

# Progress of Immunotherapy Combined with Anti-Angiogenesis Therapy in Lung Cancer

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## Abstract

Lung cancer is the most prevalent and fatal cancer in China and even around the world, and many patients are found in the late stage of lung cancer. For the treatment of advanced lung cancer, in addition to traditional chemotherapy modalities, many emerging treatments are increasingly significant, such as immunotherapy, anti-angiogenic therapy, and targeted therapy. An increasing number of studies have now shown that anti-angiogenic therapy improves the immune microenvironment by enhancing tumor immunity through normalization of tumor vessels. Immunization combined with anti-angiogenic therapy can exert synergistic effects and improve the prognosis of patients. This article summarizes the extent of benefit, current clinical study data, and future prospects of immunotherapy combined with anti-angiogenic agents in the treatment of advanced NSCLC.

## Keywords

Immunotherapy, Anti-Angiogenic Therapy, Lung Cancer, Tumor Immune Microenvironment

## 1. Introduction

Lung cancer is one of the most common types of cancer in the world and has a high mortality rate [1] [2]. Due to the lack of early diagnostic indicators, more than 70% of cancer patients have presented with local invasion, lymph node and distant metastasis at the time of first diagnosis [3]. These patients have a very poor prognosis. Before the advent of immunotherapy, the five-year survival rate of patients at this stage was only about 10% [1], and the 5-year survival rate of advanced

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lung cancer doubled after the advent of immune checkpoint inhibitors. Immune checkpoint inhibitor therapy has become the first-line standard of care for advanced driver gene-free NSCLC (non-small cell lung cancer) [4]. Neovascularization is essential during tumor growth and metastasis and is associated with tumor immune escape. These abnormalities stem from increased expression of pro-angiogenic factors, which are involved in the regulation of immune cell function and migration. Anti-angiogenic drugs can normalize blood vessels, thereby changing the tumor microenvironment from immunosuppression to immune support by increasing the infiltration and activation of immune cells. Thus, combining immunotherapy with anti-angiogenesis is a promising strategy for cancer treatment.

## 2. Progress in Immunotherapy for Non-Small Cell Lung Cancer

In recent years, cancer immunotherapy has received much attention as a method to assist the immune system to recognize and eliminate cancer cells. Immune checkpoint inhibitor therapy has become the first-line standard of care for advanced driver gene-free NSCLC. ICP (immune checkpoint protein) are proteins produced by some immune cells (e.g. T cells) and cancer cells, and their discovery is an unprecedented moment in the history of immunotherapy. Under normal physiological conditions, ICP binds to its companion protein (receptor-ligand interaction), activates inhibitory signals, turns off T-cell responses, and thus prevents indiscriminate attacks on healthy cells. They are essential for self-tolerance, normal regulation of the immune system, and immune stasis. Tumor cells use this critical regulatory process to function and express ICP protein to evade immune cell-mediated tumor cell death. Therefore, the use of immune checkpoint inhibitors can bring clinical benefits to cancer patients. Among them, PD-1 and CTLA-4 are the most studied ICP. Among them, immune checkpoint inhibitors targeting PD-1 (programmed death receptor 1)/PD-L1 (programmed death receptor-ligand 1) and CTLA-4 (cytotoxic T lymphocyte-associated protein 4) reactivate anti-tumor immune responses through co-inhibitory T cell signaling, thereby achieving anti-tumor effects [5] [6].

In advanced non-small cell lung cancer, immunotherapy has shown good anti-tumor effect from posterior-line therapy to first-line therapy, from advanced tumors to early-intermediate tumors, arriving at survival benefits for patients and rewriting the treatment guidelines for tumors. For example, pembrolizumab, as a PD-1 inhibitor, relieves the immunosuppression of tumor cells to T cells and restores tumor-specific T cell immune responses mainly by inhibiting the interaction between PD-1 and its ligands PD-L1 and PD-L2. In the early KEYNOTE-001 study [7], pembrolizumab was used to treat PD-L1-overexpressing non-small cell lung cancer with a median response time of more than 12.5 months in the second-line and above treatment groups, and pembrolizumab became the first PD-1 inhibitor to be marketed in the United States. With the deepening of clinical studies,

the role of pembrolizumab in the treatment of lung cancer has gradually risen. Based on the KEYNOTE-024 study [8], the efficacy of pembrolizumab alone and chemotherapy in metastatic NSCLC patients with high PD-L1 expression (TPS  $\geq$  50%) was compared. The 5-year OS rate in the pembrolizumab group was nearly doubled compared with the chemotherapy group (31.9% vs 16.3%), the median OS was 26.3 months vs 13.4 months, the 3-year PFS rate was 5 times that in the chemotherapy group (22.8% vs 4.1%), and the median PFS was 7.7 months vs 5.5 months, respectively. Based on the results of this study, the FDA (US Food and Drug Administration) approved pembrolizumab for first-line treatment of metastatic NSCLC patients with high PD-L1 expression [9]. The subsequent KEYNOTE-042 [10] continuation study evaluated the efficacy of first-line pembrolizumab in NSCLC patients with different PD-L1 expression levels. The results of their study showed that the survival benefit was still reflected in the immunotherapy-alone group, and this study further determined the use of pembrolizumab in its first-line treatment. The efficacy of pembrolizumab in combination with chemotherapy in the first-line treatment of patients with stage IV squamous NSCLC was assessed in the subsequent KEYNOTE-407 study [11], a phase III clinical study. Their study results showed a median OS of 17.2 months in the pembrolizumab plus chemotherapy arm and 11.6 months in the placebo plus chemotherapy arm. The 5-year OS rates were 18.4% and 9.7%, respectively. The median OS in the combination arm was significantly better than in the chemotherapy-alone arm, further expanding the use of pembrolizumab in first-line therapy. Later, with the disclosure of KEYNOTE-189 and KEYNOTE-407 data, it was further shown that chemotherapy combined with pembrolizumab treatment could benefit patients with advanced non-small cell lung cancer regardless of PD-L1 expression, and the survival benefit was more pronounced in patients with higher PD-L1 expression, further expanding the scope of the benefit population [11] [12]. Pembrolizumab clearly reflects that immunotherapy plays an increasingly important role in the treatment of patients with clinical tumors from posterior-line therapy to first-line therapy. Compared with the pre-immunotherapy era, the 5-year survival rate of NSCLC was only about 5%, while the use of immunosuppressive agents increased the 5-year survival rate of advanced NSCLC to 31%, even in patients who failed previous platinum-based therapy, the 5-year survival rate reached 15.5%.

With the development of immunotherapy, many different immunosuppressive agents have emerged in clinical use and have expressed good survival benefits. Ipilimumab is a fully humanized mAb capable of inhibiting CTLA-4, thereby allowing CTL activity to function and maintaining immune responses primarily by depleting regulatory T cells (Tregs) displaying high levels of CTLA-4 expression. A preliminary Phase II study (CA184-041) demonstrated that ipilimumab in combination with chemotherapy increased immune-related progression-free survival (irPFS) without significantly increasing toxicity compared to chemotherapy alone in metastatic Stage IIIB/IV NSCLC [13] [14]. CTLA-4 pathway inhibitors increase

infiltration of tumor-specific T cells, whereas PD-L1/PD-1 inhibitors act by preventing inhibition of T cell function [6]. Navolumab is a specific PD-1 inhibitor, and CheckMate 277 [15] evaluates the efficacy of Navolumab or Navolumab combined with ipilimumab, or Navolumab combined with platinum-based dual-agent chemotherapy versus platinum-based dual agent chemotherapy in the treatment of PD-L1 undetermined previously untreated NSCLC. The results showed that regardless of PD-L1 expression, the combination of nivolumab and ipilimumab had a positive outcome in terms of overall survival compared to the chemotherapy group. The CheckMate 9LA study showed a significant improvement in OS in patients with advanced NSCLC after nivolumab and ipilimumab combined with two cycles of chemotherapy [16] [17]. CheckMate 227 and CheckMate 9LA used chemotherapy-free immunotherapy and improved overall OS regardless of PD-L1 status.

### 3. Research Progress of Anti-Angiogenesis in Non-Small Cell Lung Cancer

Vascular endothelial growth factor mainly contains six major members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and PlGF (placental growth factor) [18], and its receptors include VEGFR 1 - 3, of which VEGFR2 plays a dominant role in angiogenesis and mitosis. Inhibition of angiogenesis is achieved mainly through the MAPK (mitogen-activated protein kinase) pathway, PI3K-Akt/PKB pathway, and Ca<sup>2+</sup>-phospholipid-dependent kinase pathway [19] [20]. The signaling cascade mediated by the binding of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 can control the proliferation, survival and migration of vascular endothelial cells, and then change the permeability of blood vessels, ultimately causing the formation of new blood vessels to be inhibited, while new blood vessels are necessary during tumor growth and metastasis, new blood vessels provide nutrients for tumor growth, and excrete tumor metabolites through blood circulation, and then control tumor growth and metastasis [20] [21]. Anti-angiogenic agents can effectively inhibit tumor growth and prevent metastasis.

Since 2006, the US Food and Drug Administration has approved the use of bevacizumab for patients with unresectable, locally advanced, locally recurrent, and metastatic non-squamous NSCLC, opening a new chapter in anti-angiogenic agents [22]. The ECOG4599 study [23] is the first large phase III clinical study to demonstrate the efficacy of anti-angiogenic agents combined with chemotherapy in the treatment of lung cancer. Adding bevacizumab to standard platinum-based dual agent chemotherapy can improve the median overall survival (OS) of advanced lung squamous cell carcinoma non-small cell lung cancer by 12.3 months vs 10.3 months, the median progression-free survival (PFS) by 6.2 months vs 4.5 months, and increase the objective response rate (ORR) by 35% vs 15%. This finding is further supported by the subsequent AVAIL study in Europe. For Chinese patients with advanced non-small cell lung cancer, BEYOND [24] research shows

that PFS has been extended to 9.2 months and OS time has reached 24.3 months for the first time, which indicates that chemotherapy combined with bevacizumab has better benefits in Chinese people. With a better understanding of the tumor microenvironment and molecular targeted therapy, the combination strategy of bevacizumab and EGFR-TKI has begun to be explored, such as the ARTEMIS (CTONG1509) study [25], which showed that bevacizumab combined with erlotinib significantly prolonged progression-free survival compared with erlotinib monotherapy, with a mPFS of 17.9 months versus 11.2 months. Patients with L858R point mutations in exon 21 and patients with brain metastases were suggested to benefit more from bevacizumab combined with erlotinib.

With the gradual study of subsequent anti-vascular therapy, a large number of anti-angiogenic drugs began to be used in clinical treatment. In ALTER0302 [26], a phase 2 randomized trial of third-line or more anlotinib in recurrent or progressive NSCLC, patients treated with anlotinib had a significant benefit in PFS of 4.83 months vs 1.23 months compared with placebo. In the subsequent phase 3 clinical trial ALTER0303 [27], compared with placebo treatment, the application of anlotinib resulted in PFS of 5.37 months vs 1.40 months and OS of 9.63 months vs 6.30 months. Subgroup analysis revealed that patients with EGFR mutations had a greater improvement in OS compared with patients with wild-type epidermal growth factor receptor (EGFR) [28]. Based on the above findings, anlotinib was approved by the National Medical Products Administration (NMPA) for the third-line treatment of patients with advanced NSCLC on May 8, 2018. In the REVEL study [28], the efficacy of ramucirumab in advanced non-small cell lung cancer was assessed, and the median survival OS was 11.2 months vs 9.8 months in patients with lung adenocarcinoma treated with ramucirumab plus docetaxel versus docetaxel alone; in patients with lung squamous cell carcinoma, the OS was 9.5 months vs 8.2 months in the ramucirumab plus docetaxel group, with a particularly significant benefit. Based on this study, the US FDA approved ramucirumab for the treatment of advanced non-small cell lung cancer on December 12, 2014. In addition, the FDA approved ramucirumab in combination with erlotinib for first-line treatment of metastatic non-small cell lung cancer with EGFR mutations [29].

Anti-angiogenesis also plays an important role in maintenance therapy after treatment. In a meta-analysis [30], randomized controlled studies comparing bevacizumab plus pemetrexed with bevacizumab or pemetrexed maintenance alone showed that bevacizumab plus pemetrexed significantly improved PFS and reduced the risk of disease progression by 26% compared with maintenance alone. Combined maintenance regimens also significantly improved OS, reducing the risk of death by 9%. The ECOG5508 study [31] showed better PFS in the combination arm compared with the single-agent maintenance arm, but no significant advantage in OS was demonstrated. Anti-angiogenic therapy from posterior-line therapy to first-line therapy plays an important role in lung cancer treatment and significantly prolongs patient survival. Future studies will continue to explore optimal combination

regimens and individualized treatment strategies.

#### 4. Progress of Immunotherapy Combined with Anti-Angiogenesis Therapy for Non-Small Cell Lung Cancer

The efficacy of immunotherapy varies widely in different patients and has been shown to be possibly related to the heterogeneity of immune cell infiltration in TME (tumor microenvironment) [32]. For most solid tumors, aberrant tumor angiogenesis impacts immune cell infiltration and function in the TME in multiple ways, leading to immunosuppressive microenvironments. New tumor vessels have abnormal morphology and structure, loose connections between adjacent endothelial cells, resulting in easy leakage of blood vessels [33], and high levels of VEGF can block the expression of vascular endothelial cell adhesion molecules, thereby reducing the adhesion and infiltration of immune cells in TME [34]; while abnormal tumor vascular perfusion ability is impaired, further leading to aggravated TME hypoxia, so that the function of tumor-infiltrating lymphocytes is damaged [35]-[38]. Anti-angiogenic drugs can improve immune cell infiltration through a variety of ways, reverse the immunosuppressive state of TME, and then synergistically enhance the efficacy of ICI (immune checkpoint inhibitors) [39] [40]. Reasonable dosage and administration time of anti-angiogenic drugs can induce normalization of tumor vessels by inhibiting the abnormal generation of tumor vessels [41], improving the coverage rate of vascular pericytes and promoting vascular maturation, and normal vascular network can directly promote the adhesion and infiltration of immune cells. The recovery of vascular perfusion capacity can alleviate TME hypoxia and reduce the secretion of VEGF, thereby reducing the recruitment of immunosuppressive cells such as bone marrow-derived suppressor cells and regulatory T cells [35], and can induce tumor-associated macrophages to polarize into an immune-supported M1-like phenotype [37], and can also reduce the expression of immune checkpoint molecules such as PD-L1, CTLA-4, and T cell immunoglobulin domain and mucin domain-3 (TIM-3) on the surface of immunosuppressive cells and reduce the secretion of immunosuppressive factors such as VEGF, transforming growth factor- $\beta$  (TGF- $\beta$ ), and interleukin 10 (IL-10) [40], and then restore the activation and function of immune cells. Anti-angiogenic agents can also promote immune cell maturation and improve infiltration by blocking VEGF binding to VEGFR-2 on the surface of macrophages and T cells [42]-[44]. At the same time, ICI can not only regulate the immune microenvironment, but also inhibit abnormal tumor angiogenesis. ICI plays a role in anti-tumor abnormal angiogenesis and promoting vascular normalization by activating immune effector cells, and secreting anti-tumor cytokines such as INF- $\gamma$ , CXCL9, CXCL10 and TNF by activated CD4+ T cells, CD8+ T cells, and Th1 cells [45] [46].

In summary, anti-angiogenic drugs can improve the immune cell infiltration status in TME, thereby synergizing the efficacy of ICI; while ICI can not only activate immune cells, but also further promote vascular normalization and TME

remodeling, ultimately contributing to long-term tumor control. Theoretically, the combination of anti-angiogenic therapy and ICI therapy creates a positive feedback loop between vascular normalization and immune remodeling, providing support for the combined use of the two in clinical practice.

The IMpower150 study (NCT02366143) [47] is the first phase III clinical study to investigate the statistical benefits of progression-free survival (PFS) and overall survival (OS) in the first-line treatment of advanced NSCLC with anti-angiogenic drugs combined with ICI. In this study, a four-drug combination regimen of bevacizumab plus atezolizumab in addition to paclitaxel plus carboplatin chemotherapy showed a significant benefit in PFS and OS in the ABCP group compared with the BCP group, with a median PFS of 8.3 months vs 6.8 months and a median OS of 19.5 months vs 14.7 months. Advanced NSCLC patients with different levels of effector T cell gene expression profiles, PD-L1 expression levels, EGFR mutation positivity, and liver metastasis also benefited to varying degrees in the ABCP group compared to the BCP group. In terms of safety, there was no significant difference in the overall incidence of treatment-related adverse reactions between the two groups, and no new adverse events occurred, which was similar to the previously reported safety. Based on the study results of IMpower150, ABCP four-drug combination regimen has become the first-line treatment recommendation for non-squamous NSCLC in the National Comprehensive Cancer Network guidelines and is expected to be the mainstream treatment regimen in the future, demonstrating that anti-angiogenic drugs combined with ICI have a good application prospect in advanced NSCLC. In the JVDF study (NCT02443324) [48], first-line ramucirumab was assessed in combination with pembrolizumab. Their results showed an overall ORR of 42.3%, a disease control rate (DCR) of 84.6%, and a median PFS of 9.3 months. In the stratified analysis, the efficacy was better in the population with high PD-L1 expression (TPS  $\geq$  50%) than in the population with low PD-L1 expression (TPS 1% - 49%), with ORR of 56.3% and 22.2%, respectively, and median PFS of not reached and 4.2 months, respectively. Overall, safety was good. The JVDF study still showed clinical advantages of anti-angiogenesis combined with immunotherapy.

In terms of exploring the efficacy and safety of the originator multi-target anti-angiogenic small molecule TKI combined with ICI in the treatment of advanced NSCLC in China, a phase I study on the efficacy and safety of nintedanib combined with anlotinib as first-line treatment for advanced NSCLC (NCT03628521) [49]. The results showed that at a median follow-up time of 15.8 months, the objective response rate was 72.7% (16/22 patients), the disease control rate was 100%, the median PFS was 15 months, and the 12-month PFS rate was 71.4%. In subgroup analysis, the ORR benefit of Sintilimab combined with Anlotinib was independent of PD-L1 expression level. This is the first study to evaluate anti-angiogenic TKIs, a PD1 inhibitor, for first-line treatment of advanced non-small cell lung cancer. With prolonged follow-up, Sintilimab combined with Anlotinib showed durable efficacy and safety. Based on this study, to further explore the efficacy and

safety of Sintilimab combined with Anlotinib in the treatment of treatment-naïve metastatic NSCLC, Professor Chu's team in China initiated the SUNRISE study [50]. By July 15, 2022, a total of 89 patients were enrolled, with a median follow-up time of 13.1 months. The objective response rate (ORR) was 50% in the Sintilimab combined with Anlotinib group and 32.6% in the chemotherapy group. The median progression-free survival (PFS) was 10.8 months in the Sintilimab combined with Anlotinib group and 5.7 months in the chemotherapy group. And regardless of PD-L1 expression, there was a benefit in the Sintilimab plus Anlotinib arm. In the future, first-line treatment of advanced driver gene-negative non-small cell lung cancer, for lung cancer patients who are not suitable for chemotherapy, or cannot tolerate platinum-based chemotherapy for a long time or have scruples about chemotherapy, in addition to the current treatment standards, immunization combined with anti-angiogenic drugs is expected to be a very good treatment strategy. In summary, clinical studies have confirmed that immunization combined with anti-angiogenic drugs has a synergistic effect, and this new combination has potential efficacy in patients with extensive stage NSCLC, regardless of PD-1 expression (Table 1).

**Table 1.** Clinical study and latest progress of immune combined with anti-angiogenic drugs in first-line advanced non-small cell lung cancer.

Clinical Study	Investigational drug	PFS (Month)
Sunrise [50]	Anlotinib + Sintilimab	10.8
NCT04203485	Apatinib + Carisovizumab	In Progress
NCT04346381 [51]	Famitinib + Carisovizumab	16.6
AK104-208	Anlotinib + Carditumumab	In Progress

Both in the first line and posterior lines, the combination regimen has good anti-tumor activity and clinical application prospects, and the overall safety is good. The organic combination of immunotherapy with anti-angiogenic therapy promises to provide new therapeutic options for patients with advanced NSCLC. In the study protocol design, most studies involve the combination of chemotherapy in addition to anti-angiogenic drugs combined with ICI, while the combination chemotherapy is bound to increase toxicity, and whether the treatment mode of anti-angiogenic drugs combined with ICI and "chemotherapy removal" alone can be the goal and direction of future exploration in advanced NSCLC.

## 5. Limitations of Immunization Combined with Anti-Angiogenic Therapy

The most common side effect of immunosuppressant use is causing immune-related adverse events, in which immune homeostasis disturbances lead to immune-related damage to normal tissues (e.g. respiratory system, skin, gastrointestinal tract, and liver system) [52]. At present, there are still many problems in the treatment of anti-angiogenic drugs: 1) There is a lack of accurate biological markers and it is not certain that those populations can benefit after use. For example,

immunological drugs can detect the expression of PD-L1/PD-1; molecular targeted drugs can detect EGFR, ALK, VEGFR, mTOR, etc. 2) The emergence of resistance problems, which may be related to compensatory activation of other signaling pathways by tumor cells. 3) Cannot determine the exact medication time window. Studies have shown that after the use of anti-angiogenic drugs, there will be a special time period, and the blood vessels of tumor cells will appear transient normalization, thereby promoting the elimination of immunosuppressive tumor microenvironment, thereby reducing the dose of ICIs, thereby improving the efficacy and reducing toxicity [53]. Therefore, there is an urgent need to optimize the dose, duration, and sequence of administration of anti-angiogenic agents prior to their combination with ICI to prolong patient survival.

## 6. Conclusion

A series of preclinical studies have shown that anti-angiogenic drugs and ICIs have synergistic anti-tumor effects and have become the focus of current research. On the one hand, anti-angiogenic drugs can reverse the immunosuppressive state of TME and enhance the efficacy of ICI through immune reprogramming, and on the other hand, ICI can restore the immune support microenvironment, promote vascular normalization, and enhance the efficacy of anti-angiogenic drugs. According to the current clinical study data, anti-angiogenic drugs combined with ICI are expected to improve the clinical benefit and prognosis of patients with advanced NSCLC, and the safety is tolerable. It is also the direction of future research to explore better drug combination regimens, optimize the dose and time and order of drug use, and find relevant biomarkers to predict efficacy to screen the corresponding dominant population. In summary, anti-angiogenic drugs combined with ICI have a good application prospect in the treatment of patients with advanced NSCLC and improving the prognosis of patients. There is also the problem of maintaining a short “period of vascular normalization”, as well as the lack of markers and criteria to represent and predict vascular normalization. This treatment strategy still faces certain tests and challenges.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018) Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **68**, 394-424. <https://doi.org/10.3322/caac.21492>
- [2] Siegel, R.L., Miller, K.D. and Jemal, A. (2020) Cancer Statistics, 2020. *CA: A Cancer Journal for Clinicians*, **70**, 7-30. <https://doi.org/10.3322/caac.21590>
- [3] He, J., Li, N., Chen, W.Q., *et al.* (2021) Chinese Guidelines for Screening, Early Diagnosis and Early Treatment of Lung Cancer. *Chinese Journal of Oncology*, **43**, 243-268.
- [4] Yang, C., Yang, J.C. and Yang, P. (2020) Precision Management of Advanced Non-Small

- Cell Lung Cancer. *Annual Review of Medicine*, **71**, 117-136.  
<https://doi.org/10.1146/annurev-med-051718-013524>
- [5] Peggs, K.S., Quezada, S.A., Chambers, C.A., Korman, A.J. and Allison, J.P. (2009) Blockade of CTLA-4 on Both Effector and Regulatory T Cell Compartments Contributes to the Antitumor Activity of Anti-CTLA-4 Antibodies. *Journal of Experimental Medicine*, **206**, 1717-1725. <https://doi.org/10.1084/jem.20082492>
- [6] Lahiri, A., Maji, A., Potdar, P.D., Singh, N., Parikh, P., Bisht, B., et al. (2023) Lung Cancer Immunotherapy: Progress, Pitfalls, and Promises. *Molecular Cancer*, **22**, Article No. 40. <https://doi.org/10.1186/s12943-023-01740-y>
- [7] Garon, E.B., Rizvi, N.A., Hui, R., Leighl, N., Balmanoukian, A.S., Eder, J.P., et al. (2015) Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **372**, 2018-2028. <https://doi.org/10.1056/nejmoa1501824>
- [8] Reck, M., Rodríguez-Abreu, D., Robinson, A.G., Hui, R., Csósz, T., Fülöp, A., et al. (2019) Updated Analysis of KEYNOTE-024: Pembrolizumab versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score of 50% or Greater. *Journal of Clinical Oncology*, **37**, 537-546. <https://doi.org/10.1200/jco.18.00149>
- [9] Theelen, W.S.M.E. and Baas, P. (2019) Pembrolizumab Monotherapy for PD-L1  $\geq$  50% Non-Small Cell Lung Cancer, Undisputed First Choice? *Annals of Translational Medicine*, **7**, S140-S140. <https://doi.org/10.21037/atm.2019.06.35>
- [10] Mok, T.S.K., Wu, Y.L., Kudaba, I., et al. (2019) Pembrolizumab versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomized, Open-Label, Controlled, Phase 3 Trial. *The Lancet*, **393**, 1819-1830.
- [11] Novello, S., Kowalski, D.M., Luft, A., Gümüş, M., Vicente, D., Mazières, J., et al. (2023) Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. *Journal of Clinical Oncology*, **41**, 1999-2006. <https://doi.org/10.1200/jco.22.01990>
- [12] Cheng, Y., Zhang, L., Hu, J., Wang, D., Hu, C., Zhou, J., et al. (2021) Pembrolizumab Plus Chemotherapy for Chinese Patients with Metastatic Squamous NSCLC in Keynote-407. *JTO Clinical and Research Reports*, **2**, Article ID: 100225. <https://doi.org/10.1016/j.jtocrr.2021.100225>
- [13] Tomasini, P., Khobta, N., Greillier, L. and Barlesi, F. (2011) Ipilimumab: Its Potential in Non-Small Cell Lung Cancer. *Therapeutic Advances in Medical Oncology*, **4**, 43-50. <https://doi.org/10.1177/1758834011431718>
- [14] Lynch, T.J., Bondarenko, I., Luft, A., Serwatowski, P., Barlesi, F., Chacko, R., et al. (2012) Ipilimumab in Combination with Paclitaxel and Carboplatin as First-Line Treatment in Stage IIIB/IV Non-Small-Cell Lung Cancer: Results from a Randomized, Double-Blind, Multi-Center Phase II Study. *Journal of Clinical Oncology*, **30**, 2046-2054. <https://doi.org/10.1200/jco.2011.38.4032>
- [15] Hellmann, M.D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S., Carcereny Costa, E., et al. (2019) Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **381**, 2020-2031. <https://doi.org/10.1056/nejmoa1910231>
- [16] Deng, H. and Zhou, C. (2021) From Checkmate 227 to Checkmate 9LA: Rethinking the Status of Chemotherapy in the Immunotherapy Era—Chemo-Free or Chemo-Reform? *Translational Lung Cancer Research*, **10**, 1924-1927. <https://doi.org/10.21037/tlcr-21-179>
- [17] Paz-Ares, L., Ciuleanu, T., Cobo, M., Schenker, M., Zurawski, B., Menezes, J., et al.

- (2021) First-Line Nivolumab Plus Ipilimumab Combined with Two Cycles of Chemotherapy in Patients with Non-Small-Cell Lung Cancer (Checkmate 9LA): An International, Randomized, Open-Label, Phase 3 Trial. *The Lancet Oncology*, **22**, 198-211. [https://doi.org/10.1016/s1470-2045\(20\)30641-0](https://doi.org/10.1016/s1470-2045(20)30641-0)
- [18] Melincovici, C.S., Bosca, A.B., Susman, S., *et al.* (2018) Vascular Endothelial Growth Factor (VEGF)—Key Factor in Normal and Pathological Angiogenesis. *Romanian Journal of Morphology and Embryology*, **59**, 67-455.
- [19] Lee, S., Rauch, J. and Kolch, W. (2020) Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *International Journal of Molecular Sciences*, **21**, Article 1102. <https://doi.org/10.3390/ijms21031102>
- [20] Mabeta, P. and Steenkamp, V. (2022) The VEGF/VEGFR Axis Revisited: Implications for Cancer Therapy. *International Journal of Molecular Sciences*, **23**, Article 15585. <https://doi.org/10.3390/ijms232415585>
- [21] Ellis, L.M. (2004) Epidermal Growth Factor Receptor in Tumor Angiogenesis. *Hematology/Oncology Clinics of North America*, **18**, 1007-1021. <https://doi.org/10.1016/j.hoc.2004.06.002>
- [22] Gentzler, R.D., Yentz, S.E. and Patel, J.D. (2013) Bevacizumab in Advanced NSCLC: Chemotherapy Partners and Duration of Use. *Current Treatment Options in Oncology*, **14**, 595-609. <https://doi.org/10.1007/s11864-013-0255-3>
- [23] Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H., Dowlati, A., *et al.* (2006) Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **355**, 2542-2550. <https://doi.org/10.1056/nejmoa061884>
- [24] Zhou, C., Wu, Y., Chen, G., Liu, X., Zhu, Y., Lu, S., *et al.* (2015) BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients with Advanced or Recurrent Nonsquamous Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, **33**, 2197-2204. <https://doi.org/10.1200/jco.2014.59.4424>
- [25] Zhou, Q., Xu, C., Cheng, Y., Liu, Y., Chen, G., Cui, J., *et al.* (2021) Bevacizumab Plus Erlotinib in Chinese Patients with Untreated, *EGFR*-Mutated, Advanced NSCLC (ARTEMIS-CTONG1509): A Multicenter Phase 3 Study. *Cancer Cell*, **39**, 1279-1291.e3. <https://doi.org/10.1016/j.ccell.2021.07.005>
- [26] Han, B., Li, K., Zhao, Y., Li, B., Cheng, Y., Zhou, J., *et al.* (2018) Anlotinib as a Third-Line Therapy in Patients with Refractory Advanced Non-Small-Cell Lung Cancer: A Multicentre, Randomized Phase II Trial (ALTER0302). *British Journal of Cancer*, **118**, 654-661. <https://doi.org/10.1038/bjc.2017.478>
- [27] Han, B., Li, K., Wang, Q., Zhang, L., Shi, J., Wang, Z., *et al.* (2018) Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients with Advanced Non-Small Cell Lung Cancer. *JAMA Oncology*, **4**, 1569-1575. <https://doi.org/10.1001/jamaoncol.2018.3039>
- [28] Yamamoto, N., Seto, T., Nishio, M., Goto, K., Yamamoto, N., Okamoto, I., *et al.* (2021) Erlotinib Plus Bevacizumab vs Erlotinib Monotherapy as First-Line Treatment for Advanced *EGFR* Mutation-Positive Non-Squamous Non-Small-Cell Lung Cancer: Survival Follow-Up Results of the Randomized JO25567 Study. *Lung Cancer*, **151**, 20-24. <https://doi.org/10.1016/j.lungcan.2020.11.020>
- [29] Nakagawa, K., Garon, E.B., Seto, T., *et al.* (2019) Ramucirumab Plus Erlotinib in Patients with Untreated, *EGFR*-Mutated, Advanced Non-Small-Cell Lung Cancer (RELAY): A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial. *The Lancet Oncology*, **20**, 1655-1669.

- [30] Liu, M., Luo, N., Fang, Z., Liu, Q., *et al.* (2021) The Efficacy and Toxicity of Maintenance Therapy with Bevacizumab Plus Pemetrexed versus Bevacizumab/Pemetrexed Alone for Stage IIIB/IV Nonsquamous Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Pharmacy and Therapeutics*, **47**, 157-167. <https://doi.org/10.1111/jcpt.13534>
- [31] Ramalingam, S.S., Dahlberg, S.E., Belani, C.P., Saltzman, J.N., Pennell, N.A., Nambudiri, G.S., *et al.* (2019) Pemetrexed, Bevacizumab, or the Combination as Maintenance Therapy for Advanced Nonsquamous Non-Small-Cell Lung Cancer: ECOG-ACRIN 5508. *Journal of Clinical Oncology*, **37**, 2360-2367. <https://doi.org/10.1200/jco.19.01006>
- [32] Lim, A.R., Rathmell, W.K. and Rathmell, J.C. (2020) The Tumor Microenvironment as a Metabolic Barrier to Effector T Cells and Immunotherapy. *eLife*, **9**, e55185. <https://doi.org/10.7554/elife.55185>
- [33] Carmeliet, P. and Jain, R.K. (2000) Angiogenesis in Cancer and Other Diseases. *Nature*, **407**, 249-257. <https://doi.org/10.1038/35025220>
- [34] Griffioen, A.W. (2008) Anti-Angiogenesis: Making the Tumor Vulnerable to the Immune System. *Cancer Immunology, Immunotherapy*, **57**, 1553-1558. <https://doi.org/10.1007/s00262-008-0524-3>
- [35] Facciabene, A., Motz, G.T. and Coukos, G. (2012) T-Regulatory Cells: Key Players in Tumor Immune Escape and Angiogenesis. *Cancer Research*, **72**, 2162-2171. <https://doi.org/10.1158/0008-5472.can-11-3687>
- [36] Huber, V., Camisaschi, C., Berzi, A., Ferro, S., Lugini, L., Triulzi, T., *et al.* (2017) Cancer Acidity: An Ultimate Frontier of Tumor Immune Escape and a Novel Target of Immunomodulation. *Seminars in Cancer Biology*, **43**, 74-89. <https://doi.org/10.1016/j.semcancer.2017.03.001>
- [37] Wang, J., Li, D., Cang, H. and Guo, B. (2019) Crosstalk between Cancer and Immune Cells: Role of Tumor-Associated Macrophages in the Tumor Microenvironment. *Cancer Medicine*, **8**, 4709-4721. <https://doi.org/10.1002/cam4.2327>
- [38] Viallard, C. and Larrivée, B. (2017) Tumor Angiogenesis and Vascular Normalization: Alternative Therapeutic Targets. *Angiogenesis*, **20**, 409-426. <https://doi.org/10.1007/s10456-017-9562-9>
- [39] Liang, H. and Wang, M. (2019) Prospect of Immunotherapy Combined with Anti-Angiogenic Agents in Patients with Advanced Non-Small Cell Lung Cancer. *Cancer Management and Research*, **11**, 7707-7719.
- [40] Huang, Y., Kim, B.Y.S., Chan, C.K., Hahn, S.M., Weissman, I.L. and Jiang, W. (2018) Improving Immune-Vascular Crosstalk for Cancer Immunotherapy. *Nature Reviews Immunology*, **18**, 195-203. <https://doi.org/10.1038/nri.2017.145>
- [41] Huang, Y., Yuan, J., Righi, E., Kamoun, W.S., Ancukiewicz, M., Nezivar, J., *et al.* (2012) Vascular Normalizing Doses of Antiangiogenic Treatment Reprogram the Immunosuppressive Tumor Microenvironment and Enhance Immunotherapy. *Proceedings of the National Academy of Sciences*, **109**, 17561-17566. <https://doi.org/10.1073/pnas.1215397109>
- [42] Long, J., Hu, Z., Xue, H., Wang, Y., Chen, J., Tang, F., *et al.* (2019) Vascular Endothelial Growth Factor (VEGF) Impairs the Motility and Immune Function of Human Mature Dendritic Cells through the VEGF Receptor 2-RhoA-Cofilin1 Pathway. *Cancer Science*, **110**, 2357-2367. <https://doi.org/10.1111/cas.14091>
- [43] Palazon, A., Tyrakis, P.A., Macias, D., Veliça, P., Rundqvist, H., Fitzpatrick, S., *et al.* (2017) An Hif-1 $\alpha$ /VEGF-A Axis in Cytotoxic T Cells Regulates Tumor Progression. *Cancer Cell*, **32**, 669-683.e5. <https://doi.org/10.1016/j.ccell.2017.10.003>

- [44] Voron, T., Colussi, O., Marcheteau, E., Pernot, S., Nizard, M., Pointet, A., *et al.* (2015) VEGF-A Modulates Expression of Inhibitory Checkpoints on CD8+ T Cells in Tumors. *Journal of Experimental Medicine*, **212**, 139-148. <https://doi.org/10.1084/jem.20140559>
- [45] Tian, L., Goldstein, A., Wang, H., Ching Lo, H., Sun Kim, I., Welte, T., *et al.* (2017) Mutual Regulation of Tumour Vessel Normalization and Immunostimulatory Reprogramming. *Nature*, **544**, 250-254. <https://doi.org/10.1038/nature21724>
- [46] Kammertoens, T., Friese, C., Arina, A., Idel, C., Briesemeister, D., Rothe, M., *et al.* (2017) Tumour Ischaemia by Interferon- $\gamma$  Resembles Physiological Blood Vessel Regression. *Nature*, **545**, 98-102. <https://doi.org/10.1038/nature22311>
- [47] Reck, M., Mok, T.S.K., Nishio, M., Jotte, R.M., Cappuzzo, F., Orlandi, F., *et al.* (2019) Atezolizumab Plus Bevacizumab and Chemotherapy in Non-Small-Cell Lung Cancer (Impower150): Key Subgroup Analyses of Patients with EGFR Mutations or Baseline Liver Metastases in a Randomized, Open-Label Phase 3 Trial. *The Lancet Respiratory Medicine*, **7**, 387-401. [https://doi.org/10.1016/s2213-2600\(19\)30084-0](https://doi.org/10.1016/s2213-2600(19)30084-0)
- [48] Herbst, R., Arkenau, H., Bendell, J., Arrowsmith, E., Wermke, M., Soriano, A., *et al.* (2019) MA14.07 Phase I Expansion Cohort of Ramucirumab Plus Pembrolizumab in Advanced Treatment-Naïve Non-Small Cell Lung Cancer (JVDF). *Journal of Thoracic Oncology*, **14**, S307. <https://doi.org/10.1016/j.jtho.2019.08.615>
- [49] Han, B., Chu, T., Zhong, R., Zhong, H., Zhang, B., Zhang, W., *et al.* (2019) P1.04-02 Efficacy and Safety of Sintilimab with Anlotinib as First-Line Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC). *Journal of Thoracic Oncology*, **14**, S439. <https://doi.org/10.1016/j.jtho.2019.08.905>
- [50] Chu, T., Zhong, R., Zhong, H., Zhang, B., Zhang, W., Shi, C., *et al.* (2021) Phase 1b Study of Sintilimab Plus Anlotinib as First-Line Therapy in Patients with Advanced NSCLC. *Journal of Thoracic Oncology*, **16**, 643-652. <https://doi.org/10.1016/j.jtho.2020.11.026>
- [51] Ren, S., Wang, X., Han, B., Pan, Y., Zhao, J., Cheng, Y., *et al.* (2024) First-Line Treatment with Camrelizumab Plus Famitinib in Advanced or Metastatic NSCLC Patients with PD-L1 TPS  $\geq$  1%: Results from a Multicenter, Open-Label, Phase 2 Trial. *Journal for ImmunoTherapy of Cancer*, **12**, e007227. <https://doi.org/10.1136/jitc-2023-007227>
- [52] Kennedy, L.B. and Salama, A.K.S. (2020) A Review of Cancer Immunotherapy Toxicity. *CA: A Cancer Journal for Clinicians*, **70**, 86-104. <https://doi.org/10.3322/caac.21596>
- [53] Tu, J., Liang, H., Li, C., Huang, Y., Wang, Z., Chen, X., *et al.* (2023) The Application and Research Progress of Anti-Angiogenesis Therapy in Tumor Immunotherapy. *Frontiers in Immunology*, **14**, Article 1198972. <https://doi.org/10.3389/fimmu.2023.1198972>