

Tumor vessel normalization and immunotherapy in gastric cancer

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Abstract: Gastric cancer (GC) is a common malignant tumor, and patients with GC have a low survival rate due to limited effective treatment methods. Angiogenesis and immune evasion are two key processes in GC progression, and they act synergistically to promote tumor progression. Tumor vascular normalization has been shown to improve the efficacy of cancer immunotherapy, which in turn may be improved through enhanced immune stimulation. Therefore, it may be interesting to identify synergies between immunomodulatory agents and anti-angiogenic therapies in GC. This strategy aims to normalize the tumor microenvironment through the action of the anti-vascular endothelial growth factor while stimulating the immune response through immunotherapy and prolonging the survival of GC patients.

Keywords: gastric cancer, immune checkpoint inhibitors, immune microenvironment, immunotherapy, vessel normalization

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Background

According to the 2018 global cancer statistics, there were more than 1 million new diagnoses of gastric cancer (GC) and more than 800,000 deaths worldwide during the same year, making it the second leading cause of cancer-related death and the fifth most common tumor worldwide.^{1–3} Treatment for GC includes a combination of surgery, radiotherapy, chemotherapy, and biotherapy.⁴ Despite numerous advances in the treatment of GC, recurrence and metastasis remain the two main challenges for GC patients.⁵ For patients with early-stage GC, the 5-year overall survival (OS) rate is 90%.⁶ However, approximately 50% of patients present with advanced GC at diagnosis, and approximately 40–60% of patients who undergo radical resection show recurrence. For such patients, palliative systemic therapy is the gold standard, and the median survival rarely exceeds 12 months.⁷

Risk factors for GC include many non-modifiable variables: age, sex, race, and ethnicity.⁸ Modifiable risk factors include *Helicobacter pylori* infection, smoking, high nitrate and nitrite diets, and some relatively rare risk factors such as history of

previous gastric surgery and family history.^{9,10} These oncogenic factors play a critical role in GC cell progression and metastasis, involving intracellular changes at the molecular level, such as genetic mutations, epigenetic changes, and abnormalities in molecular signaling pathways.¹¹

Molecular classification of GC based on gene expression profiles can be divided into four types: Epstein–Barr virus (EBV) positive, microsatellite instability (MSI), genomic stability, and chromosomal instability. Each type has different molecular features, indicating the upregulation of different molecular pathways in tumor cells.¹² MSI is an important indicator of defective DNA mismatch repair (MMR) and the primary factor involved in the rapid accumulation of genetic changes during gastric carcinogenesis.¹³ MSI and EBV-positive tumors have been shown to be key predictors of immunotherapy efficacy in GC.¹⁴

The tumor component comprises a complex tumor microenvironment (TME) containing cancer cells, stromal cells, and macrophages, as well as distantly recruited cells that secrete factors.^{15,16} Through their autocrine and paracrine effects,

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they can influence the development of tumors.¹⁷ Tumor cells cause various biobehavioral changes, such as induction of proliferation and angiogenesis, and induction of immune tolerance, through direct or indirect interactions with other TME components.¹⁵ The stromal microenvironment plays an important role in maintaining normal tissue homeostasis or promoting tumor development, and a large number of immune cells are part of the GC microenvironment.¹⁸ Based on a deeper understanding of cancer biology, which has led to the development of angiogenesis inhibitors and immunotherapy as cancer therapies, combined treatment strategies for both are being studied in a growing number of solid tumors and have shown significant improvements in the restoration of immune infiltration and response.¹⁹ Since 2018, the Food and Drug Administration (FDA) has approved five combinations of immune checkpoint inhibitors (ICIs) and anti-angiogenic drugs for the treatment of renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma, and endometrial cancer.²⁰ The combination of anti-angiogenic therapy and immunotherapy has been successfully applied for the treatment of several tumor entities such as hepatocellular carcinoma, RCC, endometrial cancer, and NSCLC (Table 1).

Fibroblast growth factors (FGFs) and their receptors control a wide range of biological functions that regulate cell proliferation, survival, migration, and differentiation, and FGF signaling can drive tumorigenesis.²¹ Indeed, aberrant FGF signaling can affect cell proliferation, cell death resistance, enhanced motility and aggressiveness,

increased angiogenesis, enhanced metastasis, and chemoresistance in a wide range of tumor types.²² This review explores the clinical application of combined treatment with anti-angiogenic drugs and immunotherapy and suggests that synergistic treatment with both is a promising therapeutic option for patients with GC.

Importance of tumoral angiogenesis in gastric cancer

The theory of carcinoma angiogenesis dependence was proposed by Dr. Folkman in 1971. It suggests that the mechanism of tumor progression is not only the uncontrolled growth of individual cancer cells but, more importantly, the dependence on nutrients and oxygen provided through blood vessels.²³ As tumor cells rapidly grow and divide, they need to consume large amounts of oxygen and nutrients, which ultimately leads to hypoxia and acidosis of the TME.²⁴ Angiogenesis is thought to be a key influence on tumor advancement and metastasis, as well as a prognostic indicator for tumors.²⁵⁻²⁷ Angiogenesis provides essential nutrients to tumor cells and removes metabolites produced in response to tumor growth, thereby starving the healthy stromal cells in their vicinity.^{28,29}

Tumor angiogenesis involves multiple molecular drivers and signaling pathways. Vascular endothelial growth factor (VEGF), platelet growth factor, FGF, and angiopoietin are all common pro-angiogenic factors.³⁰ The main driver of the angiogenic process in solid tumors is VEGF, of which VEGF-A is the most important promoter.³¹ Other

Table 1. Combinational strategies of anti-angiogenic and immunotherapy in cancer (ClinicalTrials.gov).

Tumor type	Immunotherapy	Anti-angiogenic agents	Phase	ORR	Median PFS	Trial status	Clinical trial.gov reference
Cervical cancer	Camrelizumab	Apatinib	II	55.6%	8.8 months	Active, not recruiting	NCT03816553
Renal cell carcinoma	Atezolizumab	Bevacizumab Sunitinib	I	-	2.75 years	Completed	NCT01984242
Renal cell carcinoma	Atezolizumab	Bevacizumab Sunitinib	III	-	24 months	Completed	NCT02420821
Carcinoma, hepatocellular	Atezolizumab	Bevacizumab	III	-	6.83 months	Active, not recruiting	NCT03434379
Carcinoma, non-small-cell lung	Atezolizumab	Bevacizumab + chemotherapy	III	-	8.3 months	Completed	NCT02366143, Impower150

ORR, objective response rate; PFS, progression-free survival.

common family members include VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. They all bind to different vascular endothelial growth factor receptors (VEGFRs).^{31,32} Angiogenesis is induced by VEGF under hypoxic conditions through hypoxia-inducible factor-1 α (HIF)-1 α promoter binding.³³ High expression of HIF-1 α and VEGF are strongly associated with mortality in patients with brain, breast, cervical, oropharyngeal, ovarian, and uterine cancers.^{34,35}

GC is a highly angiogenic cancer that is characterized by hypoxia. Angiogenesis, induced by hypoxia, promotes the growth and progression of GC and enhances resistance to available therapies.³⁶ The powerful angiogenic capacity of GC causes relentless proliferation and metastasis of GC cells with a poor prognosis.³⁷ More than 90% of GC patients eventually die from metastasis. Distant metastasis of GC mainly occurs through blood circulation.³⁸⁻⁴¹ VEGF- and VEGFR2-mediated angiogenesis makes GC more aggressive.⁴² VEGFR2 is the most aggressive heterodimer, leading to enhanced epithelial-mesenchymal transition (EMT) and activation of related signaling pathways.⁴² EMT is a critical process in cell biology and plays a key role in cancer metastasis and progression.^{43,44} EMT affects the expression of epithelial-calponin and enhances the ability of tumors to adhere to the cell surface, thereby enabling tumor cells invasion and metastases.⁴⁵ Fibroblast growth factor receptor-2 (FGFR2) amplification occurs in <10% of GC patients and is associated with lymphatic and venous invasion of the primary lesion, lymph node metastasis, distant metastasis, advanced TNM, and poor prognosis. Patients with FGFR2-amplified GC are particularly prone to complications such as peritoneal (malignant ascites) and/or ovarian metastases or disease recurrence.⁴⁶ Downregulation of FGFR2 not only attenuates invasiveness and proliferation but also triggers apoptosis and chemosensitivity in GC cells. FGFR2 amplification drives its oncogenic function through mitogen-activated protein kinase and phosphatidylinositol 3-kinase-AKT signaling pathways as typical downstream pathways of FGFR.⁴⁷

Anti-angiogenic therapy has become a priority in the fight against cancer, and some angiogenesis inhibitors have shown efficacy against lung, breast, and colon cancers.⁴⁸ Blocking the supply of oxygen, growth factors, and nutrients from blood vessels to tumor cells is the goal of anti-angiogenic therapy.⁴⁹ Inhibition of endothelial cell proliferation,

migration, and apoptosis by anti-angiogenic agents may impair the viability of tumor cells because destruction of endothelial cells not only limits the supply of oxygen, nutrients, and growth factors produced by endothelial cells to the surrounding tumor cells but also leads to a lack of structural support for tumor cells and, ultimately, disintegration of the tumor tissue.⁵⁰ This strategy improves perfusion to the tumor, thereby increasing oxygen and drug delivery and improving the efficacy of therapies, such as immunotherapy, and is known as vascular normalization.⁵¹

The concentration of pro-angiogenic factors in ascites is an indicator of poor tumor prognosis and correlates with tumor aggressiveness.⁵² Ascites is a poor prognostic factor and one of the most common complications in advanced GC, with nearly half of patients with advanced disease having ascites^{53,54}; this condition is characterized by high abundance of pro-angiogenic factors⁵⁵ and immunosuppressive cells.⁵³ Patients with malignant ascites show a rapidly deteriorating clinical course and often have a short survival rate.⁵³ Moreover, relevant clinical results showed that anti-tumor angiogenic therapy can be effective in the treatment of malignant ascites. The mechanism of action is that normalization of tumor vasculature reduces the interstitial fluid pressure, which ultimately reduces the occurrence of malignant ascites.⁵⁶ However, previous studies have demonstrated complex and inconclusive results regarding the correlation of VEGF levels in the bloodstream of GC patients with the response to VEGF inhibitor therapy.⁵⁷ It is noteworthy that when used at low doses, anti-angiogenic drugs only normalize blood vessels. Conversely, when used at high doses, hypoxia may worsen because too many blood vessels are pruned.⁵⁸

Importance of the immune system in gastric cancer

Peritoneal metastasis is a common site of recurrence in GC patients. If cancer cells can be detected in the peritoneal lavage fluid, this would be the most important prognostic factor for abdominal recurrence.⁵⁹ The physiological characteristics of the peritoneum make it more susceptible to tumor cell attachment and invasion while forming a pre-metastatic ecological niche (PMN) by promoting vascularization.^{60,61} PMNs provide a supportive environment for the emergent tumor cells. GC cells remotely establish PMNs from multiple perspectives, including

immunosuppression, mesenchymal remodeling, angiogenesis, and mesothelial–mesenchymal transition.⁶² Gastric epithelial cells respond to *H. pylori* by producing various pro-inflammatory cytokines and chemokines that further activate epithelial cells and macrophages in the tissues and can amplify the PMN response.⁶³

The immune system can recognize cancer cells and inhibit the development and metastasis of tumors; thus, it plays a key role in suppressing invading cancer cells.^{64,65} Interestingly, tumor cells also have the ability to suppress the immune system or enable tumor cells to avoid immune responses, a process known as immune editing.⁶⁶ Tumor cells evade immune attacks and induce immunosuppressive TME primarily through two main pathways. First, cancer cells lose cell surface expression of tumor antigens and thus avoid recognition by cytotoxic T cells. Second, immune tolerance to TME is induced by secreting immunosuppressive molecules, such as interleukin-10 and VEGF.⁶⁷ Tumors produce a variety of immunosuppressive receptors to evade immune responses, including immunosuppressive factors such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Receptors such as immune checkpoint cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death protein 1 (PD-1)/programmed cell death ligand-1 (PD-L1), T-cell immunoglobulin and mucin-containing structural domain 3 (TIM-3), lymphocyte activation gene 3, and indoleamine-2,3-dioxygenase (IDO) inhibit T-cell activation by binding to tumor cell ligands.^{66,68}

Like most solid tumors, GC has multiple complex targets and interactions between regulatory signaling pathways that affect its pathogenesis, progression, and prognosis.⁶⁹ Infection and chronic inflammation are key factors in GC pathogenesis,⁷⁰ both of which increase its risk.⁷¹ EBV and *H. pylori* infection cause 80% of gastric interstitial carcinoma and 70% of GC cases worldwide, respectively. This indicates the important role of the immune system in GC.⁷² *H. pylori* and other pathogens disrupt the M1 macrophage response, thereby inducing an M2-like activation state, which increases the risk of disease progression. The OS rate associated with various malignancies, including GC, is closely related to the density of M2 macrophages.⁷³

M2 and M1 macrophages, CD4+ and CD8+ T cells are all common immune cell components in

GC tissues.⁷⁴ Treg cells, a subpopulation of CD4+ T cells, maintain an immunosuppressive TME. Treg cells subvert anti-tumor immunity, influence CD8+ T-cell activation,^{75,76} and determine the activity of cytotoxic T cells, helper T cells, and NK cells. In addition, they maintain the presence of *H. pylori*-associated inflammation, thereby creating an immunosuppressive environment during infection.⁷⁷ They use virulence factors to evade adaptive immune responses and destroy gastric epithelial cells while mediating the inhibition of T-cell proliferation and induction of naïve T-cell formation.⁷² Therefore, Treg cells play an important role in immunosuppression and tumor progression in GC patients.⁷⁸

Owing to their immunogenicity, most GC patients can benefit from immunotherapy.^{36,79} Immunotherapies include peripheral cell therapy, monoclonal antibody-based therapies, and cancer vaccines.⁸⁰ The most commonly used immunotherapeutic strategy is targeted ICIs.⁸¹ Tumor size, lymph node metastasis, and shorter OS have been reported to be strongly correlated with the expression of PD-L1, which is expressed in 25–65% of GC patients.^{70,82} For GC patients, MMR deficiency and EBV positivity are associated with PD-L1 expression.⁸³ Immunotherapy is the most promising for EBV and MSI GC subtypes.⁸⁴ The increased number of somatic mutations due to defective MMR leads to high MSI, whereas EBV positivity is due to the presence of oncogenic viruses, which lead to increased levels of PD-L1.⁸⁵ Populations with high MSI are associated with a high DNA mutational load and DNA hypermethylation, and related tumors strongly express immunosuppressive pathways such as PD-L1, IDO, and Tregs.⁸⁶ The MSI-high non-colorectal cancers, including advanced GC, are extremely sensitive to ICIs, with an objective response rate (ORR) of 50%.⁸⁷ This is associated with a high density of CD8+ tumor-infiltrating lymphocytes due to immunogenic neoantigen stimulation, which in turn is the result of a high mutational load.⁸⁸ Owing to the apparent association of GC with infectious agents, biomarkers capable of predicting immune checkpoint blockade responses have been extensively investigated.⁸⁹

Biological rationale for the anti-angiogenic-immunotherapy combination in gastric cancer

The TME can induce angiogenesis, hypoxia, and proliferation gain, followed by inhibition of

apoptosis and immune escape accompanying invasion and metastasis.⁹⁰ The TME may also release into circulation factors that promote systemic immunosuppression and further suppress anti-tumor immunity. If reprogrammed, these components may normalize the TME and sensitize solid tumors to immunotherapy.⁹¹ Tumor tissues maintain an immunosuppressive TME by secreting extracellular molecules, such as matrix metalloproteinases, extracellular matrices, and growth factors.⁹² As previously described, for most growing solid tumors, overactive angiogenesis creates an immunosuppressive TME by affecting multiple immune steps.⁹³ Hypoxia, acidosis, oxidative stress, high lactate levels, and reduced nutritional resources are all features of the microenvironment of solid tumors.⁹⁴ Hypoxia also promotes immune tolerance by inducing the expression of chemokines, which recruit pre-tumor CD4⁺CD25⁺FOXP3⁺ Treg cells, and hypoxia-induced signaling leads to a lack of immune T-cell initiation properties.⁹⁵

In addition to its role in mediating angiogenesis, VEGF also leads to immune escape causing tumor progression.⁸¹ VEGF expression is associated with increased infiltration of Tregs, MDSCs, and M2-type tumor-associated macrophages (TAMs) into the tumor mesenchyme.⁹⁶ In turn, myeloid cells (including macrophages, neutrophils, and MDSCs) stimulate angiogenesis by expressing pro-angiogenic factors and/or matrix metalloproteinases to release VEGF from the extracellular matrix.⁹⁷ TAMs from GC patients show significantly elevated levels of PD1, which promote GC development by impairing the anti-tumor function of CD8⁺ T cells.⁹⁸ VEGF inhibits T-cell function by increasing the expression of ICIs in the TME via VEGFR2, thereby inducing T-cell failure.^{81,99} HIF1 α increases PD-L1 expression in MDSCs, dendritic cells (DCs), and macrophages.⁹⁹ Concurrently, the hypoxic TME stimulates the secretion of various immunosuppressive cytokines.¹⁰⁰ The disordered tumor vasculature, in addition to preventing CD8⁺ T cells from entering the TME, disables effector functions and can destroy T cells. Additionally, VEGF interferes with DC maturation, inhibits T-cell initiation, and mediates CD8⁺ T-cell depletion.¹⁰¹ Activated angiopoietin-2 (Ang-2) signaling promotes tumor immunosuppression.¹⁰²

In summary, VEGF inhibits the adhesion of lymphocytes to activated endothelial cells by affecting the passage of lymphocytes across the endothelium

to the tumor. It blocks T-cell mobilization to prevent T-cell infiltration into the tumor. VEGF exerts systemic effects on immunomodulatory cell function through multiple mechanisms, including induction and proliferation of suppressive immune cell subsets and inhibition of T-cell development in hematopoietic progenitors.^{96,101,103,104}

Anti-VEGF therapy reverses VEGF-mediated DC immunosuppression; it increases the number of mature DCs and also decreases the number of immature progenitor cells.¹⁰⁵ Additional targeting of the VEGF/VEGFR axis may reverse DC maturation defects and reduce VEGF-a-induced expression of PD-1, TIM3, and CTLA-4 on CD8⁺ T cells.¹⁰⁶ Over the past decade, compelling research has shown that the judicious use of anti-angiogenic therapies can temporarily normalize tumor vasculature and increase drug and anti-tumor immune cell delivery while alleviating hypoxia in the TME, thereby increasing the effectiveness of various treatments.¹⁰⁷ Tumor vascular normalization has been shown to improve the efficacy of cancer immunotherapy, and recent studies have shown that enhanced immune stimulation can in turn improve tumor vascular normalization.¹⁰⁸ Interferon γ is produced by activated T cells and induces T-cell migration; it plays an important role in this process.¹⁰⁹ It also enhances the expression of several key chemokines, including chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10, and CXCL11, which play an important role in stimulating pericyte recruitment leading to normalization of the tumor vasculature.¹¹⁰ PD-L1 expression in GC is regulated by interferon γ through the activation of the JAK-STAT pathway.¹¹¹ Zheng *et al.*¹¹² showed that ICB activation of CD8⁺ T cells alone mediated the normalization of tumor vasculature, also in an IFN- γ -dependent manner.

Ang-2 secreted by endothelial cells binds to Tie-2 and increases the angiogenic activity of the tumor by destabilizing the blood vessels in the presence of VEGF.¹¹³ Inhibition of Ang-2 or pro-inflammatory cytokines has been shown to enhance anti-angiogenic therapy.¹¹⁴ Therefore, the combination of anti-angiogenic agents and checkpoint blockers has emerged as an attractive anti-tumor treatment strategy.¹¹⁵ Studies have shown that blocking CTLA-4 or PD-1 decreases tumor vascular density, enhances blood perfusion, alleviates tissue hypoxia, and mediates vascular normalization.¹¹⁶ Concurrent T-cell infiltration promotes tumor perfusion, leading to an overall enhanced T-cell

accumulation and response to checkpoint blockade.¹¹⁷ In 2019, Wilky *et al.*¹¹⁸ presented the benefits of anti-angiogenic therapy in combination with ICIs for oncology patients. The combination of anti-angiogenic and anti-PD-1/PDL1 therapy has been shown to trigger T-cell function with concomitant activation of immune checkpoints, resulting in a more potent anti-tumor effect than anti-PD-1 therapy alone.¹¹⁹ Increasing evidence suggests that the combination of anti-angiogenic therapy with immunotherapy may improve the immune response in solid cancers in certain circumstances.¹²⁰ Anti-PD-L1 therapy sensitizes and prolongs the anti-angiogenic effect, while anti-angiogenic improves the response to anti-PD-L1 therapy. Feedback between ICB and anti-angiogenic enhances itself and ultimately drives immune-mediated tumor cell eradication.¹⁰⁷

Clinical evidence for anti-angiogenic therapy in gastric cancer

Blocking angiogenesis is a strategy that has been successfully used to treat various types of tumors, including glioblastoma, colorectal cancer, ovarian cancer, and GC.¹²¹ Current anti-angiogenic therapies include anti-VEGF monoclonal antibodies, VEGF-binding proteins, and VEGF receptor tyrosine kinase inhibitors (TKIs).^{122,123} Apatinib is a small molecule VEGFR inhibitor, and it was the first approved for the treatment of advanced or metastatic chemotherapy-refractory GC in China.¹²⁴ It selectively inhibits VEGFR by binding to the intracellular adenosine triphosphate site, which determines endothelial cell migration, proliferation, and reduction of tumor micro-vessel density.¹²⁵

In a global multicenter phase III study of apatinib in patients with GC (ANGEL study), the primary study endpoint of OS was not achieved, and the secondary study endpoint of median progression-free survival (mPFS) reached 2.8 months [95% confidence interval (CI), 1.8–2.8 months]. Patients were from Europe, the United States, Korea, Japan, and China. There were also Chinese patients with different baseline characteristics enrolled in the two studies (ANGEL study, NCT: ChiCTR-OPN-15006601), which may also affect the OS.¹²⁶ In 2014, apatinib was approved in China for two or more advanced, or metastatic, GCs that cannot be treated with prior chemotherapy and is considered the standard third-line treatment in China.¹²⁷ Apatinib showed positive results in the Chinese GC population, leading to official approval for clinical use.

However, the phase III clinical trial ANGEL, which is currently studying apatinib in a Western cohort, showed disappointing first results presented at the 2019 ESMO Annual Meeting. Specifically, no significant improvements were observed in OS and in Western populations.¹²⁸

Bevacizumab has been shown to inhibit angiogenesis in several types of solid tumors. Treatment of GC cells with bevacizumab resulted in reduced cell growth and increased rate of apoptosis.⁴⁰ Ramucirumab is the most important anti-angiogenic monoclonal antibody targeting VEGFR-2 in a variety of cancers. Ramucirumab is approved by the FDA for the treatment of advanced GC.¹²⁹ The RAINBOW trial paired second-line ramucirumab with paclitaxel for advanced gastric/gastroesophageal junction cancer (GC/GEJC). Median OS (mOS) was prolonged by 2.2 months [median 9.6 *versus* 7.4; hazard ratio (HR)=0.807, $p=0.017$] and progression-free survival (PFS) by 1.5 month (median 4.4 *versus* 2.9; HR=0.635, $p<0.0001$), with improved tumor remission (28% *versus* 16%, $p=0.0001$) and disease control rates (80% *versus* 64%, $p<0.0001$).¹³⁰ The AVAGAST study was the first phase III study to test the addition of bevacizumab to first-line chemotherapy in advanced GC. The evidence suggests that the addition of bevacizumab improves PFS and response rates.¹³¹ The REGARD clinical trial showed that ramucirumab improves survival and increases OS by 1.40 month in patients with GC as a second-line agent.¹³² The REGARD phase 3 clinical trial evaluated the safety and efficacy of ramucirumab in patients with advanced gastric/gastroesophageal junction (GEJ) adenocarcinoma whose disease had progressed after first-line platinum- or fluoropyrimidine-containing chemotherapy (3.8 months; HR=0.776, 95% CI: 0.603–0.998, $p=0.047$). Ramucirumab treatment also significantly prolonged PFS.¹³³ Notably, treatment with ramucirumab was associated with improved quality of life outcomes and longer clinical deterioration in the REGARD and RAINBOW studies.¹³⁴ In the recent phase III RAINFALL clinical trial, randomized patients received ramucirumab in combination with fluoropyrimidine and cisplatin, or placebo in combination with fluoropyrimidine and cisplatin as first-line treatment, ramucirumab chemotherapy addition was associated with an increase in PFS (HR: 0.961, 95% CI: 0.768–1.203, $p=0.74$) and OS [HR: 0.962, 95% CI: 0.801–1.156, $p=0.6757$; mOS: 11.2 months (9.9–11.9)] in the ramucirumab group and 10.7 months (9.5–11.9) in the placebo group.¹³⁵

The role of the FGFR tyrosine kinase family as oncogenic drivers is more heterogeneous than that of the typical v-raf murine sarcoma viral oncogene homolog B (BRAF), Anaplastic lymphoma kinase (ALK), or epidermal growth factor receptor (EGFR) families. The four different genes can be affected by mutations, rearrangements, or amplifications in multiple tumor types.¹³⁶ The FGFR signaling pathway is associated with multiple oncogenic progression mechanisms, such as cell proliferation, survival, migration, invasion, and angiogenesis.¹³⁷ FGFR1 signaling can lead to tumorigenesis by affecting a range of downstream signals, and FGFR inhibitors can be effective in monotherapies for the treatment of high FGFR1-amplified tumors.¹³⁸ Overexpression and activation of FGFR1 are markers of EMT and metastasis.¹³⁹ FGFR inhibitors have antitumor activity and further steps are being taken in the clinical development process. The complex rationale for targeting the FGF/FGFR pathway in human cancers also recognizes the challenges in the current drug development process.¹⁴⁰ FGFR signaling is frequently activated by aberrant activation of FGF ligands or by mutations that activate the FGFR receptor. Therefore, FGFR inhibitors are considered a promising therapeutic strategy for patients with FGFR mutations in family members.¹⁴¹ The results of the FIGHT trial, the first phase III clinical trial of a monoclonal antibody against the FGFR2b receptor in patients with advanced GC/GEJC, will lead to the availability of a new therapeutic option to improve survival and reduce toxicity in patients with advanced GC/GEJC.¹⁴² AZD4547 is a small orally bioavailable selective inhibitor of the FGFR family. AZD4547 effectively inhibits the tyrosine kinase activity of FGFR1, 2, and 3. The combination of certain chemotherapeutic agents, such as paclitaxel, showed enhanced *in vivo* anti-tumor efficacy in a GC model compared to monotherapy.¹⁴³ AZD4547 is a selective FGFR1, 2, and 3 TKI that has shown potent activity in preclinical studies. Gastric adenocarcinoma cell lines with FGFR2 amplification were sensitive to AZD4547, resulting in reduced cell proliferation and cell death. Furthermore, AZD4547 induced rapid tumor regression in two *in vivo* models of FGFR2-amplified GC.¹⁴⁴

Clinical evidence for immunotherapy in gastric cancer

Several ICIs have received FDA approval, already making a difference in the treatment of advanced solid tumors.¹⁴⁵ For patients with lung adenocar-

cinoma, leukemia, and melanoma, targeting neoantigens in T-cell based immunotherapy is a promising approach to treatment.¹⁴⁶ Immunotherapy is being used clinically for the treatment of a variety of advanced malignancies, showing high efficacy, especially in those with defective MMR. Concurrent studies confirm that a high tumor mutation burden is associated with a positive clinical response to CTLA-4 or PD-1 blockade.¹⁴⁷

Currently, the FDA approves the use of the PD1 inhibitor pembrolizumab for the treatment of the MSI subtype of GC.¹⁴⁷ The landmark phase II trial by *Le et al.*¹⁴⁸ showed that in severely pretreated MSI solid tumors, pembrolizumab treatment resulted in significantly smaller tumors and significantly longer PFS. The ATTRACTION-2 studies have demonstrated the efficacy of PD-1 monoclonal antibodies in the third-line treatment of patients with GC.¹⁴⁹ The JAVELIN Gastric 100 trial did not achieve its primary goal of improving OS with the maintenance of monoclonal antibodies in patients with advanced GC/GEJC-induced disease control after chemotherapy. However, the results suggested potential activity and a favorable safety profile in a selected subset of patients, providing guidance for future studies on this challenging disease.¹⁵⁰

KEYNOTE-059 (NCT02335411) was a phase II study involving 259 patients with advanced gastric and esophagogastric adenocarcinoma that evaluated the safety of and response rate to pembrolizumab monotherapy, with ORRs of 11.6 and 17.8%, respectively, and an overall remission time of 8.4 months.¹⁴⁵ In a phase III randomized study called ONO-4538-12 (attrion-2), 493 patients with unresectable advanced or recurrent esophageal cancer were randomly assigned to receive nivolumab or a placebo arm. GC patients who received the treatment showed improved mOS from 4.14 to 5.32 months (HR=0.63; 95% CI: 0.50–0.78; $p < 0.0001$). The 12-month survival rate almost doubled for patients treated with nivolumab: 26.6% for nivolumab and 10.9% for placebo.^{86,151} In patients with GC who had received two or more treatment regimens before a phase I/II trial (CheckMate-032), nivolumab monotherapy yielded an ORR of 14%, mPFS of 1.4 month, median survival time of 5.0 months, and a disease control rate of 32%. The 6-month survival rate was 49%, and 12-month survival rate was 36%.¹⁵² On the basis of the KEYNOTE-016, -12, -164, and -158 trials

confirming that pembrolizumab has promising efficacy in GC patients with advanced high microsatellite instability (MSI-H) or MMR deficiency, the use of pembrolizumab was approved as a second-line treatment option.¹⁵³ CheckMate 649 was the first worldwide randomized controlled trial to demonstrate superior mOS of more than 1 year in the first-line nivolumab plus chemotherapy *versus* chemotherapy of patients with non-HER2-positive gastric/GEJ/esophageal adenocarcinoma. These patients have limited treatment options, and no progress has been achieved for them in recent years.¹⁵⁴ The success of nivolumab plus chemotherapy concerns not only patients with PD-L1 combined positive score ≥ 5 or higher but also all treatment-intending populations.¹⁵⁵ The survival benefit of adding nivolumab to standard dual chemotherapy in the first-line treatment of advanced GC/GEJC should be confirmed in ATTRACTION-4.¹⁵⁶ ATTRACTION-4 is a randomized, multicenter, Asian phase II/III study with or without nivolumab as the initial treatment regimen in patients with HER2-negative, progressive gastric or GEJ adenocarcinoma. Recent phase II component results showed that nivolumab in combination with S-1 plus oxaliplatin (SOX) or CAPOX was well tolerated and had encouraging efficacy. Radiographic response rates improved when nivolumab was accompanied by chemotherapy (48% *versus* 58%, $p = 0.0088$), as did PFS: mPFS; 8.3 months in the chemotherapy group *versus* 10.5 months in the nivolumab plus chemotherapy group (HR=0.68, $p = 0.0007$).¹⁵⁷ The ATTRACTION-4 study investigated nivolumab in combination with chemotherapy in an Asian population, including patients with GC; PFS was improved, but no difference in OS between the two groups was observed (mOS: 17.5 *versus* 17.2 months; HR=0.9, $p = 0.259$).¹⁵⁸ In the phase III ATTRACTION-4 study, which was conducted in Asian countries without patients selected based on PD-L1 expression, increased nivolumab chemotherapy resulted in improved PFS, despite a higher proportion of patients receiving follow-up therapy (66%) than in CheckMate-649.¹⁵⁹

KEYNOTE 590 was the first global phase III study to demonstrate clinically meaningful improvements in OS, PFS, and objective response in patients with previously untreated, advanced, or metastatic GEJC treated with ICIs plus chemotherapy compared to chemotherapy alone.¹⁶⁰ Table 2 shows summaries of the currently available immunotherapy strategies for GC.

Clinical evidence for combination of anti-angiogenic therapy and immunotherapy

Angiogenesis and immune escape are two key processes in tumorigenesis (Figure 1).¹⁶¹ In the TME, the interaction between tumor angiogenesis and immunosuppressive cells forms a vicious circle in which tumor immune cell evasion promotes tumor angiogenesis, suppresses anti-cancer immunity, and promotes tumor progression.¹⁰¹ For a range of solid tumors, including renal cancer,¹⁶² glioma,¹⁶³ hepatocellular carcinoma,¹⁶⁴ and lung cancer,⁵⁸ the combination of anti-angiogenic therapy and immunotherapy is being increasingly administered because of the biological synergy between angiogenesis and tumor-associated immune responses.

In the treatment of metastatic breast cancer, pancreatic neuroendocrine tumors, and melanoma, the bispecific antibodies that inhibit Ang-2 and VEGFA promote vascular degeneration and normalize remaining vessels while promoting the perivascular aggregation of activated CD8+ T.³⁰ The mechanism of interaction between angiogenesis and immune cells is the basis of the combination of anti-angiogenic drugs with ICIs. Combination therapy with sunitinib plus nivolumab and pembrolizumab plus nivolumab has been used in patients with metastatic cancer.⁶¹

In a phase II study involving patients with advanced cervical cancer (NCT03816553), the objective remission rate of VEGFR2 TKI apatinib monotherapy was 14.6–15.4% in patients with disease progression after first-line chemotherapy. However, the objective remission rate for apatinib combined with the anti-PD-1 antibody camrelizumab was 55.6% (95% CI: 40.0–70.4%).²⁰ Another study combining bevacizumab with anti-CTLA-4 antibodies in patients with melanoma showed extensive morphological changes in CD31+ endothelial cells and extensive infiltration of immune cells in post-treatment tumor biopsies following combination therapy. The immune infiltrate was found to contain large numbers of CD8+ and CD163+ macrophages compared to ipilimumab treatment alone, demonstrating the ability of combined anti-VEGF and anti-CTLA-4 treatment to promote further immune cell infiltration in the TME.¹⁶⁵ The phase II IMmotion150 study showed that the combination of bevacizumab and atezolizumab was superior to sunitinib alone in metastatic RCC (mRCC). Moreover, the phase III IMmotion151 study of 915 patients with

Table 2. Currently available immunotherapy strategies for gastric cancer (ClinicalTrials.gov).

Tumor type	treatment Arm	Phase	OS	Median PFS	Trial status	Clinical trial.gov reference
Gastric cancer Gastroesophageal junction cancer	Nivolumab Ipilimumab	III	Up to 41 months after the first participant is randomized	Up to 41 months after the first participant is randomized	Active, not recruiting	NCT02872116
Esophageal carcinoma	Pembrolizumab	III	Up to 2years	Up to 2years	Withdrawn due to protocol amendment	NCT03881111
Gastric cancer Gastroesophageal junction cancer	Nivolumab	II	Estimated time frame: 54 months	Estimated time frame: 48 months	Active, not recruiting	ATTRACTION-4
Gastric cancer	Apatinib		36 months after the last subject participating in	36 months after the last subject participating in	Recruiting	NCT03878472
Gastric cancer Adenocarcinoma of the esophagogastric junction	Nivolumab Relatlimab	II			Recruiting	NCT04062656
Gastric cancer	Pembrolizumab	II	–	–	Recruiting	NCT04795661
Gastric cancer	$\gamma\delta$ T	II	–	–	Not yet recruiting	NCT02585908
Gastrointestinal cancer	Tislelizumab Anlotinib	II	Up to 2years	Up to 2years	Recruiting	NCT04777162
Gastric cancer	Atezolizumab	II	Up to 24 months	Up to 24 months	Recruiting	NCT04166721
Gastric cancer Gastroesophageal junction cancer	Durvalumab Tremelimumab	II	–	–	Recruiting	NCT04817826
Gastroesophageal adenocarcinoma	Pembrolizumab	I	–	–	Recruiting	NCT03395847
Gastroesophageal adenocarcinoma	Lenvatinib Pembrolizumab	I	–	–	Recruiting	NCT05041153
Gastric cancer	Pembrolizumab Sonidegib	I	–	–	Recruiting	NCT04007744

untreated mRCC showed that compared with sunitinib alone, bevacizumab and atezolizumab prolonged PFS in PD-L1 positive patients.¹¹⁶ In a phase III study of atezolizumab plus bevacizumab for unresectable HCC, atezolizumab in combination with bevacizumab reduced the risk of death by 42% and the risk of progression by 41% compared to the saorafenib.¹⁶⁶ A phase III clinical trial (Impower150, NCT02366143) comparing

atezolizumab, bevacizumab, carboplatin, and paclitaxel combination therapy (ABCP group) with bevacizumab, carboplatin, and paclitaxel combination therapy (BCP group) showed that PFS and OS were significantly prolonged in the ABCP group than in the BCP group (median PFS: 8.3 *versus* 6.8 months; mOS: 19.2 *versus* 14.7 months) in patients with non-squamous NSCLC. The ORR was significantly higher in the

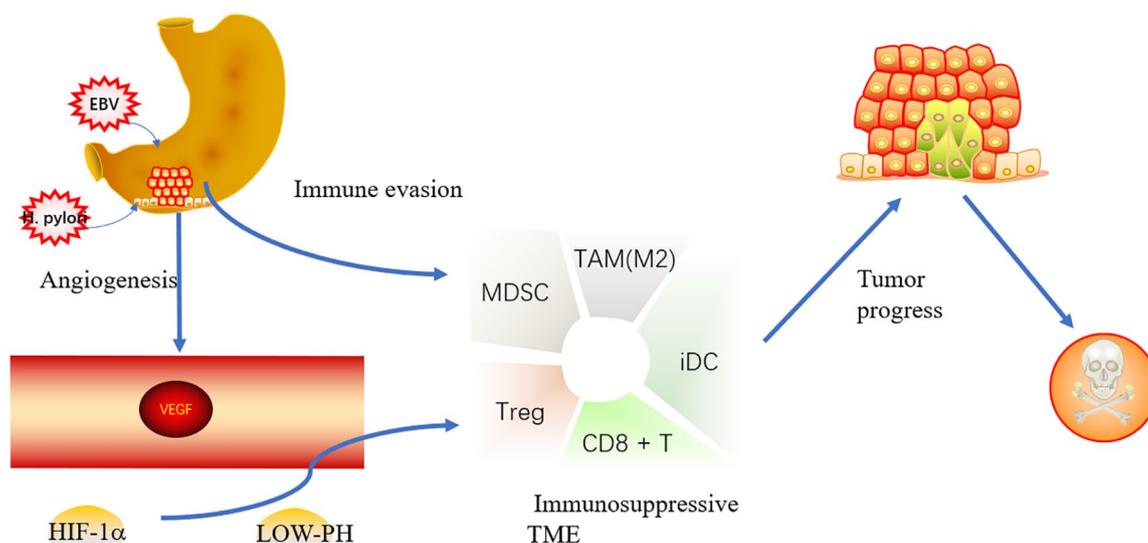


Figure 1. *Helicobacter pylori* and Epstein–Barr virus are among the major contributors to gastric cancer, and these chronic infections make gastric cancer immunogenic. Angiogenesis and immune escape are two key processes in tumorigenesis. Neovascularization leads to hypoxia and acidosis in the tumor microenvironment and refers to the production of immunosuppressive factors that promote tumor progression. HIF-1, hypoxia-inducible factor 1; iDC, immature dendritic cells; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; Treg, regulatory T cell;.

ABCP group than in the BCP group (ORR: 63.5% versus 48.0%).¹⁰¹ In the IMBrave150 (NCT03434379) clinical trial, 501 patients were randomly assigned in a 2:1 ratio to receive standard-dose atezolizumab or high-dose VEGF inhibitor bevacizumab every 3 weeks. The trial had PFS and OS as the dual primary endpoints, with median follow-up stopped at the first interim analysis after only 8.6 months, at which point improvements in the OS (HR=0.58, 95% CI: 0.42–0.79, $p=0.0006$) and PFS (HR=0.59, 95% CI: 0.47–0.76, $p<0.0001$) were observed. Atezolizumab plus bevacizumab combination has been approved by the FDA, European Medicines Agency, and other regulatory agencies globally as a first-line treatment option for HCC.¹⁶⁷ A randomized phase III trial for advanced RCC started with better OS (HR=0.53, 95% CI: 0.38–0.74, $p<0.0001$), PFS (HR=0.69, 95% CI: 0.57–0.84, $p<0.001$), and ORR (59.3% versus 35.7%, $p<0.001$). Based on this trial, axitinib in combination with pembrolizumab is now approved in the US and Europe as the preferred first-line treatment option for patients with advanced RCC.¹⁶⁸ A research study showed that an intraperitoneal injection of bevacizumab in patients with advanced ascites tumors activates the immune system, leading to an increase in effector CD8+ T-cell counts.⁵⁵ A clinical trial of patients with advanced GC/GEJC evaluating the efficacy of ramucirumab

plus pembrolizumab combination showed encouraging clinical activity and manageable toxicity.¹⁰⁷ In the REGONIVO study, the combination of regorafenib and nivolumab showed remarkable anti-tumor activity (ORR=44%) in patients with GC who had shown a poor response to prior therapy. This indicates that adding an anti-angiogenic monoclonal antibody or TKI to immunotherapy could be another treatment option for advanced GC.¹⁶⁹ A phase I trial in patients with advanced GC/GEJC showed encouraging ORR and DCR in patients treated with a combination of ramucirumab and pembrolizumab.¹¹⁶ In January 2018, the FDA approved the use of the combination of the PD-1 inhibitor pembrolizumab and the VEGF/FGF inhibitor lenvatinib, which showed an ORR of 83% and a tumor control rate of 100%, for the treatment of patients with advanced and/or mRCC. The combination of lenvatinib and pembrolizumab showed promising results for the treatment of 13 solid tumors in a phase 1b trial reported by the European Society for Medical Oncology in 2016.¹⁷⁰

The OS, mPFS, objective remission, and complete remission rates differ for different combinations of anti-angiogenic therapy and immunotherapy for patients with the same tumor type.^{171,172} Most of the currently reported combination therapy regimens belong to phase I–II studies, with very few being reported from phase III studies. Preliminary

results suggest that the combination of ICIs and anti-angiogenic agents has acceptable toxicity and considerable anti-tumor activity in patients with GC; however, there are still various challenges to overcome in achieving combination therapy.¹⁰⁴ In the EPOC1706 trial, patients with advanced GC received lenvatinib in combination with pembrolizumab as first- or second-line therapy. The trial resulted in objective remission in 20 patients out of 29, yielding an impressive ORR of 69% (95% CI: 49–85), mPFS of 7.1 months (95% CI: 5.4–13.7), and mOS not achieved (95% CI: 8–11 months not achieved).¹⁷³ The combination of ramucirumab with pembrolizumab was recently explored in a multi-cohort phase 1B trial of GC/GEJC patients; it showed a manageable safety profile with an ORR of 7% and a DCR of 44%.⁹⁶ In the GC/GEJC cohort, the mPFS was 2.6 months and OS was 12.4 months in patients treated with ramucirumab/durvalumab in the unselected population, with enhanced activity observed in patients with high PD-L1 expression (Combined positive score 25%, PFS = 5.5, and OS = 14.8 months).¹⁷⁴ A CAMILLA phase I/II clinical trial is currently underway in pretreated patients with advanced GEJC treated with cabozantinib plus durvalumab. The primary outcome of this study is the maximum tolerated dose and the results of the first phase are encouraging. The researchers reported a median PFS of 3.8 months (95% CI: 3.4–6.3), a mOS of 9.1 months (95% CI: 5.8–21.8), and a 6-month PFS rate of 34.5% (95% CI: 17.9–54.3).⁹⁶

Several clinical trials demonstrate that combinatorial strategies containing nivolumab and ramucirumab as second-line treatment achieved good clinical outcomes in previously immunotherapy treated GC patients, indicating the combination of VEGF/VEGFR inhibitors and immunotherapy could be effective regimens for immunotherapy-resistant patients with advanced GC.¹⁷⁵ VEGF induces the accumulation of immunosuppressive cells, such as MDSCs, immature DCs, Tregs, and TAMs, being responsible for treatment failure of first-line immunotherapy in GC. Anti-angiogenic therapy, for example ramucirumab, can reverse the immunosuppression.¹⁷⁶ Therefore, VEGF/VEGFR inhibitors combined with immune-checkpoint inhibitors may be the future therapeutic direction of advanced GC.

Conclusion

Immunotherapy is a novel and effective treatment strategy, and its emergence brings new hope to many tumor patients. Despite the increasing

clinical data demonstrating the therapeutic effect of ICIs on deficient mismatch repair or MSI-H GC, there is still a large proportion of GC patients who cannot benefit from immunotherapeutic agents. Many preclinical studies have revealed the complex relationship between anti-angiogenesis and immunotherapy, which provides some theoretical basis for the combination of anti-vascular and immunotherapy. This combination has a strong biological basis for treating GC, disengaging it from the inhibitory network, and activating barriers that constitute the TME. Further studies will establish and validate biomarkers to determine the direct relationship between the dose of anti-angiogenic agents and the efficacy of the combination therapy and assess the difference between anti-angiogenic therapy-mediated vascular normalization and immunotherapy-induced vascular normalization for the benefit of more GC patients.

Declarations

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Not applicable.

Consent for publication
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Competing Interests

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