged PFS (8.8 months vs 4.9 months; HR 0.52; 95% CI 0.43–0.64; $P<0.001$) and OS (not reached vs 11.3 months; HR 0.49; 95% CI 0.38–0.64; $P<0.001$) over chemotherapy alone in patients with first-line treatment metastatic nonsquamous NSCLC without anaplastic lymphoma kinase (ALK) rearrangements or EGFR mutations.¹⁴ Keynote 407 assessed the efficacy of pembrolizumab plus chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel in patients with previously untreated metastatic, squamous NSCLC. The results showed that patients in the pembrolizumab combination group had a superior PFS (6.4 months vs 4.8 months; HR 0.56; 95% CI 0.45–0.70; $P<0.001$) and OS (15.9 months vs 11.3 months; HR 0.64; 95% CI 0.49–0.85; $P=0.0008$) than chemotherapy alone.¹⁵ Keynote 042⁴³ suggested that pembrolizumab monotherapy significantly prolonged OS

in previously untreated locally advanced or metastatic patients with a PD-L1 tumor proportion score of 50% or greater (20.0 months vs 12.2 months; HR 0.69; 95% CI 0.56–0.85; $P=0.0003$), 20% or greater (17.7 months vs 13.0 months; HR 0.77; 95% CI 0.64–0.92; $P=0.002$), and 1% or greater (16.7 months vs 12.1 months; HR 0.81; 95% CI 0.71–0.93; $P=0.0018$). Based on the results of all these clinical trials, the FDA and EMA approved single-agent pembrolizumab as the first-line therapy for patients with advanced nonsquamous or squamous NSCLC and PD-L1 expression levels of 50% or more (based on keynote 024), approved pembrolizumab combined with a standard of chemotherapy as first-line therapy for patients with advanced nonsquamous or squamous NSCLC (based on keynote 189 and 407), and approved pembrolizumab as a subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression levels of 1% or more (based on Keynote 010).

Atezolizumab

Atezolizumab is a humanized antiprogrammed death-ligand 1 (PD-L1) mAb, reinvigorating anticancer immunity by inhibiting PD-L1 and PD-1 interactions. Phase III OAK trial assessed efficacy and safety of atezolizumab versus docetaxel in previously treated patients with metastatic NSCLC. The trial demonstrated that atezolizumab treatment significantly improved OS in comparison with docetaxel in previously treated NSCLC patients regardless of PD-L1 expression or histology and with acceptable toxicity (13.8 months vs 9.6 months; HR 0.73; 95% CI 0.62–0.87; $P=0.0003$).¹⁶ Based on the OAK trial result, the FDA and EMA approved atezolizumab as a subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC. IMpower130⁴⁴ showed a significant and clinically meaningful improvement in OS (18.6 months vs 13.9 months; HR 0.79; 95% CI 0.64–0.98; $P=0.0331$) and a significant improvement in PFS (7.0 months vs 5.5 months; HR 0.64; 95% CI 0.54–0.77; $P<0.001$) with atezolizumab plus nab-paclitaxel plus carboplatin versus nab-paclitaxel plus carboplatin as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no *ALK* or *EGFR* mutations. The interim analysis of the phase III IMpower131⁴⁵ study showed that the combination of carboplatin plus nab-paclitaxel with atezolizumab improved PFS, compared to carboplatin plus nab-paclitaxel alone in treatment-naïve patients with advanced squamous NSCLC (6.3 months vs 5.6 months; HR 0.72; 95% CI 0.60–0.85; $P=0.0001$).

Basic theories and preclinical studies of immunotherapy plus antiangiogenic agents in NSCLC

There is increasing evidence that suggests that the TME is closely related to the development and progression of cancer, and the key strategy for targeting TME is to inhibit angiogenesis and stimulate an effective immune response.^{2,46,47} Tumors are characterized by poorly organized, vascular abnormalities with altered permeability. Angiogenesis is essential for primary tumor growth and has a complex relationship with the immune system.^{23,48–54} The process of angiogenesis is promoted and influenced by inflammatory mediators such as cytokines and immune cells, which, in turn, can affect the immune microenvironment.⁵⁵ Antiangiogenic agents can stimulate the immune system, and immunotherapy can also be antiangiogenic.⁵⁶ When these two types of therapies are combined, they can act synergistically on the tumor. The feasibility and preclinical evidence of immunotherapy combined with antiangiogenic agents are discussed in detail in the following paragraphs.

The immunosuppressive microenvironment enables tumor cells to evade immune surveillance, and VEGF is a key mediator of the immunosuppressive microenvironment.²³ VEGF signaling can modulate the immune response by reducing tumor T cell infiltration and influencing systemic effects on immune regulatory cell function, thus reduce the antitumor response. The mechanism involves several key approaches. First, VEGF can induce the clustering defects at the endothelial cell surface by inhibiting the lymphocyte adhesion to activated endothelial cells, thereby inhibiting lymphocyte trafficking across endothelia to the tumor and blocking tumor infiltration of T cells.^{49,57} Second, VEGF can prevent T cell mobilization and T cell tumor infiltration by upregulating Fas ligand.⁵³ Third, VEGF can effectively induce and proliferate suppressive immune cells, including suppressor immune cell subsets such as regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs),^{50–52,57,58} inhibiting dendritic cell maturation^{23,51,52} and thymus differentiation, and/or T cell progenitor cells migrate from the thymus and eventually lead to systemic cancer-associated immunosuppressive status.^{51,54} Judicious dosing and administrative time of antiangiogenic agents can induce normalization of blood vessels by reducing the size and length of these abnormally dilated and tortuous vessels, decreasing hypoxia and vascular permeability, improving pericyte coverage, tumor perfusion, and blood flow, and promoting vessel maturation. This can decrease tumour interstitial fluid pressure, increase drug penetration in

tumors,^{59,60} and synergize with immunotherapy and chemotherapy.⁶¹ The normalization of blood vessels is also dose-dependent. Liang J et al⁶² suggested intermittent application of low-dose anti-angiogenic inhibitor treatment may help improve the effect of chemotherapy by reducing hypoxia-related treatment resistance and improving drug delivery. In addition, the normalization of blood vessels can also improve the perfusion and oxygenation of TME, and then increase tumor infiltration of immune cells.^{63–65} In NSCLC, anti-vascular therapy can mediate tumor metabolic changes through the LKB1/AMPK pathway and induce recruitment of macrophages and other specific bone marrow cells, thereby promoting tumor angiogenesis and tumor progression. The effect of this metabolism on the immune microenvironment is one of the potential mechanisms of immunotherapy combined with antiangiogenic therapy.^{66–70} Some preclinical evidence also suggests that immunotherapy combined with antiangiogenic agents can potentially improve the efficacy of patients with advanced NSCLC.^{57,71–74} For example, in an *in vivo* lung adenocarcinoma model, immunotherapy combined with bevacizumab synergistically inhibits tumor growth.⁷⁴ In the preclinical model of lung cancer, PD-L1 mAb combined with VEGFR2 small molecule inhibitor can significantly down-regulate the expression of PD-1 and PD-L1, increase TILs, and inhibit tumor growth by reducing Tregs and MDSCs.⁷⁵

Clinical trials of immunotherapy plus antiangiogenic agents in NSCLC

Based on the potential synergistic antitumor effects and preclinical evidence of immunotherapy combined with antiangiogenic drug therapy, several ongoing clinical trials are evaluating the efficacy and safety of this novel therapeutic combination in patients with NSCLC. Preliminary data suggest that this combination therapy is promising and well tolerated.^{76,77}

Phase III IMpower150 study evaluated the safety and efficacy of atezolizumab plus bevacizumab plus chemotherapy as first-line treatment in patients with metastatic nonsquamous NSCLC. The patients were randomly assigned (1:1:1) to receive atezolizumab plus carboplatin plus paclitaxel (ACPac) (n=402), bevacizumab plus carboplatin plus paclitaxel (BevCPac) (n=400), or atezolizumab plus BCP (ABevCPac) (n=400) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both until disease progression or unacceptable toxic effects. Atezolizumab was

administered at a dose of 1200 mg, bevacizumab at a dose of 15 mg/kg, paclitaxel at a dose of 200 mg/m² (175 mg/m² for Asian patients), and carboplatin at an area under the concentration–time curve of 6 mg/mL/min. The two primary end points were PFS and OS. The result showed that the ABevCPac group significantly improved PFS (8.4 months vs 6.8 months; HR 0.59; 95% CI 0.50–0.69) and OS (19.8 months vs 14.9 months; HR 0.76; 95% CI 0.63–0.93) compared with the BevCPac group in intention-to-treat population, regardless of PD-L1 expression status. The safety profile of ABevCPac was consistent with previously reported safety risks of the individual medicines.^{17,78}

Rizvi et al evaluated the safety and efficacy of switching to nivolumab maintenance therapy, as monotherapy or combined with bevacizumab. Patients with advanced NSCLC who did not progress within 42 days of completing more than four cycles first-line platinum-based chemotherapy (\pm bevacizumab) were assigned to nivolumab 5 mg/kg intravenously every 3 weeks + bevacizumab 15 mg/kg intravenously every 3 weeks (nonsquamous patients; n=12) or nivolumab 3 mg/kg intravenously every 2 weeks (squamous patients [n=8], nonsquamous patients [n=13]) until progression or the occurrence of unmanageable toxicity. The results showed that median PFS of patients treated with nivolumab + bevacizumab was 37.1 weeks and that PFS of patients treated with nivolumab monotherapy was 16 weeks in squamous NSCLC and 21.4 weeks in nonsquamous NSCLC. Median OS was not reached with nivolumab (range 33.3, 86.7+ weeks) or nivolumab monotherapy (range 2.1+, 56.3 + weeks). Objective response rate (ORR) of patients treated with nivolumab + bevacizumab was 8% (1/12, ongoing) and was 10% (2/21) in patients treated with nivolumab only. Any grade treatment-related AE rate in the nivolumab + bevacizumab group and in the nivolumab group were 92% (11/12) and 62% (13/21), respectively. No treatment-related grade 4 AEs were reported; Grade 3 AEs included pneumonitis, cough, and tubulointerstitial nephritis with nivolumab + bevacizumab and pneumonitis and pleural effusion with nivolumab. The toxicity was well tolerated.⁷⁷

A phase Ia study evaluated the safety and tolerability of adding ramucirumab to pembrolizumab in patients with various solid tumors including those with previously treated advanced NSCLC (n=27). The results showed that the objective response rate was 30% (1 unconfirmed). Responses occurred in both histologic subtypes and all

Table 3 Clinical trials of immune checkpoint inhibitors in combination with Antiangiogenic agents in advanced NSCLC

Clinical trial	Patients	Targeted Agent	Immunotherapy	Phase	Status
NCT01454102 (CheckMate 012)	<ul style="list-style-type: none"> Newly diagnosed and confirmed Stage IIIB/IV NSCLC 	bevacizumab	nivolumab	I	Active, not recruiting
NCT02574078 (CheckMate 370)	<ul style="list-style-type: none"> Histologically confirmed locally advanced or stage IV NSCLC 	bevacizumab	Nivolumab	I/III	Active, not recruiting
NCT02681549	Anti-PD-1/PD-L1-naïve biopsy proven metastatic melanoma or non-squamous NSCLC with at least one untreated brain metastasis	bevacizumab	Pembrolizumab	II	Recruiting
NCT02039674 (KEYNOTE- 021)	Newly diagnosed stage IIIB/IV NSCLC, progression > 1 year after adjuvant therapy for stages I-III A NSCLC and no systemic therapy for the recurrent disease	bevacizumab	Pembrolizumab	I/II	Active, not recruiting Has Results
NCT02366143 (Ipower 150)	<ul style="list-style-type: none"> Treatment-naïve Histologically or cytologically confirmed, stage IV non-squamous NSCLC 	bevacizumab	Atezolizumab	III	Active, not recruiting
NCT02856425 (PEMBIB)	Pretreated advanced solid tumors including LA/stage IV/locally recurrent NSCLC of adenocarcinoma and squamous	Nintedanib	Pembrolizumab	I	Suspended
NCT02443324	Metastatic or locally advanced, unresectable solid tumors including NSCLC progression after 0-3 prior lines of systemic therapy	Ramucirumab	Pembrolizumab	I	Active, not recruiting
NCT02572687	LA/unresectable/metastatic/unresectable solid tumors including pretreated NSCLC	Ramucirumab	Durvalumab	I	Active, not recruiting
NCT02174172	LA/metastatic solid tumors including LA/stage IV NSCLC, participants with sensitizing EGFR mutations or ALK rearrangements must have failed or are intolerant to prior treatment with EGFR or ALK inhibitors	bevacizumab	Atezolizumab	I	Active, not recruiting
NCT03786692	<ul style="list-style-type: none"> Stage IV NSCLC, Patients with targetable driver mutations (in EGFR, ALK, or ROS1) must have received prior treatments with one or more TKIs. 	bevacizumab	Atezolizumab	II	Not yet recruiting
NCT03169738	NSCLC with progression on or after treatment with PD-1/PD-L1 inhibitors	bevacizumab	Nivolumab	Ib/II	Not yet recruiting
NCT03836066	Locally Advanced or Metastatic High-intermediate Tumor Mutation Burden Selected Non-squamous NSCLC Patients	bevacizumab	Atezolizumab	II	Not yet recruiting
NCT03713944	Chemotherapy and Immunotherapy-naïve Patients With Stage IV Non-squamous NSCLC	bevacizumab	Atezolizumab	II	Recruiting
NCT03616691	Stage IIIB, IV or recurrent non-squamous cell NSCLC After Failure With Platinum-Containing Chemotherapy	bevacizumab	Atezolizumab	II	Not yet recruiting
NCT03647956	Stage IIIB or IV NSCLC Patients After Failure of EGFR-TKIs	bevacizumab	Atezolizumab	II	Recruiting

(Continued)

Table 3 (Continued).

Clinical trial	Patients	Targeted Agent	Immunotherapy	Phase	Status
NCT03786692	Stage IV NSCLC Patients Who Have Never Smoked or Have a Driver Mutation	bevacizumab	Atezolizumab	II	Not yet recruiting
NCT03735121	Pre-treated locally advanced or metastatic NSCLC	bevacizumab	Atezolizumab	Ib/II	Recruiting
NCT03527108	Pre-treated Recurrent, Advanced, Metastatic	Ramucirumab	Nivolumab	II	Not yet recruiting
NCT03689855 (RamAtezo-1)	NSCLC After Progression on Any Immune Checkpoint Blocker	Ramucirumab	Atezolizumab	II	Not yet recruiting
NCT03377023	Advanced/metastatic Non-Small Cell Lung Cancer (NSCLC) with no curative treatment options	Nintedanib	Nivolumab	I/II	Recruiting

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCL, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; LA, locally advanced.

PD-L1 groups. The disease control rate was 85%. Median PFS was not reached (95% CI 3.98 to NR). Twenty-two patients (81%) experienced a treatment-related AE, and it was well tolerated.⁷⁶ A single-center phase Ib study evaluated the tolerability, safety, and pharmacokinetics of nivolumab combined with different chemotherapy regimens in patients with advanced NSCLC, cohort C (6 patients) received a combination of nivolumab 10 mg/kg plus carboplatin target area under curve of 6.0 mg/mL/min plus paclitaxel 200 mg/m² plus bevacizumab 15 mg/kg every 3 weeks up to six cycles, followed by nivolumab 10 mg/kg plus bevacizumab 15 mg/kg every 3 weeks. The results showed that all six patients achieved partial response and that median PFS was not reached. Dose-limiting toxicity, treatment-related deaths, and nonhematologic AEs of grade 3 or worse were not observed. Hematologic AEs of grade 3 or worse were 100%. Select AEs (those with a potential immunologic cause) of any grade were 100%, and AEs leading to discontinuation of chemotherapy were 33.3%.⁷⁹

In general, the preliminary results showed an acceptable toxicity profile and encouraging antitumor activity of ICIs combined with antiangiogenic agents in patients with advanced NSCLC, but there are still many challenges to overcome in achieving combination therapy. Table 3 summarizes ongoing clinical trials evaluating antiangiogenic drug combination immunotherapy. We are expecting the further follow-up results.

Conclusion and future prospects

In this review, we reviewed the theoretical background and therapeutic potential of immunotherapy combined with antiangiogenic agents for the treatment of patients with advanced NSCLC, paying particular attention to potential treatment-related AEs resulting from combination therapy. However, our understanding of this new combination is just the tip of the iceberg, and many challenges remain to be addressed before it can be extended to clinical practice. More in-depth research is needed to explore which patients can benefit from this new combination, the optimal sequence and timing of immunotherapy in combination with anti-angiogenic agents, and the optimal dose for each drug.

Disclosure

The authors report no conflicts of interest in this work.

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