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Research status on immunotherapy trials of gastric cancer

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Abstract

The breakthrough of immune checkpoint inhibitor (ICI) therapy has created extensive opportunities for cancer immunotherapy. Especially, the block of programmed death-1/programmed death ligand 1 (PD-L1) axis using ICIs has become a new therapeutic strategy to treat advanced gastric cancer (GC). However, in the past decade, single-arm and randomized trials for single-drug ICI therapy showed that the therapeutic effect was not satisfactory, including clinical trials for advanced GC. However, after selecting suitable predictive biomarkers and developing a combination of anti-angiogenic targeted drugs and other chemotherapeutic drugs, the objective response rate and progression-free survival of patients with gastric cancer were improved significantly. The United States Food and Drug Administration has approved treatment with pembrolizumab for patients with advanced GC with PD-L1 expression or microsatellite instability-high/mismatch repair deficiency. In this review, the updated data from the latest trial results of combination immunotherapy for GC are presented. Based on the outcome of combination therapy, we discuss its possible molecular mechanism and summarize effective predictive biomarkers. We also discuss possible problems stemming from results of other clinical trials of ICI treatment and propose other directions for ICI therapy.

Key Words: Gastric cancer; Immunotherapy; Clinical trial; Immune checkpoint inhibitor; Neoadjuvant therapy

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Core Tip: Immune checkpoint inhibitors gigantically expand the methods of immunotherapy and bring a glimmer of hopefulness for patients with advanced gastric cancer (GC). Ongoing clinical trials show that the effect of monotherapy was not satisfactory, while the combination therapy manifested a better response rate. The most recent clinical trial results of GC immunotherapy are reviewed to suggest the reasons and mechanisms of the high response rate. Additionally, we propose the potential problems of these trials and speculate on the benefits of immune checkpoint inhibitors in neoadjuvant therapy.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy diagnosed worldwide and the third dominant cause of death from cancer[1]. The mild symptoms of early GC and lack of awareness of physical examination mean that most patients with GC are diagnosed at advanced stages, frequently presenting infiltration or metastasis. Cytotoxic chemotherapy for advanced GC is a first-line standard of care, which comprises treatment with fluoropyrimidine plus a platinum agent, and the decision on whether to administer a combination comprising trastuzumab depends on the presence of human epidermal growth factor receptor 2 (*HER2*) gene expression; however, the 5-year survival rate remains poor[2-4].

According to medicine development for oncology in the past decade, immune checkpoint inhibitors (ICIs), such as an anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) monoclonal antibody and anti-programmed death-1/programmed death ligand-1 (PD-1/PD-L1) monoclonal antibodies, represent a significant breakthrough[5,6]. Several studies have demonstrated that PD-L1 is constitutively expressed in various kinds of malignant tumors, including GC[7]. A meta-analysis by Chen *et al*[8] revealed that ICI treatment could enhance moderate survival benefits for patients with advanced gastric or gastroesophageal junction (G/GEJ) cancer. In particular, anti-PD-1/PD-L1 drugs could raise the 12-mo and 18-mo overall survival (OS) rates and manifested a long effective time of the therapeutic response[8]. Meanwhile, the patient's response showed that anti-PD-1/PD-L1 drugs are more efficacious in molecular subtypes that are PD-L1 positive, microsatellite instability (MSI)-high, or Epstein-Barr virus (EBV) positive, or those with a high mutation burden[8]. However, most patients with advanced GC are not sensitive to ICI monotherapies, according to the results of recent randomized trials[9-12], thus for patients with refractory advanced GC, it is critical to select the appropriate combination therapy to improve their responses to anti-PD-1 therapy or other ICIs[13]. Consequently, the development of safe and effective ICI combination strategies and predictive biomarkers has become an urgent requirement to enhance their therapeutic effect in advanced GC.

In this review, the lately reported trials of combined immunotherapy for advanced GC are summarized, focusing on the combination strategies that have a better overall therapeutic effect, analyzing the possible molecules and their mechanisms of action, and exploring their use as predictive biomarkers. The shortcomings of other cancer types in clinical trials are discussed to indicate the potential problem of developing combined immunotherapy for GC. We also discuss whether ICI could be employed as a neoadjuvant therapy.

CURRENT CLINICAL TRIALS OF COMBINATION THERAPY WITH ICI FOR GC

Since the advent of ICI-related drugs, numerous clinical trials are being carried out worldwide. As of September 2018, there were a total of 2250 ongoing clinical trials, of which 1716 trials tested regimens that combined anti-PD1/PD-L1 drugs with other

cancer treatments[14]. In these trials, lung cancer (254 trials), melanoma (139 trials), breast cancer (106 trials), lymphoma (99 trials), and head and neck cancer (72 trials) were the most studied, while research on GC was relatively limited. In this section, we list the latest clinical trial research progress of ICI drugs for advanced GC in the past two years[9,10,15-18] (Table 1). Compared with the results of previous clinical trials of ICI monotherapy, these trials of ICI combinations showed better objective response rates (ORRs) and median progression free survival (PFS) commonly. In the open-label phase 2 trial EPOC1706, patients with advanced GC were given Lenvatinib (a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors and other receptor tyrosine kinases) plus pembrolizumab as anti-tumor therapy in the first-line or second-line settings[15]. This trial enrolled 29 patients with metastatic or recurrent adenocarcinoma of G/GEJ and measured disease using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The primary endpoint of the trial was the ORR by RECIST. The results report showed that 20 [69%, 95% confidence interval (CI): 49-85] of 29 patients had an objective response at data cutoff. This indicated that Lenvatinib plus pembrolizumab has promising anti-tumor activity in patients with advanced GC.

Another non-randomized, multicenter, open-label phase IIb study, KEYNOTE-659, evaluated the efficacy and safety of pembrolizumab in combination with S-1 plus oxaliplatin (SOX) as first-line treatment in Japanese patients with G/GEJ cancer[16]. At data cutoff, 54 patients were evaluated and the median follow-up was 10.1 mo. The ORR and disease control rate by blinded independent central review were 72.2% (95% CI: 58.4-83.5) and 96.3% (95% CI: 87.3-99.5), respectively. Median duration of response, time to response, PFS, and OS were as follows: Not reached, 1.5 mo, 9.4 mo, and not reached. This result demonstrated encouraging efficacy for SOX plus pembrolizumab treatment of advanced G/GEJ cancer.

MOLECULAR MECHANISMS OF COMBINATION THERAPY WITH ICI FOR GC

The EPOC1706 trial of combination therapy trial of ICI and antivasular targeted therapy indicated that the VEGF pathway can regulate the antitumor immune response to promote better efficacy of ICIs. Previous research proved that tumor-induced angiogenic factors, including VEGF, could stimulate tumor neovascularization and produce functional and structural abnormalities, leading to an increased intratumoral stress response and hindering of the infiltration of effector T cells[19,20]. Anti-tumor cytotoxic T lymphocytes (CTLs) fail to penetrate into the tumor microenvironment (including GC). Other factors, including downregulation of vascular endothelial cell adhesion molecule-1, prevent the migration of effector T cells into the tumor stroma[21]. In addition, the accumulation of myeloid-derived inhibitor cells further suppresses the anti-tumor response of effector T cells[22]. Preventing the maturation of effector T cells and dendritic cells also inhibits the function of CTLs[22]. Therefore, the normalization of tumor blood vessels after anti-VEGFR therapy can reduce the intratumoral pressure, restore anti-CTL infiltration, and enhance the anti-tumor effect of ICI[23,24]. In addition, several types of immunosuppressive cells, including regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), are present in the tumor microenvironment of GC. Previous studies have reported that the activity of Tregs and TAMs depends in part on the VEGF/VEGF receptor (VEGFR) axis, and overexpression of VEGF promotes the recruitment, differentiation, and proliferation of Tregs in tumors[25]. Likewise, tumor-induced angiogenic factors or a hypoxic state can further enhance the function of Tregs and TAMs *via* the VEGF/VEGFR axis, resulting in downregulation of anti-tumor CTL activity[26]. These above-mentioned mechanisms provide a conceivable theoretical basis for the combined therapy of anti-vascular targeted drugs and ICIs (Figure 1). Kato *et al*[27] certified that the antivasular targeted drug lenvatinib, *via* decreasing TAMs and enhancing the activation of the interferon (IFN) signaling pathway, upregulated the anti-tumor activity of PD-1 inhibitors *in vivo*[27].

In the past decade, researchers have explored the hypothesis that traditional chemotherapy drugs might interact with the immune mechanism. For instance, chemotherapy drugs such as cyclophosphamide, gemcitabine, platinum, and paclitaxel have been reported to improve the antigenicity of tumor cells by increasing the expression of major histocompatibility complex class I molecules[28,29] and enhancing the sensitivity of tumor cells to immune therapy by upregulation of the mannose-6-phosphate receptor (*e.g.*, paclitaxel, cisplatin, and doxorubicin)[30]. Vacchelli *et al*[31]

Table 1 Current clinical trial results of immune checkpoint inhibitors for gastric cancer

Ref.	Trial phase	Cancer type	n	Drug(s) tested	Key outcome	Trial name (NCT)
Kawazoe <i>et al</i> [15], 2020	2	GC	29	Pembrolizumab + lenvatinib	ORR 69% (95%CI: 49-85) mPFS 7.1 mo (95%CI: 5.4-13.7)	EPOC1706 (NCT03609359)
Kawazoe <i>et al</i> [16], 2020	2b	GC/GEJC	54	Pembrolizumab + SOX	ORR 72.2% (95%CI: 58.4-83.5) mPFS 6.9 mo (95%CI: 5.6-8.3)	KEYNOTE-659 (NCT03382600)
Catenacci <i>et al</i> [17], 2020	1b-2	GEJC	92	Margetuximab + pembrolizumab	ORR 18% (95%CI: 11-28) mPFS 2.73 mo	CP-MGAH22-05 (NCT02689284)
Bang <i>et al</i> [9], 2019	2	GC/GEJC	25	Pembrolizumab + SOC	ORR 60.0% (95%CI: 38.7-78.9) mPFS 6.6 mo (95%CI: 5.9-10.6)	KEYNOTE-059 (NCT02335411)
			31	Pembrolizumab	ORR 25.8% (95%CI: 11.9-44.6) mPFS 3.3 mo (95%CI: 2.0-6.0)	
Tabernero <i>et al</i> [10], 2019	3	GC/GEJC	256	Pembrolizumab	ORR 14.5% (95%CI: 10.4-19.4) mPFS 2.0 mo (95%CI: 1.5-2.8)	KEYNOTE-062 (NCT02494583)
			257	Pembrolizumab + SOC	ORR 48.6% (95%CI: 42.4-54.9) mPFS 6.9 mo (95%CI: 5.7-7.3)	
			250	Placebo + SOC	ORR 36.8% (95%CI: 30.8-43.1) mPFS 6.4 mo (95%CI: 5.7-7.0)	
Boku <i>et al</i> [18], 2019	2	G/GEJ	21	Nivolumab + SOX	ORR 57.1% (95%CI: 34.0-78.2) mPFS 9.7 mo (95%CI: 5.8-NR)	ATTRACTION-4 (NCT02746796)
			18	Nivolumab + CapeOX	ORR 76.5% (95%CI: 50.1-93.2) mPFS 10.6 mo (95%CI: 5.6-12.5)	

GC: Gastric cancer; GEJC: Gastroesophageal junction cancer; SOC: Standard of care; SOX: S-1 plus oxaliplatin; CapeOX: Capecitabine plus oxaliplatin; ORR: Objective response rate; mPFS: Median progression-free survival; CI: Confidence interval.

stated that chemotherapy drugs (paclitaxel, doxorubicin, and cisplatin) could activate the immune system *via* direct effects on cytotoxic lymphocytes and the elimination of immunosuppressive cells *via* clinical trial results of certain chemotherapy drugs (paclitaxel, gemcitabine, and 5Fu)[31]. Traditional chemotherapy drugs are able to enhance the patients' antitumor immune response, and ICIs could further eliminate tumor foci that are resistant to chemotherapy, correspondingly. Thus, the combination of ICI and chemotherapeutics for the treatment of advanced refractory tumors presents clinical benefits, and numerous clinical trials seem to have verified this hypothesis (KEYNOTE-659, KEYNOTE-059, and KEYNOTE-062).

Moreover, additional combination treatment options are worth exploring. The combined use of two ICI drug treatments, such as the combination of CTLA4 and PD-1/PD-L1 blocking antibodies, can kill T lymphocytes in the immune initial and effector stages[32]. For example, the Checkmate032 trial aims to assess the efficacy of the combination treatment of nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA4 antibody) in patients with advanced solid tumors, including advanced GC. As a result, the combined scheme of nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) had a sustained antitumor effect in the treatment of advanced GC, thereby prolonging the OS[33,34]. In addition, radiotherapy is certified to cause immunogenic cell death and has a synergistic effect on anti-tumor CTLs[35]. This principle revealed the possibility of the combined application of radiotherapy and ICI, although there has been no corresponding clinical trial for GC at present. In a novel case report, a patient with HER2-negative advanced GC (stage IV, T4N3M1) received 4 mo of treatment with a combination of concurrent SOX regimen chemotherapy, radiotherapy, and ICI immunotherapy, which showed a satisfactory complete response for tumor lesions, even metastatic lesions (almost complete response, disappearance of all target lesions) [36]. This example demonstrated that the continuous exploration and advances of combined immunotherapy will improve the survival benefits of patients with GC significantly.

PREDICTIVE BIOMARKERS FROM CLINICAL TRIALS

The Cancer Genome Atlas has proposed a molecular classification dividing GC into four subtypes: EBV positive (9%), genomically stable (20%), MSI-high (22%), and

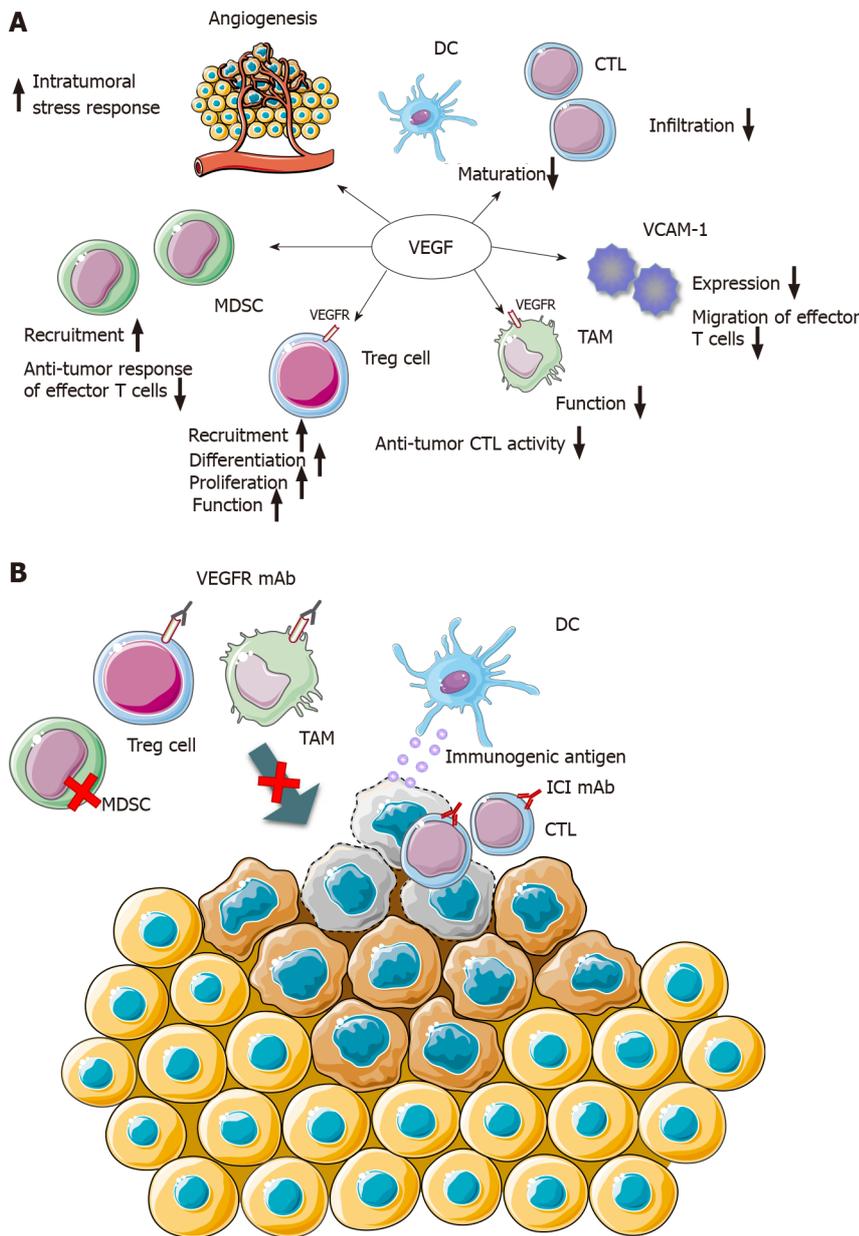


Figure 1 Combined action mechanism of vascular endothelial growth factor monoclonal antibody and immune checkpoint inhibitor monoclonal antibody. A: Impacting on immune-related mechanisms *via* vascular endothelial growth factor (VEGF); B: VEGF receptor (VEGFR) monoclonal antibody (mAb) arouses the normalization of tumor blood vessels, the down-regulation of immunosuppressive cells, and the activity and infiltration of cytotoxic T lymphocytes (CTL). Simultaneously, immune checkpoint inhibitor mAb restores the function of CTL to recognize tumor cells, thereby killing tumor cells and releasing immunogenic antigen. VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; DC: Dendritic cells; CTL: Cytotoxic T lymphocytes; VCAM-1: Vascular endothelial cell adhesion molecule-1; MDSC: Myeloidderived inhibitor cells; TAM: Tumor-associated macrophages; Treg: Regulatory T; mAb: Monoclonal antibody; ICI: Immune checkpoint inhibitor. Figure 1 was produced with the assistance of Servier Medical Art (<https://smart.servier.com>), which provides free and open pictures.

chromosomal instability (50%)[37]. Among the four molecular subtypes of GC, EBV-positive tumors and MSI-high tumors show better responses to ICIs[38]. The Food and Drug Administration (FDA) has approved treatment with pembrolizumab for patients with PD-L1 positive and MSI-high/DNA mismatch repair deficiency (dMMR) advanced GC in the second- or third-line setting[39,40]. Accordingly, PD-L1 positive and MSI-high/dMMR advanced GC patients are currently the most widely applied for ICI therapy.

PD-L1 expression in tumor cells is determined by immunohistochemistry using formalin-fixed paraffin-embedded sections, and the proportion of PD-L1-stained tumor cells and immune cells is calculated to obtain a clinical prediction score (CPS). The result of KEYNOTE-059 trial shows that patients with PD-L1 positive tumors (CPS ≥ 1) achieved 22.7% ORR and 2.7% complete response *via* anti-PD-1 treatment, compared with 8.6% ORR and 3.4% complete response of patients with PD-L1

negative tumors (CPS < 1)[39]. Another randomized phase III trial, KEYNOTE-062 [10], enrolled 763 patients with HER2-negativity and CPS ≥ 1 . The results showed that 281 (37% of the enrollees) had a CPS score of ≥ 10 . The patients were divided into three groups by their treatment options as initial therapy: Intravenous pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy plus placebo. The primary endpoint of this trial showed that for patients with HER2-negative, PD-L1-positive (CPS ≥ 1), advanced GC, combination treatment with pembrolizumab plus chemotherapy resulted in a better ORR and PFS compared with traditional chemotherapy. In addition, pembrolizumab resulted in a clinically meaningful OS improvement for patients with high levels of PD-L1 expression (CPS ≥ 10).

Microsatellites are repetitive sequences of small DNA fragments that exist in the genome, and false microsatellites are produced and accumulated during replication, which is called MSI-high status. Mismatched DNA is frequently repaired by the mismatch repair system, and therefore MSI-high status is usually related to dMMR. Once MSI-high/dMMR status occurs in tumor cells, immune mechanism could handle hypermutation generation and the formation of immunogenic neoantigens. Consequently, numerous immune cells accumulate in tumors with MSI-high/dMMR characteristics, and ICIs are more effective for such tumors[41]. In the report of the phase II KEYNOTE-059 trial, the ORR of ICI therapy of advanced GC patients in the MSI high group was significantly higher than that of the non-MSI high group (57.1% *vs* 9.0%). Meanwhile, the authors of KEYNOTE-062 trial presented a directional analysis of 50 patients with MSI-high tumors, indicating that the ORRs of patients treated with pembrolizumab monotherapy and chemotherapy were 57.1% and 36.8%, respectively, and those of patients treated with pembrolizumab plus chemotherapy *vs* chemotherapy was 64.7% *vs* 36.8%[10].

Furthermore, high tumor mutational burden (TMB), EBV-positivity, immune-related gene expression, *IFNG* (IFN- γ) gene activation, and circulating tumor DNA (ctDNA) have been explored as other biomarkers to predict the clinical endpoints of immunotherapy using ICIs[42,43]. TMB represents the total number of mutations in each coding region of a tumor genome, and it has been found that ICI-treated patients with high TMB exhibit a considerable ORR and PFS in multiple cancers[42]. Derks *et al*[38] showed that tumor or tumor infiltrating immune cells with PD-L1 expression are also a general phenomenon in EBV-positive GC, as well as enrichment of an *IFNG* gene expression signature[38]. Interestingly, in the KEYNOTE-059 trial, Fuchs *et al*[39] reported that six patients with EBV-positive tumors achieved a partial or complete remission using pembrolizumab treatment[39], suggesting that EBV-positive tumors show an effective response to ICI treatment. In the same report, the expression profile of 18 immune-related genes [*CCL5*, *CD27*, *CD274* (PD-L1), *CD276* (B7-H3), *CD8A*, *CXCL9*, *CMKLR1*, *CXCR6*, *HLADQA1*, *HLA-DRB1*, *HLA-E*, *NKG7*, *IDO1*, *LAG3*, *PDCD1-KLG2* (PD-L2), *PSMB10*, *STAT1*, and *TGIT*] illustrated that the statistical score of responders among patients with GC was significantly higher than that of non-responders. Similarly, six IFN- γ -related gene signatures were remarkably associated with the improvement of PFS in ICI-treated patients with GC[43]. Thus, the proposed association with IFN- γ signal transduction and T cell activation of immune-related gene biological signatures, can be used as a biomarker to predict the efficacy of ICI treatment. ctDNA is released into the circulatory system from apoptotic or necrotic tumor cells, and could be used for early diagnosis of some cancers. Moreover, ctDNA mutational burden score is related to the clinical response of patients with GC to pembrolizumab treatment, indicating that ctDNA can be used to screen those patients with GC that are sensitive to ICI treatment[44].

CONSIDERATION OF IMMUNE COMBINATION TRIALS IN OTHER CANCER TYPES

To explore the best schemes of immune combination treatments, it is essential to determine the best endpoints in early phase clinical trials to better opt the correct schemes for confirmatory randomized trials[45]. The development and ratification of single-agent ICIs depended largely on the FDA accelerated approval, and ORR is typically adopted as the primary endpoint in the ICI clinical trials leading to accelerated approval[46]. Table 1 lists these clinical trials that employed ORR as the primary endpoint, and the use of the ORR seemed to prove the excellent effect of ICI treatment. However, traditional clinical trial endpoints, like ORR and PFS, might not be able to predict the long-term survival of patients receiving ICI treatments because the mechanisms of action and reaction patterns for ICI agents differ substantially from

those of conventional chemotherapy. Equally, conventional RECIST criteria might underestimate the benefit from ICI agents[47,48]. For instance, pseudoprogression was initially described in advanced melanoma treated with ipilimumab and was incapable of being assessed by the conventional RECIST criteria[49,50]. Chiu *et al*[50] reported that ORR is correlated insufficiently with PFS and OS in the single-arm and randomized trials of ICI treatment (the r correlation coefficients of ORR with 6-mo PFS and 12-mo OS were 0.37 and 0.08, respectively). By contrast, a conspicuous correlation between 6-mo PFS and 12-mo OS was discovered (the r correlation coefficient was 0.74)[51]. Thus, in single-arm trials, ICI efficacy analysis by selecting the PFS rate at particular time points (*e.g.*, 6 or 12 mo) might be considered as a better surrogate endpoint than ORR, thereby also improving the evaluation criteria of solid tumors under ICI treatment.

ICI-related trials with multiple primary endpoints require rigorous methods to control the overall type I error rate, yet the generally recognized clinical benefits of ICI therapy in patients with advanced cancer might not be "statistically significant"[46], as demonstrated by the IMvigor211 trial of atezolizumab for the treatment of urothelial carcinoma and the KEYNOTE-240 trial of pembrolizumab for the treatment of advanced hepatocellular carcinoma[52,53]. The demand for volunteers has greatly increased with the development of more and more clinical trials, especially in past few years, and ICI trials have been recruiting patients faster than other interventional oncology trials. However, the recruitment rate has recently declined significantly, from 1.15 patients per site every month in 2014 to 0.35 patients per site every month in 2018, indicating that combination trials may face recruitment challenges in the near future [14]. Furthermore, the low recruitment rate not only affects the progress of clinical trials, but also incurs greater costs. Formulating innovative, efficient, and rational trial schemes to allocate patient volunteers reasonably is required.

PROSPECTS OF ICIS FOR NEOADJUVANT TREATMENT OF GC

Neoadjuvant chemotherapy with FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) regimen is the standard treatment in the West. In contrast, SOX regimen is the preferred neoadjuvant chemotherapy regimen in the East. The phase II randomized clinical trial NCT03636893 reported 74 patients with locally advanced resectable GC, and the primary outcomes did not show statistically significant differences between neoadjuvant FLOT and SOX regimens[54]. The FLOT and SOX groups showed desired therapeutic effect, yet several hematological grade 3–4 adverse events were observed (29.0% and 16.1%, respectively). It is necessary to explore more treatment methods to expand the scope of medication, and to design the best combined treatment plan for patients to maximize anti-tumor effects and reduce adverse events.

The neoadjuvant treatment of ICI is applied presurgically, playing a pivotal role in radical treatment for tumors, such as anti-CTLA-4 treatment for bladder cancer and melanoma[55,56]. Mechanistically, compared with adjuvant therapy directed only against micrometastatic foci after resection, neoadjuvant ICI makes full use of higher tumor antigen load *in vivo* before surgery, resulting in more tumor-specific T cells being present in the systemic circulation[57]. Anti-PD-L1/anti-PD-1 monoclonal antibody restores the activity of tumor-specific cytotoxic T cells that already exist in the tumor microenvironment and promotes their activation, proliferation, and transfer to micrometastases. Afterwards, the focus of anti-PD-(L)1 activity might be in the tumor draining lymph nodes, where dendritic cells present tumor antigens to T cells, and then these tumor-specific T cells enter the bloodstream and migrate to the tumor sites[57,58]. The aforementioned hypothetical mechanism was verified in a spontaneously metastatic transplantable mouse breast cancer model, showing that survival after neoadjuvant immunotherapy was significantly better than that after adjuvant immunotherapy[59]. Topalian *et al*[57] proposed several potential clinical advantages of neoadjuvant therapy, including preoperative tumor shrinkage and the capability to assess the pathological response as an early surrogate indicator for relapse-free survival and OS, offering sufficient tissue availability therapies for in-depth scientific research to explore mechanism of drug action and predictive biomarkers[57]. Currently, clinical trials of neoadjuvant immunotherapy based on ICIs have started, such as the first trial report of neoadjuvant anti-PD-1 therapy, which is a phase II trial of nivolumab in 21 patients with high-risk (stage I, II, or IIIA) non-small-cell lung cancer, which has indicated that 45% of resected tumors have a major pathological response[60]. However, few clinical trials have been carried out on the application of ICI as neoadjuvant treatment in GC, and only one clinical trial (NCT03064490) is

registered in ClinicalTrials.gov. Jin *et al*[61] submitted a notable case report, in which a patient with PD-L1 positive and MSI-high advanced GC (cT4aN+M0 state) received a single dose of anti-PD-1 therapy in combination with chemotherapy and radical gastrectomy, resulting in a pathological complete response (pTONOM0)[61]. This case report suggested that a combined ICI scheme might be feasible as neoadjuvant treatment of GC.

CONCLUSION

Through the continuous exploration of clinical trials, the combined scheme of immunotherapy for GC is being implemented. Based on previous feedback, identifying the most valuable predictive biomarkers and trial schemes to promote the further development of clinical trials is required. In terms of prolonging the survival of patients with GC, ICI might possess merit as a neoadjuvant treatment.

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