Narrative Review Article

Combination Therapy with Immune Checkpoint Inhibitors and Anti-Angiogenic Agents: Mechanisms, Clinical Applications, and Challenges

Eunchan Jung

Fulton Science Academy, 3035 Fanfare Way, Alpharetta, GA 30009, United States

ABSTRACT

Combination therapy with immune checkpoint inhibitors (ICIs) and anti-angiogenic agents has recently been an important therapeutic strategy in cancer treatment. This review discusses the mechanisms, clinical applications, limitations, and future research directions of this combination therapy. ICIs may restore exhausted T-cell activity and modify immune responses within the tumor microenvironment (TME), thereby contributing to tumor control in selected contexts. Anti-angiogenic agents target abnormal tumor angiogenesis, which can impair immune-cell infiltration and function and support tumor progression. By modulating vascular dysfunction and VEGF-mediated immunosuppression, anti-angiogenic therapy may enhance the activity of ICIs in certain tumor types, while ICI-induced immune activation may also influence vascular remodeling and antitumor immunity. Several ICI and anti-angiogenic agent combinations have been approved by the U.S. Food and Drug Administration (FDA) for selected malignancies and have demonstrated clinical benefit in specific patient populations. However, important questions remain regarding long-term efficacy, optimal dosing, treatment timing and sequencing, duration of therapy, immune-related adverse events, and tumor-specific resistance mechanisms. Responses may also differ across tumor types, drug classes, and tumor microenvironment states. Future research should focus on validating integrated biomarker strategies, improving toxicity prediction and management, clarifying resistance mechanisms, optimizing treatment sequencing, and extending follow-up to determine the durability of clinical benefit and safety. These efforts will be essential for improving the clinical use of combination therapy with ICIs and anti-angiogenic agents in appropriately selected patients.

Keywords: Immune Checkpoint Inhibitors; Anti-Angiogenic Agents; Tumor Microenvironment; Immune-Related Adverse Events; Predictive Biomarkers

INTRODUCTION

Cancer has been recognized since antiquity, with descriptions of tumor-like diseases appearing in ancient Egyptian medical texts. Despite centuries of medical progress, cancer remains a major global health burden. According to data from the National Cancer Institute released in January 2026, an estimated 2,041,910 new cancer cases and 618,120 cancer-related deaths were expected to occur in the United States in 2025. Globally,

Corresponding author: Eunchan Jung, E-mail: eskywalker2000@gmail.com.

Accepted July 22, 2026
https://doi.org/10.70251/HYJR2348.44435450

approximately 20 million new cancer cases and 9.7 million cancer-related deaths were reported in 2022, and by 2050, the annual number of new cancer cases is projected to increase to 33 million, with cancer-related deaths reaching 18.2 million (1).

Modern cancer therapy developed more recently, beginning with advances in surgery and the early use of radiation therapy in the late nineteenth and early twentieth centuries, followed by the development of chemotherapy in the 1940s. Although these approaches have substantially improved cancer management, cancer remains one of the leading causes of death worldwide and continues to pose significant challenges to global health care systems.

The use of the immune system as a therapeutic strategy for cancer can be traced to William B. Coley in the late nineteenth century. Coley attempted to stimulate antitumor immune responses using bacterial toxins, later known as Coley's toxins, and reported responses in several malignancies, including sarcoma, lymphoma, and testicular cancer. However, the mechanisms underlying these responses were not understood at the time, and concerns regarding safety, reproducibility, and severe inflammatory toxicity limited broader clinical adoption. Surgery and radiotherapy therefore became more established treatment approaches during the early twentieth century. Subsequent research suggested that the effects of Coley's toxins were related, at least in part, to immune activation involving cytokines such as interleukins and interferons (2, 3).

A major advance in cancer immunotherapy came from the identification of immune regulatory pathways that control T-cell activation and antitumor immunity. Key immune checkpoints, including cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), help regulate immune responses by limiting excessive immune activation and preventing damage to normal tissues. However, tumors can exploit these pathways to evade immune surveillance. Understanding these checkpoint mechanisms provided the foundation for modern immune checkpoint inhibitors, which are now used in clinical practice for multiple cancer types (4).

Since Folkman proposed in 1971 that angiogenesis plays a critical role in the growth and metastasis of solid tumors, anti-angiogenic therapy has become an important area of cancer research. As tumors enlarge beyond approximately 2–3 mm in diameter, limited diffusion of oxygen and nutrients can contribute to intratumoral hypoxia and stimulate the production of pro-angiogenic factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) (5). Overexpression of these pro-angiogenic factors can disrupt the balance between pro-angiogenic and anti-angiogenic signals, promoting the formation of new blood vessels. However, tumor-associated vessels are often structurally abnormal, disorganized, and functionally inefficient, creating an aberrant vascular network that can support tumor expansion and facilitate invasion (6). Angiogenesis inhibitors target this abnormal vascular process by interfering with angiogenic signaling pathways within the tumor microenvironment (TME).

Numerous clinical trials have evaluated combination therapy with immune checkpoint inhibitors (ICIs) and anti-angiogenic agents, leading to several U.S. Food and Drug Administration (FDA)-approved regimens that have improved outcomes in selected patient populations. This review focuses on the biological pathways involved in ICI and anti-angiogenic combination therapy, summarizes current clinical applications, identifies existing limitations, and highlights areas requiring further research.

BIOLOGICAL RATIONALE FOR COMBINATION THERAPY

Immune Checkpoint Biology

The development of immunotherapy, particularly ICIs, has transformed the treatment of several malignancies (7). Cancer immunoediting describes how interactions between tumor cells and the immune system can both eliminate tumor cells and select for immune-resistant tumor populations. This process is commonly divided into three phases: elimination, equilibrium, and escape. During the elimination phase, innate and adaptive immune responses recognize and eliminate tumor cells expressing tumor-associated or tumor-specific antigens. Some tumor cells may survive this immune pressure and enter the equilibrium phase, in which the adaptive immune system restrains but does not completely eradicate residual tumor cells. Over time, immune selection may favor tumor-cell populations capable of evading antitumor immunity. These cells can then enter the escape phase, during which tumors progress despite the presence of host immune responses. Proposed mechanisms of immune escape include antigen loss or alteration, changes in cytokine signaling, and upregulation of immune checkpoint pathways (8). Immune checkpoint receptors expressed on immune

cells regulate the activation and inhibition of immune responses and play a central role in maintaining immune balance (9).

Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) was one of the first immune checkpoints identified as a negative regulator of T-cell activation. CTLA-4 is expressed on activated T cells and regulatory T cells (Tregs) and primarily regulates the early priming phase of the immune response. By competing with CD28 for binding to B7 ligands on antigen-presenting cells, CTLA-4 limits T-cell activation and proliferation. In preclinical studies, CTLA-4 blockade has been associated with increased T-cell proliferation, enhanced interleukin-2 (IL-2) production, and depletion of Tregs within the TME through macrophage-dependent mechanisms (10).

PD-1 is another major immune checkpoint that helps regulate the balance between effective antitumor immunity and excessive inflammation (11). PD-1 interacts with two ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) (12). PD-L1 is expressed on activated immune cells, many normal tissues, and tumor cells, whereas PD-L2 is expressed primarily on macrophages and dendritic cells (13). High PD-1 expression may reflect a dysfunctional or exhausted T-cell state, characterized by reduced proliferation, impaired cytokine production, and decreased cytotoxic activity, although its significance can vary across tumor contexts (14). When PD-1 binds to PD-L1 or PD-L2, inhibitory signaling can suppress T-cell activity and reduce the production of key immune cytokines, including interferon gamma (IFN-γ), tumor necrosis factor beta (TNF-β), and IL-2.

The molecular and immunologic determinants of response to anti-PD-1 and anti-PD-L1 therapy remain incompletely understood. However, clinical benefits, including prolonged survival, have been associated in some settings with increased PD-L1 expression on tumor cells and tumor-infiltrating immune cells. ICIs are currently used across a wide range of malignancies. PD-L1 inhibitors, including atezolizumab, avelumab, and durvalumab, have been used in multiple cancer types, including non-small cell lung cancer (NSCLC), bladder cancer, and Merkel cell carcinoma (4). Dual immune checkpoint blockade with anti-CTLA-4 and anti-PD-1 agents, such as ipilimumab plus nivolumab, has demonstrated clinical benefit in selected tumor types, including melanoma, renal cell carcinoma, colorectal cancer with specific molecular features, hepatocellular carcinoma, NSCLC, pleural mesothelioma, and esophageal squamous cell carcinoma. In these settings, combined CTLA-4 and PD-1 inhibition has been associated with improved response rates, overall survival, or progression-free survival compared with selected standard treatments, although the magnitude of benefit varies by cancer type, biomarker status, treatment line, and patient population (15).

Tumor Angiogenesis, Vascular Dysfunction, and Immune Regulation

The rapid and disorganized growth of tumor neovascular forms an extensive vascular supply system, which drives uncontrolled tumor growth and invasion. Among the molecules identified as angiogenic factors, endothelial growth factor-VEGF has contributed significantly to our understanding of the angiogenic mechanisms that sustain tumor growth. VEGF acts as a growth and survival factor on endothelial cells by targeting two receptor tyrosine kinases, VEGF receptors 1 and 2 (16). VEGFR2 is expressed in endothelial cells, whereas VEGFR1 is expressed in endothelial cells, smooth muscle cells, fibroblasts, myeloid progenitor cells, macrophages, and various types of cancer cells (17). VEGF factors are overexpressed in most solid tumors, and inhibition of the VEGF signaling pathway has been shown to suppress tumor growth in several animal studies (18). FDA approved bevacizumab in 2004, marking the first anti-angiogenic agent that specifically targets VEGF to inhibit tumor angiogenesis (19).

The TME can regulate tumor angiogenesis, and angiogenesis in turn can affect the function and state of immune cells. In addition, immune-mediated responses may modulate angiogenic processes in a context-dependent manner (20). The TME is one of the major factors that may limit the effectiveness of ICIs. In the TME, interactions between tumor blood vessels and peritumoral immune cells can impair antitumor immunity and contribute to a cycle that supports tumor progression (4). Abnormal tumor angiogenesis may also facilitate immune evasion and further promote pro-angiogenic signaling (21, 22). As a result, dual targeting of tumor angiogenesis and immune-checkpoint pathways may enhance immune activity within the TME and improve the efficacy of immunotherapy in selected tumor settings (23).

Tumor growth relies on an adequate supply of oxygen and nutrients from blood vessels (24). In rapidly developing tumors, however, tumor growth can outpace the supplying capacity of existing blood vessels, which may lead to hypoxia within the tumor. The hypoxic environment activates hypoxia-inducible factor 1 (HIF-

1), a key regulator of angiogenesis, and upregulates vascular endothelial growth factor (VEGF) in the tumor (24). VEGF facilitates endothelial cell proliferation and survival, resulting in aberrant and dysfunctional tumor vessels that can interfere with multiple steps of anticancer immunity and may reduce the effectiveness of ICIs in certain tumors (25, 26). These abnormal tumor vasculatures can also form a physical barrier to cytotoxic T lymphocytes (CTLs). Tumor-specific CTLs circulating in the bloodstream may be unable to effectively penetrate the TME because of this disorganized vascular structure, preventing them from reaching and eliminating tumor cells (27).

Tumor vasculature may express a variety of immunosuppressive molecules, including PD-L1 and Fas ligand (FasL), which can impair CTL function or survival. PD-L1 on tumor endothelial cells can be upregulated by chronic hypoxia or interferon-γ, although the effect of IFN-γ may vary depending on tumor type, timing, and local immune context. This may contribute to T-cell inactivation within the vessel lumen. In addition, The TME is often marked by chronic overexpression of inflammatory mediators, which can impair the immune system's ability to recognize and eliminate abnormal cells and contribute to the functional inactivation of immune cells against tumor cells (28). T cells may remain functionally limited until they cross the blood vessel wall and enter the TME. Additionally, many tumor vessels overexpress FasL, a death signal for activated T cells. FasL on tumor vasculature can selectively eliminate CTLs while sparing regulatory T cells (Tregs). Consequently, in some TME, CTL infiltration may be limited, whereas Tregs may accumulate more abundantly (29). VEGF is an important immunosuppressive factor and a key driver of tumor angiogenesis, as shown in Figure 1.

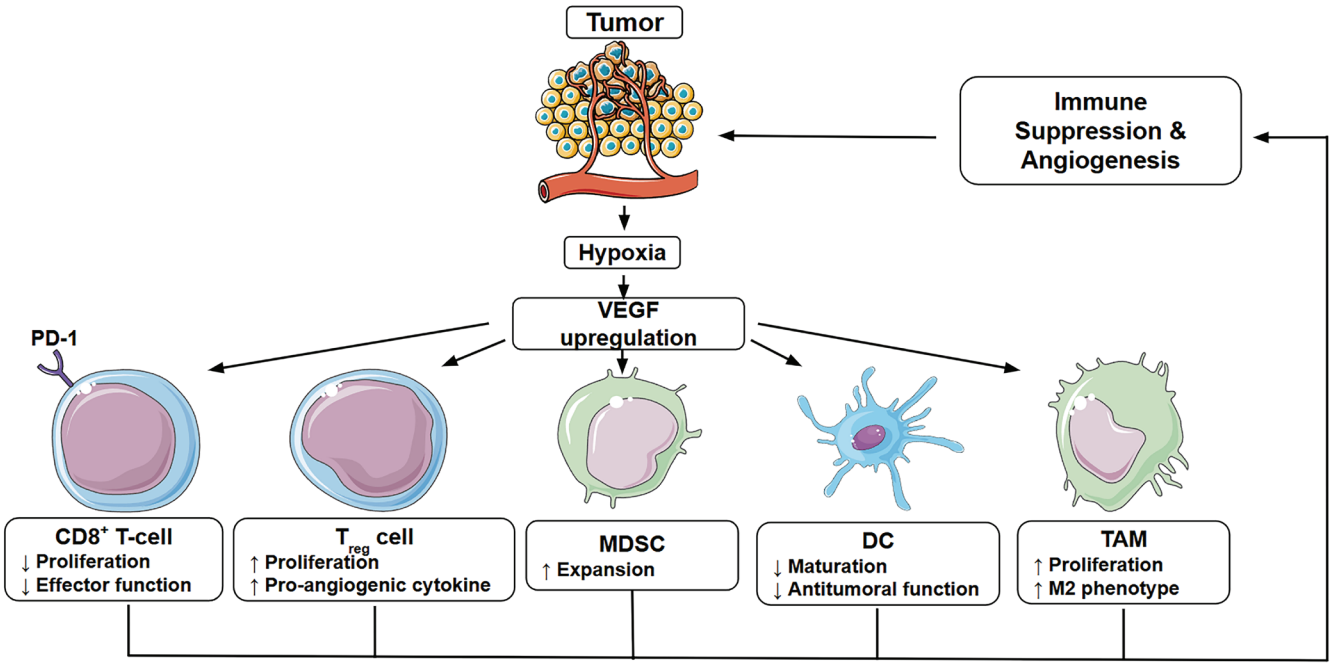

Figure 1. *Proposed VEGF-mediated regulation of immune suppression and angiogenesis in the TME. Tumor hypoxia can induce VEGF upregulation, which may reduce CD8⁺ T-cell proliferation and effector function, increase Treg proliferation and pro-angiogenic cytokine production, expand MDSCs, impair dendritic cell maturation and antitumor function, and promote TAM proliferation with M2-like polarization. These VEGF-associated changes may collectively promote immune suppression and angiogenesis in a tumor- and context-dependent manner. This schematic presents proposed mechanisms and was created by the author using modified images from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Abbreviations: VEGF, vascular endothelial growth factor; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; TAM, tumor-associated macrophage; TME, tumor microenvironment.*

VEGF in the TME can interfere with the maturation of dendritic cells (DCs) from immature progenitor cells, thereby limiting the priming of T cells against tumors. Preclinical studies have shown that inhibition of the VEGF signaling pathway increases the total number of mature dendritic cells in mouse glioblastoma models (30). Therefore, anti-VEGF therapy may reverse VEGF-mediated immunosuppression on dendritic cells by reducing immature progenitors and increasing mature DCs in preclinical settings, although the magnitude of this effect may depend on tumor type and treatment conditions. VEGF also contributes to immunosuppression by promoting the accumulation of Tregs in the TME and by driving tumor-associated macrophages (TAMs) toward an M2-like phenotype, as suggested by experimental and preclinical studies (21). VEGF has been reported to directly affect T cell function, including inhibition of the differentiation of hematopoietic progenitor cells in the thymus into CTLs in preclinical studies (31). Furthermore, experimental studies have shown that VEGF binding to VEGFR2 on the T cell surface can upregulate PD-1 expression on CTLs, thereby suppressing T cell proliferation and cytotoxicity. VEGF binding to VEGFR2 on Tregs and myeloid-derived suppressor cells (MDSCs) may also promote the infiltration of these immunosuppressive cells into the TME (32).

Conversely, the immune system can have a major impact on the regulation of tumor angiogenesis. Macrophages show considerable versatility in regulating angiogenesis throughout the TME. In experimental and preclinical studies, macrophages exposed to TME-derived signals can shift their transcriptional programs along a spectrum, adopting M1-like or M2-like phenotypes depending on the cytokines and growth factors present. M1-like TAMs may target abnormal tumor angiogenesis by secreting anti-angiogenic cytokines, such as interleukin (IL)-12 and TNF-α, whereas M2-like TAMs can promote tumor angiogenesis through the production of pro-angiogenic growth factors, including VEGF, EGF, and FGF family members; angiogenic CXC chemokines, including CXCL8/IL-8 and CXCL12; and additional angiogenesis-related factors such as TGF-β and TNF-α (33).

DCs are a crucial immune component in the TME and may also participate in the regulation of tumor angiogenesis. Experimental studies suggest that mature conventional dendritic cells (cDCs) can inhibit tumor angiogenesis through the secretion of anti-angiogenic cytokines, such as IL-12 and IL-18, and anti-angiogenic chemokines, including CXCL9 and CXCL10. CXCL9 is generally associated with the recruitment of CXCR3-positive effector T cells and may contribute to an antitumor immune environment, although its functional significance may vary across tumor contexts. In comparison, mature plasmacytoid dendritic cells (pDCs) may suppress tumor proliferation and angiogenesis through the secretion of IFN-γ and the upregulation of anti-angiogenic cytokines and chemokines. Cancer cells, however, can preferentially recruit immature DCs (iDCs) from peripheral blood vessels by releasing several cytokines, such as VEGF, CXCL12, and CXCL8, in the TME, which may make iDCs a prominent DC subset in certain tumors (34).

Preclinical studies suggest that tumor-infiltrating Treg cells can support angiogenesis by secreting VEGF and promoting the recruitment and expansion of endothelial cells (35). They may also promote tumor angiogenesis by inducing the activation of M2-like macrophages (36). MDSCs, a heterogeneous population of immature myeloid cells, can promote angiogenesis by upregulating IL-10 and downregulating IL-12 in the TME, as reported in preclinical studies (37).

Among adaptive immune cells, $CD8^+$ CTLs can play an important role in targeting abnormal tumor angiogenesis by secreting IFN-γ. Experimental and preclinical studies have shown that IFN-γ can inhibit the proliferation and migration of endothelial cells and reduce angiogenesis through IFN-γ-inducible chemokines, including IFN-induced protein 10 (IP-10/CXCL10) and monokine induced by gamma interferon (MIG/CXCL9) (38, 39). Furthermore, IFN-γ signaling may downregulate VEGF-A, thereby targeting abnormal tumor angiogenesis in certain contexts. IFN-γ may also contribute to the reprogramming of TAMs from an M2-like phenotype toward an M1-like phenotype, which may suppress vascular remodeling and support antitumor activity in some preclinical settings (40). However, the effects of IFN-γ on vascular regulation and immune activation are not uniform across all tumors and may depend on tumor type, dose, timing, and the baseline immune and vascular status of the TME.

Mechanistic Rationale for Combination Therapy

Combination therapy with ICIs, including anti-PD-1/PD-L1 therapy, and anti-angiogenic therapy may produce complementary or synergistic antitumor effects in selected tumor contexts. Preclinical and translational studies suggest that anti-angiogenic drugs can increase the infiltration and function of antitumor immune cells and may reduce certain immunosuppressive signals

within the TME. Conversely, ICI therapy can restore exhausted T-cell activity and may contribute to a more immune-supportive TME under appropriate conditions (41). In some preclinical models and selected clinical settings, anti-CTLA-4 and anti-PD-1 blockade have also been associated with vascular changes consistent with vascular normalization.

Anti-PD-1/PD-L1 therapy can restore and activate exhausted T cells, and preclinical studies suggest that IFN-γ secreted by these activated T cells may contribute to vascular remodeling and antitumor immune responses in certain tumor settings (42). However, the effects of IFN-γ on tumor vasculature are not uniform across all tumors and may depend on tumor type, dose, timing, and the baseline immune and vascular status of the TME. Experimental studies have shown that direct signaling through IFN-γ receptors (IFNγR) can inhibit endothelial cell proliferation and survival through STAT signaling pathways, which may contribute to regression or remodeling of tumor vasculature in certain contexts (38). In addition, experimental and preclinical studies have shown that IFN-γ can induce chemokines such as CXCL9 and CXCL10, which are generally associated with recruitment of CXCR3-positive effector immune cells, including T cells and NK cells, into the TME (43). CXCL10 has been reported to exert anti-angiogenic effects by inhibiting endothelial cell proliferation and reducing vascular density in some tumor models. Similarly, CXCL9 is an IFN-γ-inducible chemokine that is generally associated with recruitment of CXCR3-positive effector immune cells and has been reported to have anti-angiogenic activity in some tumor models (44). Figure 2 summarizes this proposed preclinical mechanism.

Allen *et al*. reported that PD-L1 expression increased following anti-angiogenic therapy, providing a rationale for combining PD-1/PD-L1 pathway blockade with anti-angiogenic agents in mouse models of refractory pancreatic, breast, and brain tumors. In these preclinical

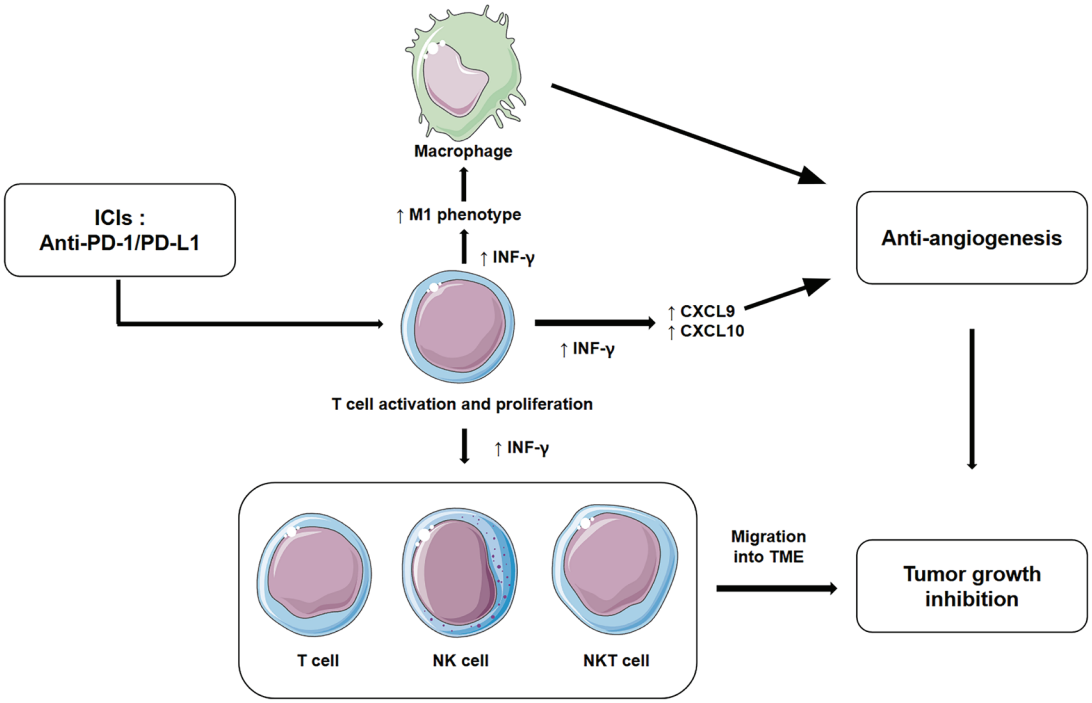

Figure 2. *Proposed preclinical pathway linking anti-PD-1/PD-L1 therapy to antitumor immunity and anti-angiogenesis. Anti-PD-1/PD-L1 blockade may promote T-cell activation and proliferation, increasing IFN-γ secretion. IFN-γ may induce CXCL9 and CXCL10 expression, support M1-like macrophage polarization, enhance immune-cell migration into the TME, and contribute to anti-angiogenic effects. Together, these processes may inhibit tumor growth in a tumor- and context-dependent manner. This schematic presents proposed preclinical mechanisms summarized from the literature and was created by the author using modified images from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Abbreviations: ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; IFN-γ, interferon gamma; CXCL9, C-X-C motif chemokine ligand 9; CXCL10, C-X-C motif chemokine ligand 10; NK cell, natural killer cell; NKT cell, natural killer T cell; TME, tumor microenvironment.*

models, anti-PD-1 therapy enhanced and prolonged the effects of anti-angiogenic treatment in pancreatic and breast cancer models. Conversely, anti-angiogenic therapy improved the activity of anti-PD-L1 treatment, particularly through increased CTL infiltration associated with therapy-induced intratumoral high endothelial venule (HEV) formation. HEVs are specialized postcapillary venules commonly located in secondary lymphoid organs, where they facilitate the migration of lymphocytes from the bloodstream into lymphoid tissues (45). HEVs can also be associated with the development of tertiary lymphoid structures, which contain organized regions enriched with dendritic cells, T cells, and B cells. These structures have been linked to improved responses to ICIs in some tumor settings, although their predictive and mechanistic significance in patients remains under investigation (46). In mouse models of breast and pancreatic cancer, combination therapy with ICIs and anti-angiogenic drugs has been reported to induce HEV formation, reduce tumor growth, and increase survival (47). These preclinical findings support a mechanistic rationale for combination therapy, although the extent of synergy and the clinical relevance of HEV induction may differ according to tumor type, drug target, dosing schedule, and the immune and vascular features of the TME.

CLINICAL EVIDENCE

Several studies have reported that combining ICIs with anti-angiogenic drugs may produce complementary or synergistic antitumor effects in selected experimental and clinical settings (48). For instance, combination therapy with immunotherapy and the anti-VEGF agent bevacizumab has been reported to inhibit the growth of lung adenocarcinoma in vivo (49). Furthermore, in preclinical models, combination therapy with anti-PD-L1 antibodies and small-molecule inhibitors of VEGFR2 has been associated with reduced PD-1/PD-L1 signaling, increased tumor-infiltrating lymphocytes, and decreased regulatory T cells and MDSCs, thereby contributing to tumor growth inhibition (50). Merder *et al*. found that combination therapy was associated with improved survival in a transgenic SCLC mouse model and suggested that adding anti-VEGF therapy to anti-PD-L1 treatment may help overcome features of anti-PD-L1 resistance related to T-cell depletion in this model (51). Based on this biological rationale, multiple small and large clinical trials have investigated the combination of immunotherapy and anti-angiogenic therapy across different tumor types. Combination therapy with anti-VEGF agents and PD-1/PD-L1 inhibitors has demonstrated clinical benefit in several settings and has been approved by the FDA for selected cancer indications. Tables 1 and 2 summarize FDA-approved ICI and anti-angiogenic combination therapies and their supporting clinical trial evidence. Table 1 presents the approved regimens, indications, treatment line, key trial, and study population, whereas Table 2 summarizes the primary endpoint, comparator, key efficacy result, and principal safety findings.

Table 1. *FDA-Approved ICI and Anti-Angiogenic Combination Therapies and Supporting Trials. In this table, VEGF indicates vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient; TKI, tyrosine-kinase inhibitor. References listed in the "Key trial" column indicate the primary clinical trial sources supporting the efficacy and safety findings summarized in each row.*

Cancer type	Combination / target	Indication / line (FDA approval year)	Key trial	Phase / population
Hepatocellular carcinoma	Atezolizumab / PD-L1 + Bevacizumab / VEGF-A	Unresectable or metastatic HCC; 1st line (2020)	IMbrave150 (52)	Phase III; previously untreated unresectable HCC
Non-small cell lung cancer	Atezolizumab / PD-L1 + Bevacizumab / VEGF-A + Carboplatin + Paclitaxel	Metastatic nonsquamous NSCLC, EGFR/ALK-negative; 1st line (2018)	IMpower150 (53)	Phase III; chemotherapy-naïve metastatic nonsquamous NSCLC
Renal cell carcinoma	Pembrolizumab / PD-1 + Axitinib / VEGFR-1/2/3	Advanced RCC; 1st line (2019)	KEYNOTE-426 (54)	Phase III; previously untreated advanced RCC

Continued Table 1. *FDA-Approved ICI and Anti-Angiogenic Combination Therapies and Supporting Trials. In this table, VEGF indicates vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient; TKI, tyrosine-kinase inhibitor. References listed in the "Key trial" column indicate the primary clinical trial sources supporting the efficacy and safety findings summarized in each row.*

Cancer type	Combination / target	Indication / line (FDA approval year)	Key trial	Phase / population
Renal cell carcinoma	Avelumab / PD-L1 + Axitinib / VEGFR-1/2/3	Advanced RCC; 1st line (2019)	JAVELIN Renal 101 (55)	Phase III; previously untreated advanced RCC
Renal cell carcinoma	Nivolumab / PD-1 + Cabozantinib / VEGFR-2 and other kinases	Advanced RCC; 1st line (2021)	CheckMate 9ER (56)	Phase III; previously untreated advanced RCC
Endometrial carcinoma	Pembrolizumab / PD-1 + Lenvatinib / VEGFR-1/2/3 and other kinases	Advanced endometrial carcinoma, non–MSI-H/ dMMR, progressed after prior therapy and not candidate for curative surgery/radiation; ≥2nd line (2021)	KEYNOTE-775 / Study 309 (57)	Phase III; advanced endometrial cancer after prior platinum therapy
Renal cell carcinoma	Pembrolizumab / PD-1 + Lenvatinib / VEGFR-1/2/3 and other kinases	Advanced RCC; 1st line(2021)	CLEAR (58)	Phase III; previously untreated advanced RCC
Cervical cancer	Pembrolizumab / PD-1 + chemotherapy ± Bevacizumab / VEGF-A	Persistent, recurrent, or metastatic cervical cancer with PD-L1 CPS ≥1; 1st line (2021)	KEYNOTE-826 (59)	Phase III; persistent, recurrent, or metastatic cervical cancer

Table 2. *Key Efficacy and Safety Findings from Supporting Clinical Trials. In this table, VEGF indicates vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; RCC, renal cell carcinoma; CPS, combined positive score; OS, overall survival; PFS, progression-free survival; TKI, tyrosine-kinase inhibitor.*

Cancer type	Combination / target	Primary endpoint / Comparator	Key efficacy result	Principal safety findings
Hepatocellular carcinoma	Atezolizumab / PD-L1 + Bevacizumab / VEGF-A	OS and PFS / Sorafenib	Improved OS and PFS versus sorafenib; 12-month OS was 67.2% vs 54.6%, respectively.	Safety was consistent with atezolizumab and bevacizumab; important concerns included hypertension, proteinuria, bleeding risk, and immune-related adverse events.
Non-small cell lung cancer	Atezolizumab / PD-L1 + Bevacizumab / VEGF-A + Carboplatin + Paclitaxel	PFS and OS / Bevacizumab + carboplatin + paclitaxel	Addition of atezolizumab to bevacizumab plus chemotherapy improved PFS and OS.	Safety reflected combined immunotherapy, anti-VEGF therapy, and chemotherapy; key toxicities included immune-related events, hypertension, bleeding risk, and chemotherapy-associated toxicity.
Renal cell carcinoma	Pembrolizumab / PD-1 + Axitinib / VEGFR-1/2/3	OS and PFS / Sunitinib	Pembrolizumab plus axitinib improved OS, PFS, and objective response rate versus sunitinib.	Overall toxicity frequency was similar between groups, but hepatic toxicity required attention with pembrolizumab plus axitinib.

Continued Table 2. *Key Efficacy and Safety Findings from Supporting Clinical Trials. In this table, VEGF indicates vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; RCC, renal cell carcinoma; CPS, combined positive score; OS, overall survival; PFS, progression-free survival; TKI, tyrosine-kinase inhibitor.*

Cancer type	Combination / target	Primary endpoint / Comparator	Key efficacy result	Principal safety findings
Renal cell carcinoma	Avelumab / PD-L1 + Axitinib / VEGFR-1/2/3	PFS and OS, especially in PD-L1-positive tumors / Sunitinib	Avelumab plus axitinib significantly prolonged PFS versus sunitinib in advanced RCC.	Grade ≥3 adverse events were frequent in both arms; hypertension, diarrhea, fatigue, and liver enzyme abnormalities were clinically relevant toxicities.
Renal cell carcinoma	Nivolumab / PD-1 + Cabozantinib / VEGFR-2 and other kinases	PFS / Sunitinib	Nivolumab plus cabozantinib improved PFS, OS, and objective response rate versus sunitinib.	Grade ≥3 adverse events were common; safety reflected both immune-related toxicity and TKI-associated toxicity.
Endometrial carcinoma	Pembrolizumab / PD-1 + Lenvatinib / VEGFR-1/2/3 and other kinases	PFS and OS / Physician's choice chemotherapy		Adverse events were frequent and often required dose interruption or reduction; hypertension and other lenvatinib-associated toxicities were important.
Renal cell carcinoma	Pembrolizumab / PD-1 + Lenvatinib / VEGFR-1/2/3 and other kinases	PFS / Sunitinib	Lenvatinib plus pembrolizumab improved PFS and OS versus sunitinib.	Grade ≥3 treatment-related adverse events were frequent, reflecting the toxicity burden of combined ICI and TKI therapy.
Cervical cancer	Pembrolizumab / PD-1 + chemotherapy ± Bevacizumab / VEGF-A	OS and PFS / Placebo + chemotherapy ± bevacizumab	Pembrolizumab plus chemotherapy, with or without bevacizumab, improved PFS and OS versus placebo plus chemotherapy.	Safety was consistent with pembrolizumab, chemotherapy, and bevacizumab; immune-related events, myelosuppression, hypertension, and bleeding/thrombotic risks were clinically relevant.

SAFETY AND RESISTANCE

ICIs can lead to the deactivation of T-cell regulatory pathways which results in various immune-related adverse events (irAEs). Mechanisms of irAE development are unknown but are likely to be mediated through a complex cascade of autoreactive T cells, autoantibodies and cytokine mediated inflammation (60). IrAEs present in different patterns, processes and clinical manifestations with potential toxicities affecting virtually any organ system. The most frequently reported irAE is dermatologic toxicity, and other commonly reported irAEs, such as colitis, hepatitis, endocrine dysfunction, pituitary toxicity, and pneumonitis have also been reported to a great extent. Neurologic, renal, ocular, and cardiovascular toxicities have been less frequently noted (61). These toxicities frequently necessitate targeted treatments such as corticosteroids or other immunomodulatory treatments (62). Recognizing and appropriately managing the unique toxicity profile of immunotherapy is essential for reducing irAEs, and further research is needed to clarify the underlying pathophysiologic mechanisms that drive these toxicities.

In addition to safety concerns, therapeutic resistance remains a major limitation of ICI and anti-angiogenic combination therapy. Resistance may arise from tumor-intrinsic mechanisms, vascular adaptation, and immune remodeling within the TME. One important mechanism is activation of alternative angiogenic pathways. Although VEGF/VEGFR signaling is a central target of many anti-angiogenic agents, tumors may compensate through other pro-angiogenic pathways, including fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR), platelet-derived growth factor/platelet-derived

growth factor receptor (PDGF/PDGFR), angiopoietin-2/tyrosine-protein kinase receptor TIE2 (ANGPT2/TIE2), hepatocyte growth factor/mesenchymal-epithelial transition factor (HGF/MET), and other angiogenesis-related signals (63, 64). These compensatory pathways may allow tumors to maintain vascular supply despite VEGF pathway inhibition and may partially explain why some tumors respond poorly or eventually progress after anti-angiogenic therapy (63, 64).

Tumors may also evade anti-angiogenic therapy through vessel co-option, in which cancer cells use pre-existing host vessels rather than generating new vessels. This mechanism allows tumor growth and invasion without depending entirely on VEGF-driven angiogenesis (65). In addition, excessive or prolonged inhibition of angiogenesis may worsen hypoxia in some tumors. Hypoxia can promote adaptive resistance by increasing invasive behavior, altering tumor metabolism, upregulating immunosuppressive signaling, and recruiting suppressive myeloid populations (63, 64). These changes may reduce the immune-supportive effects expected from vascular normalization and may limit the benefit of combination therapy with anti-angiogenic therapy and ICIs (63, 64).

Resistance to ICIs may also arise through immune evasion mechanisms. Tumors with impaired antigen presentation, including defects in major histocompatibility complex expression, antigen-processing machinery, or interferon signaling, may be less visible to tumor-specific T cells (66 , 67). In addition, T-cell exclusion from the tumor parenchyma can prevent activated lymphocytes from reaching malignant cells even when systemic immune activation occurs. Recruitment of immunosuppressive myeloid cells, including MDSCs, M2-like TAMs, and other stromal populations, can further suppress cytotoxic T-cell activity and promote resistance (67). Acquired resistance may also involve upregulation of alternative immune checkpoints or compensatory inhibitory pathways after initial response to PD-1/PD-L1 or CTLA-4 blockade (66 , 67).

These resistance mechanisms are important because they help explain why combination therapy with ICIs and anti-angiogenic agents is effective in some tumor types and patient populations but not in others. The success of combination therapy likely depends on whether anti-angiogenic treatment improves vascular function and immune cell infiltration, or instead promotes vascular pruning, hypoxia, myeloid recruitment, and immune exclusion (63, 64, 67). Therefore, future studies should define tumor-specific resistance mechanisms and evaluate strategies that target both VEGF-dependent and VEGF-independent angiogenic pathways, immune exclusion programs, antigen presentation defects, and compensatory checkpoint signaling. A better understanding of these mechanisms may support more rational treatment sequencing, biomarker-guided patient selection, and development of next-generation combination therapies.

BIOMARKERS

Predictive biomarkers indicate the likelihood of response or benefit from a specific therapeutic strategy. Predictive biomarkers are needed to identify patients most likely to benefit from ICI and anti-angiogenic combination therapy, while minimizing unnecessary treatment exposure, financial burden, and treatment-related toxicity. In the context of ICI and anti-angiogenic combination therapy, an ideal biomarker should predict not only treatment response but also the risk of irAEs and resistance.

PD-L1 expression has been widely investigated as a biomarker for ICI response. PD-L1 expression on tumor cells, tumor-infiltrating immune cells, and immune cells within the TME may reflect dependence on the PD-1/PD-L1 immune escape pathway. However, PD-L1 expression is an imperfect and context-dependent biomarker. Some studies have reported an association between higher PD-L1 expression and improved response to anti-PD-1 or anti-PD-L1 therapy, whereas others have found no clear relationship between PD-L1 expression and survival benefit in patients receiving combination therapy (68, 69). In addition, PD-L1 is not specific to ICI and anti-angiogenic combination therapy, and its interpretation is limited by assay variability, differences in scoring systems, spatial heterogeneity within tumors, temporal changes during treatment, and tumor-specific thresholds. Therefore, PD-L1 expression alone is insufficient to guide patient selection for combination therapy.

Tumor mutational burden (TMB) is another biomarker associated with ICI response. Tumors with high TMB may generate more neoantigens, increasing the likelihood of immune recognition and response to ICIs (70, 71). However, TMB is also imperfect and context-dependent. Its predictive value varies across tumor types, and high TMB does not always translate into effective antitumor immunity. In addition, TMB measurement can be influenced by differences in sequencing platforms, cutoff values, tumor purity, sample quality, and bioinformatic pipelines. TMB is also not specific to ICI and anti-

angiogenic combination therapy. Although patients with both high TMB and high PD-L1 expression may experience greater benefit from ICI-based therapy in some settings, TMB and PD-L1 levels are not strongly correlated, suggesting that they represent different aspects of tumor immunobiology (72).

Microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) is another clinically important biomarker for immunotherapy. MSI-H/dMMR tumors often have increased neoantigen formation and may respond well to ICIs. However, MSI-H/dMMR status is present only in selected tumor types and does not specifically predict benefit from adding anti-angiogenic therapy. Therefore, MSI-H/dMMR should be interpreted as part of a broader biomarker framework rather than as a standalone marker for combination therapy with ICIs and anti-angiogenic agents (73).

Because anti-angiogenic therapy directly targets vascular signaling, angiogenesis-related biomarkers may be particularly relevant for combination therapy. VEGF-associated markers, VEGFA expression, VEGFR pathway activation, angiopoietin-related markers, and broader angiogenesis-related gene signatures may help identify tumors in which vascular dysfunction contributes to immune suppression. In hepatocellular carcinoma, exploratory biomarker analyses of atezolizumab plus bevacizumab have suggested that immune and angiogenesis-related gene-expression patterns may be associated with treatment response, supporting the potential value of integrated gene-signature approaches (74). However, these signatures remain investigational and require prospective validation before clinical use.

Immune cell infiltration within the TME may also help predict response. High baseline infiltration of $CD8^+$ T cells, activated effector T cells, dendritic cells, or IFN-related immune signatures may indicate a pre-existing antitumor immune response that can be enhanced by ICIs. In contrast, enrichment of Tregs, MDSCs, M2-like macrophages, or other immunosuppressive cell populations may be associated with resistance or reduced response. However, immune-cell infiltration is highly heterogeneous within and between tumors, and biopsy-based assessment may not fully represent the entire tumor immune landscape (75, 76)

Circulating biomarkers may provide a less invasive method for monitoring response and resistance. Potential circulating markers include circulating VEGF or angiopoietin-2 levels, soluble PD-L1, cytokine profiles, circulating immune-cell subsets, circulating tumor DNA (ctDNA), and blood-based TMB. These markers may be useful for dynamic monitoring because they can be measured repeatedly during treatment. However, circulating biomarkers are influenced by tumor burden, systemic inflammation, prior therapy, and assay platform, and their clinical utility in ICI and anti-angiogenic combination therapy remains under investigation (77) .

Radiomic and imaging-based biomarkers may also contribute to patient selection and response monitoring. Imaging features related to tumor vascularity, perfusion, hypoxia, necrosis, and spatial heterogeneity may help assess vascular normalization or immune-related changes in the TME. Radiomic models using CT, MRI, or PET imaging have been investigated as noninvasive predictors of immunotherapy response, but these approaches require further standardization and external validation before clinical application (78).

Overall, no single biomarker is sufficient to predict response to combination therapy with ICIs and anti-angiogenic agents. Future studies should focus on composite biomarker strategies that integrate PD-L1 expression, TMB, MSI/dMMR status, angiogenesis-related gene signatures, VEGF-associated markers, immune-cell infiltration, circulating biomarkers, radiomic features, and clinical factors. Such multidimensional approaches may better capture the complexity of vascular-immune regulation in the TME. However, future biomarker development must address major limitations, including assay variability, tumor heterogeneity, temporal changes during treatment, differences between primary and metastatic lesions, prior treatment effects, and tumor-specific thresholds. Prospective validation in well-defined cohorts will be essential before these biomarker strategies can guide clinical use of combination therapy with ICIs and anti-angiogenic agents.

FUTURE RESEARCH DIRECTIONS

Future research should focus on optimizing combination therapy with ICIs and anti-angiogenic agents through more precise patient selection, improved treatment sequencing, and better long-term safety evaluation. Although this therapeutic strategy has demonstrated clinical benefit and has been approved for selected cancer indications, several questions remain regarding the mechanisms, durability, and optimal clinical use of these combinations.

One important priority is to clarify the role of vascular normalization in combination therapy. Anti-angiogenic therapy may improve antitumor immunity by

reducing hypoxia, improving perfusion, and facilitating the infiltration and function of antitumor immune cells. However, vascular normalization should not be viewed as a universal or permanent effect. Its extent and duration may vary according to tumor type, disease stage, baseline vascular structure, anti-angiogenic target, dose, treatment schedule, and patient-specific factors. Therefore, further studies are needed to determine whether the clinical benefit of anti-angiogenic therapy results primarily from vascular normalization, vascular disruption, immune modulation, or a combination of these mechanisms.

The optimal timing, dosing, and sequencing of ICIs with anti-angiogenic agents also require further investigation. Some studies suggest that anti-angiogenic therapy may create a temporary period of improved vascular function, but the duration of this window has been described mainly in limited experimental or tumor-specific settings and should not be generalized across all agents, tumor types, or patients (79). In addition, optimal sequencing may differ between monoclonal antibodies and small-molecule tyrosine-kinase inhibitors because of differences in half-life, target specificity, pharmacodynamic effects, and dose-dependent vascular responses. Future studies should therefore define agent-specific dosing schedules and treatment durations that maximize immune activation while minimizing excessive vascular pruning, hypoxia, and toxicity.

Research should also focus on predicting and preventing irAEs. Biomarkers that identify patients at higher risk for organ-specific inflammatory toxicities could improve clinical monitoring, guide early intervention, and reduce unnecessary treatment burden. This is particularly important because combination therapy may influence both therapeutic efficacy and immune-related toxicity through changes in angiogenic signaling, immune-cell trafficking, and the TME.

Another major priority is the development and validation of integrated biomarker strategies for treatment response, toxicity risk, resistance, and patient selection. Because single biomarkers such as PD-L1 expression, TMB, and MSI/dMMR status have imperfect and context-dependent predictive value, future studies should move toward composite models that integrate immune, angiogenic, molecular, circulating, imaging-based, and clinical features. These may include immune-cell infiltration, IFN-related signatures, VEGF-associated markers, angiogenesis-related gene signatures, ctDNA or other circulating biomarkers, radiomic features, and TME characteristics. Such models may help identify patients most likely to benefit from combination therapy with ICIs and anti-angiogenic agents while also predicting irAE risk and resistance. Prospective validation will be essential because biomarker interpretation remains limited by assay variability, tumor heterogeneity, temporal changes during treatment, prior therapy, and tumor-specific thresholds.

Finally, longer follow-up studies are needed to evaluate the durability of clinical benefit and long-term safety outcomes. Since many ICI and anti-angiogenic combinations have only recently been developed and approved, evidence regarding long-term efficacy remains limited. Future prospective trials and real-world studies should also clarify whether these therapies produce true synergistic effects or primarily provide additive benefits across different tumor types and organ systems. Distinguishing synergy from additive benefit will be essential for optimizing treatment selection, dosing, timing, duration, and toxicity management in patients receiving ICI and anti-angiogenic combination therapy.

CONCLUSION

Combination therapy with ICIs and anti-angiogenic agents provides a biologically rational strategy for improving antitumor immunity by targeting reciprocal interactions between tumor vasculature and the immune microenvironment. Anti-angiogenic therapy may reduce VEGF-mediated immunosuppression, improve vascular function under selected conditions, and facilitate antitumor immune-cell infiltration, whereas ICIs can restore exhausted T-cell activity and enhance immune-mediated tumor control. These mechanisms are partly established through preclinical, translational, and clinical studies, but their effects remain tumor-specific, drug-specific, dose-dependent, and context-dependent.

Clinically, Combination therapy with ICIs and anti-angiogenic agents has demonstrated benefit in selected tumor types, including hepatocellular carcinoma, non-small cell lung cancer, renal cell carcinoma, endometrial carcinoma, and cervical cancer. However, the magnitude of benefit differs across cancer types, treatment lines, and regimens. Therefore, these combinations should not be viewed as uniformly effective across all solid tumors.

Important challenges remain, including irAE, anti-angiogenic toxicities, acquired resistance, and uncertainty regarding optimal dose, timing, sequencing, and duration of therapy. Resistance may arise through alternative angiogenic pathways, vessel co-option, hypoxia-driven adaptation, myeloid-cell recruitment,

T-cell exclusion, antigen-presentation defects, and compensatory immune-checkpoint signaling.

Future research should focus on prospective validation of integrated biomarker strategies, improved prediction and management of toxicity, clarification of tumor-specific resistance mechanisms, optimization of treatment sequencing, and longer follow-up to determine durability of clinical benefit and long-term safety. Addressing these priorities will be essential for refining ICI and anti-angiogenic combination therapy and expanding its effective use in appropriately selected patients.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

REFERENCES

1. National Cancer Institute. Cancer Statistics. Available from: https://www.cancer.gov/about-cancer/understanding/statistics (accessed on 2026-01-15).
2. Munir M, Cheema AY, Ogedegbe OJ, Aslam MF, Kim S. William coley: the pioneer and the father of immunotherapy. *Cureus*. 2024 Sep 10; 16 (9): e69113. https://doi.org/10.7759/cureus.69113
3. Di Trolio R, Simeone E, Di Lorenzo G, Buonerba C, Ascierto PA. The use of interferon in melanoma patients: a systematic review. *Cytokine Growth Factor Rev.* 2015 Apr; 26 (2): 203-12. https://doi.org/10.1016/j.cytogfr.2014.11.008
4. Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH. A review of cancer immunotherapy: from the past, to the present, to the future. *Curr Oncol*. 2020 Apr 1; 27 (Suppl 2): S87-97. https://doi.org/10.3747/co.27.5223
5. Raica M, Cimpean AM. Platelet-Derived Growth Factor (PDGF)/PDGF Receptors (PDGFR) Axis as Target for Antitumor and Antiangiogenic Therapy. *Pharmaceuticals (Basel)*. 2010 Mar 11; 3 (3): 572-99. https://doi.org/10.3390/ph3030572
6. Ribatti D. The fundamental contribution of judah folkman in the setting of angiogenesis assays. *Methods Mol Biol.* 2021; 2206: 15-25. https://doi.org/10.1007/978-1-0716-0916-3_2
7. Muik A, Garralda E, Altintas I, Gieseke F, Geva R, Ben-Ami E, *et al*. Preclinical Characterization and Phase I Trial Results of a Bispecific Antibody Targeting PD-L1 and 4-1BB (GEN1046) in Patients with Advanced Refractory Solid Tumors. *Cancer Discov*. 2022 May 2; 12 (5): 1248-65. https://doi.org/10.1158/2159-8290.CD-21-1345
8. Bhatia A, Kumar Y. Cellular and molecular mechanisms in cancer immune escape: a comprehensive review. *Expert Rev Clin Immunol*. 2014 Jan; 10 (1): 41-62.https://doi.org/10.1586/1744666X.2014.865519
9. O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat Rev Clin Oncol*. 2019 Mar; 16 (3): 151-67. https://doi.org/10.1038/s41571-018-0142-8
10. Funt SA, Page DB, Wolchok JD, Postow MA. CTLA-4 antibodies: new directions, new combinations. Oncology (Williston Park, NY). 2014 Nov; 28 Suppl 3: 6-14.
11. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest*. 2015 Sep 1; 125 (9): 3384-91. https://doi.org/10.1172/JCI80011
12. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer*. 2016 May; 16 (5): 275-87. https://doi.org/10.1038/nrc.2016.36
13. Reiss KA, Forde PM, Brahmer JR. Harnessing the power of the immune system via blockade of PD-1 and PD-L1: a promising new anticancer strategy. *Immunotherapy*. 2014; 6 (4): 459-75. https://doi.org/10.2217/imt.14.9
14. Chen Y, Yu D, Qian H, Shi Y, Tao Z. CD8+ T cell-based cancer immunotherapy. *J Transl Med*. 2024 Apr 29; 22 (1): 394. https://doi.org/10.1186/s12967-024-05134-6
15. Park J, Skålhegg BS. Combination of PD-1/PD-L1 and CTLA-4 inhibitors in the treatment of cancer - a brief update. *Front Immunol*. 2025 Oct 13; 16: 1680838. https://doi.org/10.3389/fimmu.2025.1680838
16. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003 Jun; 9 (6): 669-76. https://doi.org/10.1038/nm0603-669
17. Fischer C, Mazzone M, Jonckx B, Carmeliet P. FLT1 and its ligands VEGFB and PlGF: drug targets for anti-angiogenic therapy? *Nat Rev Cancer*. 2008 Dec; 8 (12): 942-56. https://doi.org/10.1038/nrc2524
18. Goel HL, Mercurio AM. VEGF targets the tumour cell. *Nat Rev Cancer*. 2013 Dec; 13 (12): 871-82. https://doi.org/10.1038/nrc3627
19. Ferrara N, Hillan KJ, Gerber H-P, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov*. 2004 May; 3 (5): 391-400. https://doi.org/10.1038/nrd1381
20. Zhang J, Shi Z, Xu X, Yu Z, Mi J. The influence of microenvironment on tumor immunotherapy. *FEBS*

J. 2019 Nov; 286 (21): 4160-75. https://doi.org/10.1111/febs.15028
21. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol.* 2018 May; 15 (5): 325-40. https://doi.org/10.1038/nrclinonc.2018.29
22. Rahma OE, Hodi FS. The Intersection between Tumor Angiogenesis and Immune Suppression. *Clin Cancer Res.* 2019 Sep 15; 25 (18): 5449-57. https://doi.org/10.1158/1078-0432.CCR-18-1543
23. Scharping NE, Delgoffe GM. Tumor Microenvironment Metabolism: A New Checkpoint for Anti-Tumor Immunity. *Vaccines (Basel)*. 2016 Dec 6; 4 (4). https://doi.org/10.3390/vaccines4040046
24. Park J-S, Kim I-K, Han S, Park I, Kim C, Bae J, *et al*. Normalization of tumor vessels by tie2 activation and ang2 inhibition enhances drug delivery and produces a favorable tumor microenvironment. *Cancer Cell*. 2017 Jan 9; 31 (1): 157-8. https://doi.org/10.1016/j.ccell.2016.12.009
25. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer.* 2019 Mar 30; 18 (1): 60. https://doi.org/10.1186/s12943-019-0974-6
26. Schaaf MB, Garg AD, Agostinis P. Defining the role of the tumor vasculature in antitumor immunity and immunotherapy. *Cell Death Dis.* 2018 Jan 25; 9 (2): 115. https://doi.org/10.1038/s41419-017-0061-0
27. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cell Mol Life Sci.* 2020 May; 77 (9): 1745-70. https://doi.org/10.1007/s00018-019-03351-7
28. Tsai M-J, Chang W-A, Huang M-S, Kuo P-L. Tumor microenvironment: a new treatment target for cancer. *ISRN Biochem*. 2014 Apr 10; 2014: 351959. https://doi.org/10.1155/2014/351959
29. Motz GT, Santoro SP, Wang L-P, Garrabrant T, Lastra RR, Hagemann IS, *et al*. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat Med*. 2014 Jun; 20 (6): 607-15. https://doi.org/10.1038/nm.3541
30. Malo CS, Khadka RH, Ayasoufi K, Jin F, AbouChehade JE, Hansen MJ, *et al*. Immunomodulation Mediated by Anti-angiogenic Therapy Improves CD8 T Cell Immunity Against Experimental Glioma. *Front Oncol*. 2018 Aug 20; 8: 320. https://doi.org/10.3389/fonc.2018.00320
31. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet A-L, *et al*. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med*. 2015 Feb 9; 212 (2): 139-48. https://doi.org/10.1084/jem.20140559
32. Lee WS, Yang H, Chon HJ, Kim C. Combination of anti-angiogenic therapy and immune checkpoint blockade normalizes vascular-immune crosstalk to potentiate cancer immunity. *Exp Mol Med*. 2020 Sep 11; 52 (9): 1475-85. https://doi.org/10.1038/s12276-020-00500-y
33. Hughes R, Qian B-Z, Rowan C, Muthana M, Keklikoglou I, Olson OC, *et al*. Perivascular M2 Macrophages Stimulate Tumor Relapse after Chemotherapy. *Cancer Res*. 2015 Sep 1; 75 (17): 3479-91. https://doi.org/10.1158/0008-5472.CAN-14-3587
34. Padzińska-Pruszyńska IB, Taciak B, Kiraga Ł, Smolarska A, Górczak M, Kucharzewska P, *et al*. Targeting cancer: microenvironment and immunotherapy innovations. *Int J Mol Sci*. 2024 Dec 18; 25 (24). https://doi.org/10.3390/ijms252413569
35. Facciabene A, Motz GT, Coukos G. T-regulatory cells: key players in tumor immune escape and angiogenesis. *Cancer Res*. 2012 May 1; 72 (9): 2162-71. https://doi.org/10.1158/0008-5472.CAN-11-3687
36. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol*. 2010 Oct; 11 (10): 889-96. https://doi.org/10.1038/ni.1937
37. Albini A, Bruno A, Noonan DM, Mortara L. Contribution to tumor angiogenesis from innate immune cells within the tumor microenvironment: implications for immunotherapy. *Front Immunol*. 2018 Apr 5; 9: 527. https://doi.org/10.3389/fimmu.2018.00527
38. Kammertoens T, Friese C, Arina A, Idel C, Briesemeister D, Rothe M, *et al*. Tumour ischaemia by interferon-γ resembles physiological blood vessel regression. *Nature*. 2017 May 4; 545 (7652): 98-102. https://doi.org/10.1038/nature22311
39. Fathallah-Shaykh HM, Zhao LJ, Kafrouni AI, Smith GM, Forman J. Gene transfer of IFN-gamma into established brain tumors represses growth by antiangiogenesis. *J Immunol*. 2000 Jan 1; 164 (1): 217-22. https://doi.org/10.4049/jimmunol.164.1.217
40. Bromley SK, Mempel TR, Luster AD. Orchestrating the orchestrators: chemokines in control of T cell traffic. *Nat Immunol*. 2008 Sep; 9 (9): 970-80. https://doi.org/10.1038/ni.f.213
41. Zhou Y, Liu Z, Yu A, Zhao G, Chen B. Immune Checkpoint Inhibitor Combined with Antiangiogenic Agent Synergistically Improving the Treatment Efficacy for Solid Tumors. *Immunotargets Ther.* 2024 Dec 31; 13: 813-29. https://doi.org/10.2147/ITT.S494670
42. Kuo H-Y, Khan KA, Kerbel RS. Antiangiogenic-immune-checkpoint inhibitor combinations: lessons from phase III clinical trials. *Nat Rev Clin Oncol*. 2024 Jun; 21 (6): 468-82. https://doi.org/10.1038/s41571-024-

00886-y
43. House IG, Savas P, Lai J, Chen AXY, Oliver AJ, Teo ZL, *et al*. Macrophage-Derived CXCL9 and CXCL10 Are Required for Antitumor Immune Responses Following Immune Checkpoint Blockade. *Clin Cancer Res.* 2020 Jan 15; 26 (2): 487-504. https://doi.org/10.1158/1078-0432.CCR-19-1868
44. De Zutter A, Crijns H, Berghmans N, García-Caballero M, Vanbrabant L, Pörtner N, *et al*. The Chemokine-Based Peptide, CXCL9(74-103), Inhibits Angiogenesis by Blocking Heparan Sulfate Proteoglycan-Mediated Signaling of Multiple Endothelial Growth Factors. *Cancers (Basel)*. 2021 Oct 12; 13 (20). https://doi.org/10.3390/cancers13205090
45. Asrir A, Tardiveau C, Coudert J, Laffont R, Blanchard L, Bellard E, *et al*. Tumor-associated high endothelial venules mediate lymphocyte entry into tumors and predict response to PD-1 plus CTLA-4 combination immunotherapy. *Cancer Cell*. 2022 Mar 14; 40 (3): 318-334.e9. https://doi.org/10.1016/j.ccell.2022.01.002
46. Ruddle NH. From lymphotoxin to tertiary lymphoid structures and beyond. *Immunol Rev*. 2025 Oct; 335 (1): e70062. https://doi.org/10.1111/imr.70062
47. Allen E, Jabouille A, Rivera LB, Lodewijckx I, Missiaen R, Steri V, *et al*. Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation. *Sci Transl Med*. 2017 Apr 12; 9 (385). https://doi.org/10.1126/scitranslmed.aak9679
48. Pircher A, Wolf D, Heidenreich A, Hilbe W, Pichler R, Heidegger I. Synergies of Targeting Tumor Angiogenesis and Immune Checkpoints in Non-Small Cell Lung Cancer and Renal Cell Cancer: From Basic Concepts to Clinical Reality. *Int J Mol Sci*. 2017 Oct 31; 18 (11). https://doi.org/10.3390/ijms18112291
49. Tao L, Huang G, Shi S, Chen L. Bevacizumab improves the antitumor efficacy of adoptive cytokine-induced killer cells therapy in non-small cell lung cancer models. *Med Oncol*. 2014 Jan; 31 (1): 777. https://doi.org/10.1007/s12032-013-0777-3
50. Manegold C, Dingemans A-MC, Gray JE, Nakagawa K, Nicolson M, Peters S, *et al*. The potential of combined immunotherapy and antiangiogenesis for the synergistic treatment of advanced NSCLC. *J Thorac Oncol*. 2017 Feb; 12 (2): 194-207. https://doi.org/10.1016/j.jtho.2016.10.003
51. Meder L, Schuldt P, Thelen M, Schmitt A, Dietlein F, Klein S, *et al*. Combined VEGF and PD-L1 Blockade Displays Synergistic Treatment Effects in an Autochthonous Mouse Model of Small Cell Lung Cancer. *Cancer Res*. 2018 Aug 1; 78 (15): 4270-81. https://doi.org/10.1158/0008-5472.CAN-17-2176
52. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, *et al*. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020 May 14; 382 (20): 1894-905. https://doi.org/10.1056/NEJMoa1915745
53. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, *et al*. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med*. 2018 Jun 14; 378 (24): 2288-301. https://doi.org/10.1056/NEJMoa1716948
54. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, *et al*. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019 Mar 21; 380 (12): 1116-27. https://doi.org/10.1056/NEJMoa1816714
55. Motzer RJ, Penkov K, Haanen J, Rini BI, Albiges L, Campbell MT, *et al*. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019 Mar 21; 380 (12): 1103-15. https://doi.org/10.1056/NEJMoa1816047
56. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, *et al*. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2021 Mar 4; 384 (9): 829-41. https://doi.org/10.1056/NEJMoa2026982
57. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, *et al*. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *N Engl J Med*. 2022 Feb 3; 386 (5): 437-48. https://doi.org/10.1056/NEJMoa2108330
58. Motzer R, Alekseev B, Rha S-Y, Porta C, Eto M, Powles T, *et al*. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021 Apr 8; 384 (14): 1289-300. https://doi.org/10.1056/NEJMoa2035716
59. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, *et al*. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med*. 2021 Nov 11; 385 (20): 1856-67. https://doi.org/10.1056/NEJMoa2112435
60. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med*. 2018 Jan 11; 378 (2): 158-68. https://doi.org/10.1056/NEJMra1703481
61. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020 Mar; 70 (2): 86-104. https://doi.org/10.3322/caac.21596
62. Horvat TZ, Adel NG, Dang T-O, Momtaz P, Postow MA, Callahan MK, *et al*. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*. 2015 Oct 1; 33 (28): 3193-8. https://doi.org/10.1200/JCO.2015.60.8448

63. Haibe Y, Kreidieh M, El Hajj H, Khalifeh I, Mukherji D, Temraz S, *et al*. Resistance mechanisms to anti-angiogenic therapies in cancer. *Front Oncol*. 2020 Feb 14; 10: 221. https://doi.org/10.3389/fonc.2020.00221
64. Montemagno C, Pagès G. Resistance to anti-angiogenic therapies: A mechanism depending on the time of exposure to the drugs. *Front Cell Dev Biol*. 2020 Jul 3; 8: 584. https://doi.org/10.3389/fcell.2020.00584
65. Ribatti D, Annese T, Ruggieri S, Tamma R, Crivellato E. Vascular co-option in resistance to anti-angiogenic therapy. *Cancers (Basel)*. 2023 Nov 24; 15 (23): 5532. https://doi.org/10.3389/fonc.2023.1323350
66. Nowicki TS, Hu-Lieskovan S, Ribas A. Mechanisms of resistance to PD-1 and PD-L1 blockade. *Cancer J.* 2018 Jan/Feb; 24 (1): 47-53. https://doi.org/10.1097/PPO.0000000000000303
67. Zhou X, Yao Z, Bai H, Duan J, Wang Z, Wang X, *et al*. Mechanisms of tumor resistance to immune checkpoint blockade and combination strategies to overcome resistance. *Front Immunol*. 2022 Sep 23; 13: 915094. https://doi.org/10.3389/fimmu.2022.915094
68. Wang Q, Liu F, Liu L. Prognostic significance of PD-L1 in solid tumor: An updated meta-analysis. *Medicine (Baltimore)*. 2017 May; 96 (18): e6369. https://doi.org/10.1097/MD.0000000000006369
69. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, *et al*. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018 Apr 5; 378 (14): 1277-90. https://doi.org/10.1056/NEJMoa1712126
70. Kakimi K, Karasaki T, Matsushita H, Sugie T. Advances in personalized cancer immunotherapy. *Breast Cancer.* 2017 Jan; 24 (1): 16-24. https://doi.org/10.1007/s12282-016-0688-1
71. Gandara DR, Agarwal N, Gupta S, Klempner SJ, Andrews MC, Mahipal A, *et al*. Tumor mutational burden and survival on immune checkpoint inhibition in >8000 patients across 24 cancer types. *J Immunother Cancer.* 2025 Feb 6; 13 (2). https://doi.org/10.1136/jitc-2024-010311
72. Zhang M, Liu C, Tu J, Tang M, Ashrafizadeh M, Nabavi N, *et al*. Advances in cancer immunotherapy: historical perspectives, current developments, and future directions. *Mol Cancer.* 2025 May 7; 24 (1): 136. https://doi.org/10.1186/s12943-025-02305-x
73. Marcus L, Fashoyin-Aje LA, Donoghue M, Yuan M, Rodriguez L, Gallagher PS, *et al*. FDA Approval Summary: Pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clin Cancer Res*. 2021 Sep 1; 27 (17): 4685-9. https://doi.org/10.1158/1078-0432.CCR-21-0327
74. Yim SY, Lee SH, Baek SW, Sohn B, Jeong YS, Kang SH, *et al*. Genomic biomarkers to predict response to atezolizumab plus bevacizumab immunotherapy in hepatocellular carcinoma: Insights from the IMbrave150 trial. *Clin Mol Hepatol*. 2024; 30: 807-23. https://doi.org/10.3350/cmh.2024.0333
75. Garris CS, Arlauckas SP, Kohler RH, Trefny MP, Garren S, Piot C, *et al*. Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving the cytokines IFN-γ and IL-12. *Immunity*. 2018 Dec 18; 49 (6): 1148-61.e7. https://doi.org/10.1016/j.immuni.2018.09.024
76. Zhu AX, Abbas AR, de Galarreta MR, Guan Y, Lu S, Koeppen H, *et al*. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. *Nat Med*. 2022 Aug; 28 (8): 1599-611. https://doi.org/10.1038/s41591-022-01868-2
77. Goh KY, Heong V, Wang YT. Circulating biomarkers for prediction of immunotherapy benefit in non-small cell lung cancer. *Biomedicines*. 2023 Feb; 11 (2): 508. https://doi.org/10.3390/biomedicines11020508
78. Summers RM. Imaging biomarkers to assess response to immune checkpoint inhibitor therapy. *Diagnostics*. 2021 Apr; 11 (4): 693.
79. Goel S, Duda DG, Xu L, Munn LL, Boucher Y, Fukumura D, *et al*. Normalization of the vasculature for treatment of cancer and other diseases. *Physiol Rev.* 2011 Jul; 91 (3): 1071-121. https://doi.org/10.1152/physrev.00038.2010