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REVIEW

Immune Checkpoint Inhibitor Combined with Antiangiogenic Agent Synergistically Improving the Treatment Efficacy for Solid Tumors

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Abstract: In recent years, the combination of immune checkpoint inhibitors (ICIs) with antiangiogenic agents has led to significant breakthroughs in cancer treatment. Such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Antiangiogenic therapy plays a pivotal role in normalizing blood vessels and remodeling the tumor immune microenvironment while ICIs not only enhance the host's antitumor immune response by blocking negative regulatory signals but also promote vascular normalization. The communication between the vasculature and immune system enables the combined use of ICIs and antiangiogenic therapy to have a synergistic effect. Clinical research has also demonstrated that this combination therapy can significantly improve the efficacy and survival of patients with various solid tumors, the addition of pembrolizumab to axitinib can significantly improve PFS (15.4 m vs 11.1 m) compared to sunitinib in first-line treatments of advanced renal cell carcinoma (RCC). Bevacizumab is the first approved anti-VEGF monoclonal antibody. Bevacizumab in combination with atezolizumab obtain significant benefit in terms of PFS (6.9 m vs 4.3 m) compared to sorafenib in advanced hepatocellular carcinoma (HCC). In addition, a series of investigations have been conducted in other solid tumors, such as colorectal cancer (CRC). Future research directions include the development of novel antiangiogenic agents and ICIs, the exploration of other combination strategies (eg, with chemotherapy or targeted therapy), and the identification of biomarkers for patient selection and monitoring response to therapy. Additionally, more studies are needed to understand the optimal timing and sequencing of these therapies to maximize patient benefit. This review aims to elucidate the mechanisms of action of ICIs plus antiangiogenic drugs and provide summaries of related clinical trials. Meanwhile, we outline the current challenges faced and future directions, include the identification of biomarkers for patient selection and monitoring response to therapy, particularly highlighting the newer therapy strategies.

Keywords: immune checkpoint inhibitors, antiangiogenic agents, combination regimen, solid tumors

Introduction

According to data from the World Health Organization (WHO), cancer has become the second leading cause of death worldwide. This burden is particularly significant in low- and middle-income countries, where cancer mortality rates are higher. Through innovative treatment methods, there is potential to effectively alleviate the impact of tumors on global health, thereby enhancing both the quality of life and prognosis for patients. Since Folkman's proposal in 1971 that solid tumor growth and metastasis rely on angiogenesis,[1] there has been a surge of interest in antiangiogenic therapy research. As tumors exceed 2–3 mm in diameter, absence of oxygen and nutrients in the center stimulates the production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and angiogenin.[2,3] Overexpression of such pro-angiogenic factors disrupts the equilibrium between pro-angiogenic and antiangiogenic factors, ultimately resulting in the formation of new blood vessels. The rapid and disorganized growth of the tumor neovasculature forms an extensive supply system that facilitates uncontrolled tumor growth and invasiveness.[4] Angiogenesis inhibitors arrest this abnormal vessel formation by blocking active signaling

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pathways in the tumor microenvironment (TME), thereby depleting essential nutrients and oxygen supply to the tumor. Current antiangiogenic agents primarily consist of monoclonal antibodies targeting VEGF and tyrosine kinase inhibitors (TKIs) developed against multiple targets such as VEGFR, PDGFR, and FGFR. Bevacizumab, approved in 2004, was the first antiangiogenic agent to accurately target VEGF, inhibiting tumor vascularization.[5] Small molecule TKIs act on multiple targets and their associated downstream signaling pathways, effectively inhibiting tumor angiogenesis. However, malignant tumors inevitably develop resistance to angiogenesis inhibitors, resulting in poor efficacy when used as standalone treatments.[6,7]

The advent of immunotherapy, exemplified by immune checkpoint inhibitors (ICIs), has revolutionized the treatment paradigm for malignant tumors.[8] Cytotoxic T lymphocyte antigen-4 (CTLA-4) was the first reported immune checkpoint molecule implicated in the negative regulation of T cells. In the early stages of the immune response, CTLA-4 competes with CD28 for binding to the B7 molecule, thereby restricting the release of interleukin-2 (IL-2) and suppressing T-cell proliferation. Other pivotal immune checkpoints include programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1). PD-1, expressed on various immune cells, such as T cells, natural killer (NK) cells, and B cells, inhibits T-cell proliferation and decreases the secretion of IFN-γ, TNF-α, and IL-2 by interacting with its ligands in the advanced phases of the immune response. Ipilimumab, targeting CTLA-4, was the first approved ICI in 2011, significantly extending the median overall survival (mOS) for patients with advanced melanoma, achieving an mOS of 10.1 months.[9] The clinical efficacy of ipilimumab has inspired researchers to delve deeper into monoclonal antibodies targeting PD-1 and PD-L1. While ICIs can enhance the body's antitumor immune response by obstructing inhibitory pathways, their effectiveness shows notable discrepancies among various tumor types, with an overall objective response rate (ORR) of around 20% to 30% for monotherapy.

In the tumor microenvironment, the interactions among the immune microenvironment, angiogenesis, and the status of immune cells exhibit a highly dynamic and complex nature. The immune microenvironment has the capacity to regulate angiogenesis, while angiogenesis can, in turn, modify the state of immune cells. Additionally, immune-mediated responses can further impact the formation of blood vessels.[10] Antiangiogenic agents play a critical role in normalizing tumor vasculature, alleviating immunosuppressive states, and fostering the infiltration of immune effector cells.[11] The combination of antiangiogenic drug and ICI further enhances treatment efficacy for various solid tumors when compared with monotherapy, proving increasingly valuable in clinical applications. Some biomarkers that can predict the efficacy of ICI therapy have been identified. The expression level of PD-L1 is one of the most widely used predictive biomarkers for the efficacy of ICIs. High expression of PD-L1 on the surface of tumor cells is associated with a favorable response to ICI treatment in certain cancer patients. Other known predictive biomarkers for efficacy include TMB and MSI. Furthermore, anti-angiogenic therapy may exacerbate hypoxia in the tumor microenvironment. The combination approach may exhibit antagonistic effects, on the other hand, anti-angiogenic therapy may lead to an increase in immunosuppressive cells in the tumor microenvironment, such as regulatory T cells and myeloid-derived suppressor cells. These immunosuppressive cells can inhibit effective anti-tumor immune responses by releasing immunosuppressive factors such as TGF-β and IL-10, thereby reducing the efficacy of ICIs.[12] The potential economic impact of immunotherapy combined with anti-angiogenic treatment is complex; it may alleviate economic burdens by improving treatment outcomes and reducing the risk of recurrence, while also facing the challenge of high treatment costs. This article presents an extensive review of the ongoing research progress concerning the combination therapy of ICIs and antiangiogenic agents in tumors. It also aims to elucidate the mechanisms and provide a comprehensive summary of the latest developments in related clinical studies. By doing so, it endeavors to serve as a valuable reference for clinicians involved in the management for solid tumors.

The Mechanism of ICIs Combined with Antiangiogenic Therapy

Antiangiogenic agents are originally designed to block angiogenesis to suppress tumor growth by inhibiting the VEGF-VEGFR.[1] Besides VEGF-VEGFR, several antiangiogenic drugs are developed to inhibitor multiple targets related to angiogenic growth factor pathway.[13] The targets of angiogenesis inhibitors are summarized in Table 1. Antiangiogenic therapy shows a synergistic effect with ICIs due to induce immunostimulatory TME by promoting vascular normalization and relief of hypoxic. Furthermore, the combination approach could also be antagonistic in vivo as a result of

Table 1 Common Anti-Angiogenic Drugs and Their Targets

Anti-angiogenic Agents	Targets
Bevacizumab	VEGF
Ramucirumab	VEGF
Vanucizumab	VEGF, ANG
Apatinib	VEGFR
Cediranib	VEGFR
Vandetanib	VEGFR
Aflibercept	VEGFR
Elpamotide	VEGFR
Lenvatinib	VEGFR, FGFR
Surufatinib	VEGFR, FGFR
Sunitinib	VEGFR, PDGFR
Axitinib	VEGFR, PDGFR
Sorafenib	VEGFR, PDGFR
Regorafenib	VEGFR, FGFR, PDGFR
Nintedanib	VEGFR, FGFR, PDGFR
Anlotinib	VEGFR, FGFR, PDGFR

antiangiogenic drugs may lead to the increase infiltration both of immune effector and suppressive cells simultaneously and the reduce of drug penetration.[14]

Antiangiogenic Agents Enhance Dendritic Cells (DC) Presentation of Tumor Antigens

DCs are the primary antigen-presenting cells and play a crucial role in anti-tumor immune responses.[15] Tumor antigens are typically recognized by DCs and presented via major histocompatibility complex-II (MHC-II), initiating a process where DCs break down the antigen into smaller peptides that are presented on the surface in conjunction with MHC-II molecules, thereby activating T cells.[16] Due to the lack of expression of surface MHC-I, MHC-II, and co-stimulatory molecules, immature DCs fail to present tumor antigens to T cells, leading to T cell anergy. VEGF can bind to VEGFR on the surface of DCs, enhancing the expression of PD-1 in DCs, inhibiting DC development, and reducing the number of DCs.[17] Studies have found that blocking the VEGF signaling pathway can lead to an increased presence of mature DCs in a mouse glioma model.[18] The isoforms of VEGF which are generated by alternative splicing suppress DCs function through multiple dimensions,[19] including inhibition of DC maturation by VEGFR1,[20] weakening of DC migration by VEGFR,[21] and limitation of trafficking of DC to lymph nodes.[22] Therefore, antiangiogenic agents can alleviate the inhibitory effect of VEGF on DCs, thus enhancing antigen presentation by DCs, while the efficacy of ICI is dependent on the antigen presentation capabilities of DCs.[23]

Antiangiogenic Drugs Promote Lymphocyte Infiltration and TME

The mechanism of antiangiogenic combined ICIs is essentially immunomodulation.[24] One of the primary mechanisms by which tumors evade immune surveillance is the establishment of an immunosuppressive TME, typically characterized by diminished lymphocyte infiltration.

Lymphocytes are crucial cellular components of the immune response, with T cells playing a major role in anti-tumor immunity by directly killing tumor cells.[25] Tumor vasculature is generally abnormal in both structure and function. Persistent vascular abnormalities maintain a hypoxic state in the TME. This hypoxia promotes the expression of immunosuppressive factors such as VEGF (predominantly VEGFA), TGF-β and indoleamine 2,3-dioxygenase (IDO), which inhibit the activity of immune cells and promote the expression of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) recruitment.[26–28] Additional Tregs and MDSCs enhance the expression of VEGF in tumors,

which directly inhibits DC, NK cell, and T cell activity, thereby promoting immune tolerance.[29,30] The antiangiogenic agents that target VEGF have been demonstrated to normalize tumor vasculature. This normalization facilitates improved infiltration of cytotoxic T lymphocytes (CTLs) and other immune effector cells, while concurrently reducing the quantity and activity of Tregs and MDSCs.[31] Meanwhile, TKIs have been shown to reduce the population of suppressor immune cells in the TME, while simultaneously enhancing the infiltration of CD4+ and CD8+ T cells at the tumor site.[32] Effective tumor control depends on the ability of reactive T cells to infiltrate the tumor. In mouse models, it was found that VEGFR-A reduces the expression of adhesion molecules crucial for T cell infiltration on endothelial cells, and the abnormal structure and function of the tumor vasculature prevent T cell infiltration into solid tumors.[33] Meanwhile, various studies indicate that antiangiogenic therapies may facilitate the establishment of a more favorable immune microenvironment by modulating the expression of adhesion molecules and chemokines that regulate lymphocyte migration. Antiangiogenic therapy upregulates intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin on endothelial cells and promotes T-cell extravasation into the tumor.[34–37] Furthermore, in tumors with abnormal vasculature, VEGF prompts tumor-associated macrophages (TAMs) to transition to an immunosuppressive M2-like phenotype within tumor tissues and organs, thus facilitating tumor growth and immune evasion. Antiangiogenic therapy reprograms TAMs from an M2-like pro-tumorigenic state to an M1-like pro-inflammatory state.[38,39] This phenotypic transition improves antigen presentation and increases activation of T cells. Transforming the TME into a more immune-friendly state enhances the effectiveness of ICIs.

ICIs Promote the Normalization of Tumor Vessels

ICIs not only act to activate immune cells but also possess the capability to inhibit abnormal tumor angiogenesis.[40,41] Anti-PD-1/PD-L1 treatment can restore T cells from an exhausted state. Interferon-gamma (IFN-γ) secreted by the activated T cells could induce the recruitment of monocytes into the tumor microenvironment but inhibits the differentiation and VEGF-secreting ability of tumor-associated macrophages, thus suppressing tumor angiogenesis.[42] Besides, the direct engagement of IFNγR by IFN-γ could impair the proliferation and survival of endothelial cells by STAT signaling, leading to efficient and rapid tumor vessel regression.[43–45] Additionally, IFN-γ can induce the upregulation of multiple chemokines, including CXCL9, CXCL10, and CXCL11,[46,47] which promote T cell, NK cell, and NKT cell trafficking into the tumor microenvironment.[48,49] Well-established evidence proved that CXCL10 has anti-angiogenic effects on tumor blood vessels by blocking the proliferation of endothelial cells, leading to a decrease in vessel density in tumor tissue.[50,51] Similarly, CXCL9 is reported to be an angiogenesis factor that counter-regulates VEGF and prevents its binding to endothelial cells.[52,53]

Synergistic Effects of ICI Plus Antiangiogenic Treatments

Only 10–15% patients with cancer types considered response to ICIs could acquire clinical benefits from immune monotherapy.[54] Additionally, antiangiogenic agents cannot induce durable and deep response for patients unlike ICIs.[55] Previous studies revealed antiangiogenic drugs possess a 2–8 days of vascular normalization window.[56,57] This may make it difficult to maintain activity of cytotoxic agents frequently used in combination with antiangiogenic treatment, such as fluorouracil with a short half-life circulation, when the vascular normalization appears.[58] Nevertheless, ICIs could remain effective blood concentrations for weeks, and thus could better exploit the effectiveness with angiogenic inhibitors.[59]

Furthermore, ICIs plus angiogenic inhibitors may induce high endothelial venules (HEVs), which are associated with aiding anti-tumor immune response and favorable prognosis.[60] HEVs are specialized postcapillary venules commonly located in secondary lymphoid organs, and play a unique role in facilitating the migration of lymphocytes from the blood into lymph nodes.[61] Additionally, HEVs frequently result in the development of tertiary lymphoid structures, characterized by distinct areas rich in DCs, T cells and B cells, which are correlated with positive response to ICIs.[62] Co-administration of ICIs and antiangiogenic drugs is demonstrated resulting in the development of HEVs in mouse model of breast and pancreatic cancer, leading to decreased tumor growth and improved survival rates.[63]

In summary, antiangiogenic therapy normalizes tumor vasculature, contributing to the improvement of the tumor immune microenvironment. ICIs activate T lymphocytes to secrete IFN-γ, which in turn alleviates local hypoxia and

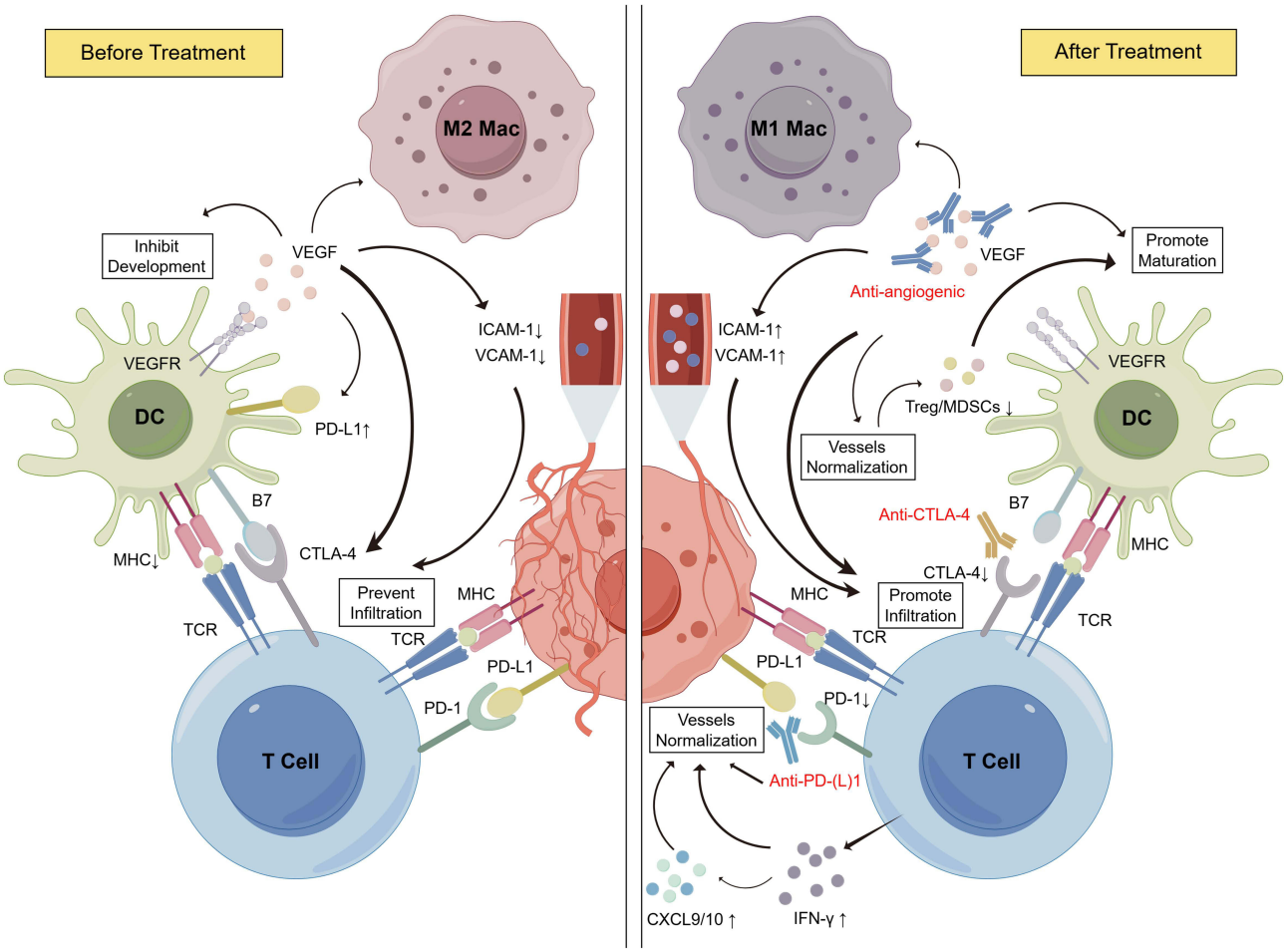

Figure 1 Mechanism of Enhanced Efficacy of ICI combined with antiangiogenesis treatment (by Figdraw).
Before Treatment: VEGF signaling through VEGFR facilitates the development of immunosuppressive cells, such as Treg and MDSCs. VEGF induces the down-regulation of endothelial cell adhesion molecules ICAM-1 and VCAM-1, leading to reduced T-cell infiltration in tumors. Additionally, increased expression of PD-L1 on both tumor cells and immune cells inhibits T cell activation by binding to PD-1. This interaction results in decreased TCR signaling and a reduction in the infiltration of effector T cells into the tumor.
After Treatment: Following the combined treatment, antiangiogenic agents help normalize tumor vasculature, reducing the accumulation of Tregs and MDSCs. Antiangiogenesis therapy upregulates ICAM-1, VCAM-1 on endothelial cells and promotes T-cell extravasation into the tumor. The blockade of CTLA-4 enhances T cell activation and infiltration, while anti-PD-L1 therapy mitigates the interactions between PD-1 and PD-L1, thereby promoting T cell responses. Furthermore, this treatment promotes the production of IFN-γ, which facilitates anti-tumor immunity and enhances therapeutic efficacy.

promotes the normalization of tumor blood vessels. The synergistic enhancement effect of ICIs combined with antiangiogenic agents provides a theoretical basis for their combined application in treating solid tumors (Figure 1).

Clinical Trials of the Antiangiogenesis and Anti-PD-(L)1 Combination Therapy

Renal Cell Carcinoma (RCC)

Renal cell carcinoma represents 3 to 5% of all malignant tumors, showing a rising trend in developed countries.[64] With the progress in the comprehension of RCC pathogenesis, VEGFR has been identified as a significant pathway in clear cell RCC (ccRCC) carcinogenesis. Consequently, since 2005, anti-VEGFR TKI emerged as the new standards of care for metastatic ccRCC (mccRCC).[65,66]

In recent years, the standard of care for mccRCC has undergone significant changes due to the emergence of ICIs, either as monotherapy or in combination with antiangiogenic agents.

Present findings suggest that combining antiangiogenic agents with ICIs can yield a synergistic effect, further enhancing antitumor efficacy in RCC (Table 2). The KEYNOTE-426 study is a randomized Phase III clinical trial

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Table 2 Phase III Clinical Trials Evaluating the Effects of ICI Plus Antiangiogenic Agents

Cancer Types	Clinical Trial ID	Combination Regimen vs Control Group	Clinical Outcomes (Experimental vs Control Group)	TRAE Leading to Discontinuation %	Approval FDA
Advanced RCC	KEYNOTE-426 NCT02853331[67]	Pembrolizumab + Axitinib vs Sunitinib	PFS: 16 m vs 11 m, HR 0.71 (95% CI 0.60–0.84) OS: 44.4 vs 25.8 m, HR 0.63 (95% CI 0.50–0.77)	6 vs 10	YES
Advanced RCC	JAVELIN Renal 101 NCT02684006[68,69]	Avelumab + Axitinib vs Sunitinib	PFS: 13.8 m vs 7.2 m, HR 0.61 (95% CI 0.47–0.79) OS: NE vs 28.6 m, HR 0.83 (95% CI 0.596–1.151)	4 vs 8	YES
Advanced RCC	CheckMate 9ER NCT03141177[70]	Nivolumab + Cabozantinib vs Sunitinib	PFS: 16.6 m vs 8.3 m, HR 0·56 (95% CI 0·46–0·68) OS: 37.7 m vs 34.3 m, HR 0·70 (95% CI 0·55–0·90)	3 vs 9	YES
Advanced RCC	CLEAR NCT02811861[71]	Pembrolizumab + Lenvatinib vs Sunitinib	PFS: 23.9 m vs 9.2 m, HR 0.39 (95% CI 0.32–0.49) OS: not reached, HR 0.66 (95% CI 0.49–0.88)	13 vs 14	YES
Advanced RCC	IMmotion151 NCT02420821[72]	Atezolizumab + Bevacizumab vs Sunitinib	PFS: 11.2 m vs 7.7 m, HR 0.74 (95% CI 0.57–0.96) OS: 36.1 m vs 35.3 m, HR 0.91 (95% CI 0.76–1.08)	5 vs 8	NO
Advanced RCC	RENOTORCH NCT04394975[73]	Toripalimab + Axitinib vs Sunitinib	PFS: 18.0 m vs 9.8 m, HR 0.65 (95% CI 0.49–0.86) OS: NE vs 26.8 m, HR 0.61 (95% CI 0.40–0.92)	14 vs 8	NO
Advanced RCC	CHECKMATE-214 NCT02231749[74]	Nivolumab + Ipilimumab vs Sunitinib	PFS: 12.4 vs 12.3 m HR 0.88 (95% CI 0.75–1.03) OS: 52.7m vs 37.8m, HR 0.72 (95% CI 0.62–0.83)	24 vs 13	YES
Advanced RCC	CONTACT-03 NCT04338269[75]	Atezolizumab + Cabozantinib vs Cabozantinib	PFS: 10.6 m vs 10.8 m, HR 1.03 (95% CI 0.83–1.28) OS: 25.7 m vs NE, HR 0.94 (95% CI 0.70–1.27)	16 vs 4	NO
Advanced HCC	IMbrave150 NCT03434379[76]	Atezolizumab + Bevacizumab vs Sorafenib	PFS: 6.9 m vs 4.3 m, HR 0.65 (95% CI 0.53–0.81) OS: 19.2 m vs 13.4 m, HR 0.66 (95% CI 0.52–0.85)	22 vs 12	YES
Advanced HCC	ORIENT-32 NCT03794440[77]	Sintilimab + IBI305 vs Sorafenib	PFS: 4.6 m vs 2.8 m, HR 0.56 (95% CI 0.46–0.70) OS: NR vs 10.4 m, HR 0.57 (95% CI 0.43–0.75)	14 vs 6	YES
Advanced NSCLC	IMPOWER 150 NCT02366143[78,79]	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel vs Bevacizumab + Carboplatin + Paclitaxel	PFS: 8.3 m vs 6.8 m, HR 0.62 (95% CI 0.52–0.74) OS: 19.2 m vs 14.7 m, HR 0.78 (95% CI 0.64–0.96)	/	YES

exploring the combination of pembrolizumab with axitinib versus sunitinib as first-line treatment for advanced ccRCC.[67] The results of the KEYNOTE-426 study were first reported at the 2019 ASCO GU conference, marking the beginning of immune-based combination therapy for advanced kidney cancer. At the 2021 ASCO Annual Meeting, the KEYNOTE-426 study provided an update with long-term follow-up data of 42.8 months. The results showed consistent findings with previous reports, demonstrating that pembrolizumab in combination with axitinib significantly improves progression-free survival (PFS), OS, and ORR in the overall population compared to sunitinib. The median OS reached 46 months, and the ORR reached 60%. It is worth noting that while the overall population benefited significantly, the data for the IMDC risk stratification were inconsistent. The results showed that the combination of pembrolizumab and axitinib did not show a significant improvement in PFS and OS compared to sunitinib in low-risk patients, with no significant difference between the two groups. However, for intermediate and high-risk patients, the combination therapy showed significant benefits, highlighting the importance of personalized treatment. For instance, the phase III Keynote-426 study demonstrated that pembrolizumab plus axitinib resulted in a significant benefit in PFS, OS, and ORR compared with sunitinib in all untreated advanced RCC, regardless of the International mRCC Database Consortium (IMDC) risk classification. Similarly, the phase III trial JAVELIN Renal 101 evaluated avelumab plus axitinib versus sunitinib as first-line treatment for advanced RCC, revealing a notable prolongation in PFS by 6.6 months when compared with sunitinib monotherapy alone (median, 13.8 versus 7.2 months). Given these findings, the FDA approved the two ICI plus antiangiogenic combinations mentioned above for advanced RCC in 2019. Subsequent phase III clinical trials of ICI plus antiangiogenic combinations, CheckMate9ER and CLEAR trials, demonstrated superior efficacy over sunitinib in previously untreated advanced RCC.

Although several combinations of ICI plus antiangiogenic therapies have gained approval as first-line therapies for advanced RCC in all IMDC risk groups, TKI monotherapy remains a viable option for IMDC favorable-risk patients, taking into account considerations such as toxicity profiles and economic factors. Given the variety of approved TKI monotherapy and combination therapies in advanced RCC, it is imperative to tailor the treatment regimen to each patient based on the number of individual IMDC risk factors.[80] Additionally, there is a pressing need for greater focus on second- and third-line treatment options for advanced RCC, particularly for patients who have experienced treatment failure with ICI plus antiangiogenic combination therapies. The first-line combination of PD-1 inhibitors and TKIs has demonstrated promising results, exhibiting an ORR between 55% and 73%. PFS can extend up to 2 years, while OS exceeds 45 months. As a result, this combination therapy has been established as the recommended standard treatment regimen in major clinical guidelines. However, there remains a lack of sufficient evidence in evidence-based medicine regarding the effectiveness of second-line, third-line, and other subsequent therapies.

Drug therapy has rapidly advanced, reshaping the treatment landscape for advanced renal cell carcinoma. Immune combination targeted therapy has become the standard first-line treatment, but it has also brought new challenges. For instance, with an increasing number of available drugs, how can we select benefiting populations guided by effective biomarkers? Additionally, while first-line treatments are evolving swiftly, there is a lack of high-level evidence recommending subsequent therapies.

Hepatocellular Carcinoma (HCC)

HCC accounts for over 90% of primary liver cancers and represents a growing global healthcare challenge. The majority of HCC cases arise in the context of chronic liver diseases, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, often accompanied by fibrosis or cirrhosis.[81–83] These underlying conditions are likely to significantly influence tumor immunity. Over the past fifteen years, the field of liver cancer treatment has experienced transformative changes. Initially dominated by multi-target small molecule TKIs like sorafenib and lenvatinib, the landscape has evolved significantly with the advent of ICIs in the last five years, including combinations like atezolizumab with bevacizumab. These groundbreaking therapies have emerged as a powerful driving force, fostering ongoing innovation in first-line treatment strategies.

The IMbrave150 study marked a breakthrough in the advanced HCC treatment (Table 2). This phase III trial assessed the efficacy of atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC who had not received systemic treatment.[76] Compared with sorafenib, atezolizumab plus bevacizumab combination therapy significantly

improved OS and PFS.[76,84] Interestingly, better efficacy was observed in the Chinese subpopulation, achieving a mOS of 24 months.[85] In addition, there was no significant difference in severe adverse events between the combination therapy and sorafenib monotherapy in the IMbrave150 trial.[76] The ORIENT-32 trial demonstrated that the combination of sintilimab and bevacizumab biosimilar (IBI305) also resulted in superior PFS and OS compared with sorafenib in patients with unresectable HCC, and the safety was acceptable.[77]

Simultaneously, combinations of different ICIs and small molecule antiangiogenic TKIs are currently being explored as another strategy to enhance clinical activity. Several phase III trials assessing this strategy have reported promising results. The COSMIC-312 represented the inaugural phase III trial assessing the ICIs and antiangiogenic TKIs combination (atezolizumab plus cabozantinib versus sorafenib) in advanced HCC within the first-line context.[86,87] Another phase III study, LEAP-002, compared pembrolizumab plus lenvatinib with lenvatinib plus placebo in patients with advanced HCC.[88] Unfortunately, neither of these clinical trials achieved an OS benefit. The CARES-310 trial was the first phase III study to report significant PFS and OS benefits with the combination of the antiPD-1 antibody camrelizumab and the VEGFR2-targeting TKI rivoceranib compared with sorafenib as first-line treatment for advanced HCC. mPFS was 5.6 months (95% CI, 5.5–6.3 months) in the camrelizumab combined with rivoceranib group and 3.7 months (95% CI, 2.8–3.7 months) in the sorafenib monotherapy group (hazard ratio, 0.52; 95% CI, 0.41–0.65). mOS was 22.1 months (95% CI, 19.1–27.2 months) in the camrelizumab plus rivoceranib group and 15.2 months (95% CI, 13.0–18.5 months) in the sorafenib alone group (hazard ratio, 0.62; 95% CI, 0.49–0.80).[89] The combination of camrelizumab and rivoceranib was well tolerated, and no new safety signals emerged.

With ICIs in combination with antiangiogenic agents emerging as the new standard of care (SOC) for first-line treatment of unresectable HCC, this approach is being further explored in the postoperative adjuvant treatment of HCC. The IMbrave50 study is the first phase III trial to investigate adjuvant treatment for HCC to report positive results, indicating that atezolizumab plus bevacizumab significantly improved recurrence-free survival (RFS) compared with active surveillance in patients at high risk for HCC recurrence.[90] In addition, ongoing phase III trials like EMERALD-2 evaluate durvalumab in combination with bevacizumab in patients with HCC at high risk of recurrence after curative treatment. Neoadjuvant therapy for resectable HCC, a single-arm, Phase II clinical trial (NCT04297202) included 18 patients treated with the combination of camrelizumab plus apatinib, demonstrated a major pathological response (MPR, ≥90% tumor necrosis) of 17.6% and a complete pathological response (pCR) of 5.9%. The 1-year RFS rate was 53.85% with 16.7% grade 3 or 4 AEs (Table 3).[91]

Non-Small Cell Lung Cancer (NSCLC)

NSCLC is the most common type of lung cancer, accounting for approximately 85% of all cases. Currently, significant progress has been made in specific targeted therapy and combined therapies for NSCLC. Multiple clinical trials assessing the efficacy and safety of ICI plus antiangiogenic combinations have yielded positive results. The IMpower150 study is a Phase III trial aimed at evaluating the efficacy and safety of atezolizumab in combination with bevacizumab and carboplatin-paclitaxel for the treatment of non-squamous NSCLC. The study enrolled patients with stage IV or recurrent metastatic non-squamous NSCLC who had not previously received chemotherapy, including those with *EGFR* or *ALK*-sensitive mutations. For patients with these genetic mutations, enrollment required that they had experienced disease progression or intolerable side effects following at least one prior targeted therapy.[78] Patients were divided into the following three groups randomly: atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), and atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP). In the intention-to-treat (ITT) *EGFR* and *ALK* wild-type (WT) population, the ABCP group demonstrated a significant prolongation in PFS and OS compared with the BCP group, with no significant difference in the incidence rate of adverse events (AE) between the two groups.[79,100] The addition of atezolizumab to BCP improved the survival time of patients with non-squamous metastatic NSCLC, regardless of their PD-L1 expression status. Furthermore, the key subgroup analysis of Impower 150 suggested that the ABCP regimen could be preferentially considered clinically for patients with NSCLC with liver metastasis.[101] In 2018, the four-drug combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel was approved by the FDA as the first-line regimen for advanced non-squamous NSCLC patients harboring no *EGFR* or *ALK* variants. Another phase III study, ONO-4538-52/TASUKI-52, evaluated the efficacy of nivolumab with carboplatin,

Table 3 Phase I and Phase II Clinical Trials Evaluating the Effects of ICI and Angiogenic Inhibitor

Cancer Types	Combination Regimen	Study Phase	Treatment	Clinical Trial ID(ref)	Clinical Outcomes
Resectable HCC	Camrelizumab + Apatinib	II	Neoadjuvant therapy	NCT04297202[91]	MPR: 17.6%; pCR: 5.9%
Advanced non-squamous NSCLC (TMB high)	Atezolizumab + Bevacizumab	II	First-line	NCT03836066[92]	12-month PFS rate: 51.3% 12-month OS rate: 72.0%
EGFR+/ALK+ advanced NSCLC	Camrelizumab + Apatinib	Ib/II	≥Second line	NCT03083041[93]	ORR: 18.6% PFS: 2.8 m (95% CI 1.9–5.5)
Advanced NSCLC (PD-L1 positive)	Pembrolizumab + Ramucirumab	Ia/b	≥Second line	JVDF NCT02443324[94]	ORR: 42.3% PFS: 9.3 (95% CI 4.0-NR)
MSS mCRC	Regorafenib + Nivolumab	Ib	≥Second line	REGONIVO NCT03406871[95]	ORR: 33.3% 1-year PFS rate:41.8% 1-year OS rate: 68.0%
Non-MSI-H mCRC	Regorafenib + Avelumab	II	≥Second line	REGOMUNE NCT03475953[96]	PFS: 3.6 m (95% CI 1.8–5.4) OS: 10.8 m (95% CI: 5.9–NA)
MSS/MSI-L/pMMR, relapsed or metastatic CRC	Regorafenib + Toripalimab	Ib/II	Second line	REGOTORI NCT03946917[97]	ORR: 15.2% PFS: 2.1 m (95% CI 2.0–4.3) OS: 15.5 m (95% CI 10.3-NA)
Advanced MSS CRC	Fruquintinib + Sintilimab	Ib/II	Second line	NCT03903705[98]	ORR: 22.7% (5mg-intermittent group) PFS: 6.8 (95% CI:5.6-NA)
Non–MSI-H/Pmmr advanced CRC	Lenvatinib + Pembrolizumab	II	≥Second line	LEAP-005 NCT03797326[99]	ORR: 22%

paclitaxel, and bevacizumab for first-line treatment of advanced non-squamous NSCLC. The study met its primary endpoint with a significant improvement in PFS.[102] Moreover, ICI plus antiangiogenic combinations of advanced NSCLC are currently exploring chemotherapy-free regimens, with several phase I and phase II clinical trials already demonstrating promising results.[92,94,103,104] For instance, a multicenter, single-arm Phase 2 trial (NCT03836066) explored the clinical benefits of atezolizumab plus bevacizumab as first-line treatment for patients with metastatic non-squamous NSCLC with high tumor mutation burden (TMB), achieving a 1-year PFS rate of 51.3%, meeting the primary endpoint.[105]

Targeted drugs aimed at specific gene mutations have significantly improved the survival of advanced NSCLC patients. However, acquired resistance inevitably occurs in these patients following prolonged molecularly targeted treatment. Epidermal growth factor receptor (*EGFR*) mutation stands as one of the most common mutations in NSCLC, making novel treatment options after EGFR-TKI resistance a pressing concern. Patients with NSCLC with *EGFR* mutations often exist within a suppressive tumor immune microenvironment.[106,107] Despite this, the therapeutic efficacy of multiple clinical trials using ICI monotherapy or ICI combined with chemotherapy in *EGFR*-positive patients after disease progression on EGFR-TKI has been unsatisfactory.[69] Previous research has indicated an association between *EGFR* mutation and higher levels of VEGF expression.[108] Additionally, the EGFR and VEGF pathways share common downstream signaling.[109] Hence, combining ICI with antiangiogenic therapy presents a promising strategy for patients with *EGFR*-positive NSCLC after EGFR-TKI resistance. The *EGFR* mutation subgroup analysis of Impower150 and the ORIENT-31 studies (sintilimab plus IBI305 plus pemetrexed plus cisplatin) achieved positive results by adding antiangiogenic agents to ICI combined with chemotherapy, demonstrating the synergistic effect of ICI combined with antiangiogenic therapy for NSCLC patients with EGFR-TKI-resistant. In a Phase 1b/2 clinical trial (NCT03083041),

camrelizumab in combination with apatinib was evaluated in patients with advanced $EGFR^{+}/ALK^{+}$ NSCLC who previously received targeted therapy. The chemotherapy-free regimen demonstrated moderate antitumor activity and was well-tolerated (ORR: 18.6%; mPFS: 2.8 months).[93]

Colorectal Cancer (CRC)

CRC is a type of cancer that originates in the colon or rectum, which are parts of the large intestine. It is the third most commonly diagnosed cancer and a leading cause of cancer-related deaths worldwide. SOC treatment for advanced CRC primarily relies on chemotherapy, typically resulting in a mOS of approximately 20–30 months.[110] However, patients have limited treatment options and benefits after progressing on standard first- and second-line treatments. In the CORRECT trial, the third-line drug regorafenib extended the OS of metastatic CRC (mCRC) patients by only 1.4 months compared with placebo.[111] Therefore, more effective therapeutic strategies for advanced CRC are still needed, particularly for patients who progress after standard treatments and are unable to tolerate intensive chemotherapy.

Previous studies have suggested that different tumor immune microenvironments may lead to different responses to ICIs between MSI and MSS mCRC.[112–114] Hence, a rational strategy is combining ICIs with antiangiogenic agents to modulate the immunosuppressive TME of MSS mCRC. Several early clinical trials are already underway to evaluate the efficacy of ICI combined with antiangiogenic agents in MSS mCRC as subsequent treatment regimens after the failure of standard treatment (Table 3). The REGONIVO Japanese study, a phase Ib trial, evaluated the combination of nivolumab plus regorafenib for treating MSS refractory mCRC. This study demonstrated a high ORR of 33.3%, a 1-year PFS rate of 41.8%, and a 1-year OS rate of 68.0%.[115] Subsequent multiple single-arm studies assessed various combinations of ICIs and antiangiogenic agents as second- or third-line treatments for MSS mCRC, including the REGNIVO North American study,[95] the REGOMUNE study (regorafenib plus avelumab),[96] the REGOTORI study (regorafenib plus tiragolumab),[97] the study of fruquintinib combined with sintilimab,[116] the CRC cohort of LEAP-005 study (lenvatinib plus pembrolizumab),[99] etc. Although these studies did not achieve the high ORR observed in the REGNIVO Japanese study, each study involved different drugs, and the doses of antiangiogenesis agents varied as well. Overall, the above studies on using immunotherapy combined with an antiangiogenesis strategy as the third-line treatment for MSS mCRC reported an ORR of approximately 7% to 27%, and a mOS of 7.5 to 15.5 months. The phase III LEAP-017 trial, which compared pembrolizumab and lenvatinib with standard treatments (TAS-102 or regorafenib), has already been initiated to directly compare the safety and efficacy of ICI plus antiangiogenic therapy against standard third-line and subsequent treatments (Table 2).[117] Recently, a randomized phase II trial, CAPability-01, reported that the addition of the histone deacetylase (HDAC) inhibitor chidamide to sintilimab and bevacizumab achieved an ORR of 44.0% and a mPFS of 7.3 months in MSS/pMMR advanced CRCs who failed standard chemotherapy.[118]

Exploration in first-line treatment for MSS mCRC primarily focuses on ICI plus angiogenic inhibitor and chemotherapy (Table 3). The phase II AtezoTRIBE study compared the efficacy of FOLFOXIRI plus bevacizumab plus atezolizumab with FOLFOXIRI plus bevacizumab, demonstrating statistically significant differences in the primary endpoint of mPFS between two groups (13.1 months versus 11.5 months, $p = 0.012$).[119] Similarly, the phase II CheckMate 9X8 study demonstrated that the addition of nivolumab to mFOLFOX6 plus bevacizumab (SOC) did not improve the mPFS for MSS mCRC in the first-line treatment; however, the 1-year PFS rates and ORR were higher in the combination group than in the SOC group.[120] Additionally, the results of a phase II study on the first-line treatment of patients with RAS mutant MSS mCRC with sintilimab plus bevacizumab, oxaliplatin, and capecitabine demonstrated an ORR of 84% and a mPFS of 18.2 months.[121] In addition, the ORR for CRCs with liver metastases was higher than that in the overall population (93% versus 84%).

Further Directions and Challenges

Significant progress has been made in the clinical application of ICIs combined with antiangiogenic agents. The results of current clinical trials demonstrated that this combination treatment approach has the most significant effects in patients with RCC and HCC, as evidenced in several phase III studies in first-line treatment settings, leading to FDA approval of the corresponding indications. Researchers are exploring the clinical practice of ICI plus antiangiogenesis therapy strategy to more types of cancer, as well as its potential at different stages of cancer. Clinical trials have shown that

the combination of ICIs can be significantly effective in certain cases, the CheckMate 214 study evaluated the efficacy of nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA-4 inhibitor) in patients with advanced renal cell carcinoma.[74] The results showed that the median OS in the combination group reached 48.1 months, which is the longest OS reported in a Phase 3 study of combination therapies to date. But it may also be associated with higher side effects and a greater economic burden.

Both antiangiogenic agents and ICIs carry their own set of side effects, and the occurrence of adverse reactions can become more intricate following combined treatment. In the IMpower 150 study, the safety profile of the ABCP group remained generally consistent with that of the BCP group, with no new safety signals identified with the four-drug regimen.[78] On the contrary, the combination of pembrolizumab plus pazopanib in advanced RCC (NCT02014636) resulted in significant hepatotoxicity, leading to the discouragement of further clinical trials.[122] Moreover, the dosage of antiangiogenic agents can significantly impact safety and tolerability. For instance, in the NSCLC LEAP 007 study, where lenvatinib was administered at a concentration of 20 mg/day, the incidence of grade 3–5 toxicity for pembrolizumab plus lenvatinib reached 57.2%. Consequently, LEAP-007 failed to meet its primary endpoint of OS, possibly due to the severe toxicity caused by treatment, which ultimately negated any potential benefits.[123] However, in the HCC LEAP-002 study, which utilized an administration dose of lenvatinib of 8 or 12 mg/day, the grade 3–5 toxicity in the pembrolizumab plus lenvatinib group was only 9%.[88] Preclinical study results suggest that the dosage and duration of antiangiogenic therapy have bidirectional effects on the TME. Excessive doses or prolonged usage may paradoxically reduce the blood supply to the tumor, exacerbating hypoxia and weakening the efficacy of combination therapy. Furthermore, different ICIs exhibit varying mechanisms of action and toxicities, and there exist differences in the efficacy of antiangiogenic agents based on whether large molecule monoclonal antibodies or small molecule TKIs are chosen. Addressing how to appropriately select drug combinations, determine dosages and treatment cycles, and effectively manage adverse reactions are crucial issues in the context of ICIs combined with antiangiogenic treatment.

Despite numerous clinical trials of ICIs combined with antiangiogenic agents, some trials have failed to meet expectations. Identifying the potential benefit population of ICIs combined with antiangiogenic therapy is a huge clinical challenge. It is crucial to explore response biomarkers to determine patients who may benefit the most from this combination therapy. The JAVELIN Renal 101 study indicated that neither PD-L1 expression levels nor TMB could differentiate PFS between the avelumab plus axitinib group and the sunitinib group. A 26-gene Immunosignature may serve as a potential biomarker of response to ICIs combined with antiangiogenic therapy in advanced RCC cases.[124] The IMmotion151 trial demonstrated that the use of atezolizumab plus bevacizumab remarkably prolonged PFS compared with sunitinib. Nevertheless, the mOS was similar between the two treatment groups. Biomarker analysis based on RNA sequencing data suggested that patients with mRCC with three transcriptomic profiles (T-effector/proliferative cluster, proliferative cluster, and small nucleolar RNA cluster) can achieve more OS benefit from atezolizumab and bevacizumab combination therapy.[78] In addition, the results of a subgroup analysis of the IMpower150 study demonstrated that patients from the high PD-L1 expression subgroup or high effector T-cell expression subgroup can obtain more benefit from the ABCP regimen.[78]

The efficacy of immune combination anti-angiogenic therapy also varies across different geographical regions. The LEAP-002 study,[88] although it did not achieve statistically significant differences in the overall global population, showed a certain trend of improvement in the subgroup of Chinese patients. The study included a total of 150 Chinese liver cancer patients with a median follow-up of 31.9 months. The results indicated that the mOS for patients in the lenvatinib combined with pembrolizumab group was 32.3 months, while the mOS for patients in the lenvatinib combined with placebo group was only 26.0 months (HR=0.76, 95% CI: 0.50–1.17). This may be related to the different national conditions, disease characteristics, and population habits between China and Western countries regarding liver tumors. For example, in many countries, including those in Southeast Asia, the incidence of HBV and HCV is very high.

The challenges currently facing ICI and antiangiogenic combination therapy highlight the requirement for a deeper mechanistic understanding of the interactions between components within the TME.[125,126] The application of bispecific antibodies (bsAbs) provides a potential strategy for optimizing complex ICI and angiogenesis combinations.[127] A novel BsAb AK112 that simultaneously targets PD-1 and VEGF is currently undergoing clinical research (Akeso Biopharma, Inc). Considering the co-expression of VEGF and PD-1 in the TME, AK112 may offer a more effective blockade of these

two pathways compared with combination therapies, simultaneously reducing adverse reactions caused by off-target toxicity. In a phase II trial (NCT04736823) for the treatment of advanced NSCLC, AK112 in combination with chemotherapy has demonstrated promising antitumor activity and safety.[128] Based on current phase II study results, two phase III trials of AK112 in combination with chemotherapy are ongoing, one clinical trial enrolled patients with advanced squamous NSCLC (NCT05840016), and the other enrolled those non-squamous NSCLC patients harboring *EGFR* variants who have failed prior EGFR-TKI treatment (NCT05184712). In addition to NSCLC, AK112 is also being evaluated in multiple phase I and II clinical trials on other solid tumors such as gynecological tumors (NCT04870177), triple-negative breast cancer (NCT05227664), SCLC (NCT05116007), and HCC (NCT05432492). Moreover, the development of novel therapeutic strategies may pave the way for future breakthroughs. In the CAPability-01 study, the three-drug regimen comprising the HDAC inhibitor chidamide, PD-1 monoclonal antibody sintilimab, and the antiangiogenic agent bevacizumab has shown promise in overcoming treatment barriers for MSS/pMMR CRC.[118] The phase III CAPability-02 clinical trial has been initiated to explore the potential of the triple regimen as a second-line treatment for advanced MSS/pMMR CRC. In summary, the combination of immunotherapy and chemotherapy exhibits favorable tolerance and manageable safety profiles. No novel safety signals were identified during the follow-up period, thereby providing reassurance for the long-term administration of these treatments in patients.

Conclusion

Recently, the development of ICIs in combination with antiangiogenic agents has progressed rapidly which is becoming routine treatment regimen for various malignant tumors. However, the alteration of the TME involves the complex interplay among tumor cells, immune cells, and stromal cells with intertwined signaling pathways. The synergistic mechanism of action between ICIs and antiangiogenic agents has not yet been fully elucidated. In the area of tumor treatment, such as immunotherapy, radiotherapy, chemotherapy, targeted therapy and surgical treatments, has shown considerable progress. Meanwhile, various new therapies are continuous emergence. How to select the most appropriate treatment strategies for different patients, how to achieve precise treatment of tumors, how to screen for prognostic biomarkers to identify potential benefit populations remain major challenges for the future. In general, further basic research and clinical trials are required to optimize the ICI combined with antiangiogenesis regimen to achieve greater clinical benefits for patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

No potential conflicts of interest were disclosed.

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