**Name of Journal:** *World Journal of Meta-Analysis*

**Manuscript NO:** 46535

**Manuscript Type:** MINIREVIEWS

**PD-1/PD-L1 antagonists in gastric cancer: Current studies and perspectives**

Li J *et al.* Immunotherapy in gastric cancer

Jian Li, Xiao-Hong Zhang, Song-Hua Bei, Li Feng

**Jian Li, Xiao-Hong Zhang, Song-Hua Bei, Li Feng,** Endoscopy Center, Minhang Branch of Zhongshan Hospital, Fudan University, Shanghai 201100, China

**ORCID number:** Jian Li (0000-0001-8415-4389); Xiao-Hong Zhang (0000-0002-2404-517X); Song-Hua Bei (0000-0002-5454-2409); Li Feng (0000-0001-7760-2737).

**Author contributions:** Feng L conceived this topic and organized the manuscript; Li J wrote the first draft of the manuscript and drew the figures; Zhang XH and Bei SH contributed to manuscript revision; all authors have read and approved the submitted version and are accountable for all aspects of the work.

**Supported by** Minhang District University Building Project, No. 2017MWDXK03.

**Conflict-of-interest statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Corresponding author: Li Feng, MD, Chief Doctor,** Endoscopy Center, Minhang Branch of Zhongshan Hospital, Fudan University, No. 170, Xinsong Road, Minhang District, Shanghai 201100, China. [13247793069@163.com](mailto:13247793069@163.com)

**Telephone:** +86-21-64923400-6307

**Fax:** +86-21-64923400-6307

**Received:** February 18, 2019

**Peer-review started:** February 18, 2019

**First decision:** March 20, 2019

**Revised:** March 26, 2019

**Accepted:** March 26, 2019

**Article in press:**

**Published online:**

**Abstract**

Immune checkpoints release suppressive signals for T cells, which enable the tumors to escape from immune destruction and provide a new concept that uses the capabilities of the immune system as a therapeutic target for tumors. At present, programmed death receptor 1 (PD-1)/programmed death ligand-1 (PD-L1) has become the most promising therapeutic target. PD-1/PD-L1 blockades exhibit long-lasting antitumor efficacy and safety in patients with various cancers, such as melanoma and non-small-cell lung cancer. Moreover, PD-L1 is highly expressed in the peripheral blood and tumor specimens of patients with cancer, and the expression of PD-L1 is positively correlated with various pathological features and may serve as a predictor of poor prognosis or a diagnostic tool. Clinical trials have verified that PD-1/PD-L1 blockade therapy benefits patients with advanced gastric cancer or gastroesophageal junction cancer. Furthermore, there are many molecules involved in the regulation of PD-1/PD-L1 expression, and the modification of these molecules *via* drugs and combinations with PD-1/PD-L1 inhibitors may further improve the efficacy of immunotherapy for gastric cancer. In this review, the efficacy, safety, and possible combination treatment options of PD-1/PD-L1 in gastric cancer are reviewed in experimental and clinical settings.

**Key words:** Immunotherapy; PD-1/PD-L1 inhibitors; Programmed death-ligand 1; Gastric cancer

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Programmed death receptor 1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors have been defined as a distinct type of immunotherapy for various cancers. A growing number of studies have investigated the role of PD-1/PD-L1 inhibitors in gastric cancer. This manuscript presents a comprehensive overview of the mechanism of PD-1/PD-L1 blockade therapy, summarizes the efficacy and safety of some critical clinical trials, and highlights possible combination treatment options in gastric cancer. This manuscript also provides insight into the current research limitations and indicates the development direction for future research of PD-1/PD-L1 checkpoint inhibitors.

Li J, Zhang XH, Bei SH, Feng L. PD-1/PD-L1 antagonists in gastric cancer: Current studies and perspectives. *World J Meta-Anal* 2019; In press

**INTRODUCTION**

Cancer immunotherapy is one of the most successful therapies in the field of cancer treatment in recent years[1]. Following surgery, radiation, chemotherapy, and targeted therapy, immunotherapy has become a new method for the treatment of cancer. As early as 2013, cancer immunotherapy was rated as one of the top ten scientific breakthroughs[2]. Evading immune destruction is one of the hallmarks of cancer, as illustrated by Hanahan and Weinberg[3]. The concept that the immune system can recognize and control the growth of tumors can be traced back to 1893 when William Coley used live bacteria as an immunostimulant to treat cancer. However, due to its limited clinical efficacy, cancer immunotherapy has been met with moderate enthusiasm. This limited efficacy results from the ability of the tumor cells to avoid being identified and eliminated by the immune system, which allows the tumor cells to be part of the host[4]. Over the past few decades, enormous progress has been made in illuminating how cancer evades the immune system, which in turn provides novel methods to stop cancer immune evasion by eliminating cancer cells. Cancer immunotherapy utilizes the host's natural defense mechanism to enhance antitumor immunity for a stronger antitumor effect. At present, cancer immunotherapy includes adoptive cellular immunotherapy, checkpoint inhibitors, and therapeutic cancer vaccines[5-7]. The immunological checkpoint molecules include programmed cell death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). The application of immune checkpoint inhibitors has shown significant antitumor effects on several cancers and has tremendously changed the treatment of melanoma, lung cancer, and kidney cancer. Compared with CTLA-4 inhibitors, checkpoint blockades targeting the PD-1/programmed death ligand-1 (PD-L1) axis have more advantages in efficacy and fewer side effects[8], which allows PD-1/PD-L1 antagonists to be developed into a more promising and efficient approach for anticancer therapy.

Gastric cancer is a malignant cancer of the digestive tract that has serious implications for human health worldwide[9]. According to the recent global statistics, gastric cancer remains a significant cancer globally, and there were more than 1000000 newly diagnosed gastric cancer cases in 2018 along with an estimated 783000 deaths (1 in every 12 deaths globally), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death[10]. *Helicobacter pylori* is the main risk factor for gastric cancer, with almost 90% of new cases of stomach cancer being ascribed to an infection with *Helicobacter pylori*[11,12]. Due to the lack of specific symptoms and signs in the early stage, most patients are diagnosed with gastric cancer at the advanced stage, which severely affects the prognosis of the patients. Although there are some advances in early gastric cancer screening and treatment, the 5-year survival rate of patients with advanced gastric cancer is still below 10%[13]. Endoscopic resection is a critical method in the treatment of early gastric cancer. The treatment of advanced gastric cancer is usually based on surgery and supplemented by chemotherapy[14]. Combination chemotherapy is the first-line treatment for patients with advanced gastric cancer. Several cytotoxic drugs, such as fluoropyrimidine, platinum, paclitaxel, and irinotecan, have curative effects on gastric cancer. Although tremendous progress has been made in chemotherapy, the overall prognosis is still poor[15]. Furthermore, an increasing number of patients who were initially sensitive to chemotherapy gradually acquired drug resistance during treatment, which limits the further application of chemotherapy drugs. Additionally, targeted therapies against HER2 and VEGFR have also been approved for the treatment of advanced gastric cancer, but the 5-year overall survival (OS) is only 20%-30%[16].

Recently, cancer immunotherapy, especially with checkpoint antagonists, has been transforming the entire field of cancer treatment and has achieved optimistic effects in solid tumors such as melanoma, lung cancer, and kidney cancer. Furthermore, PubMed and The American Society of Clinical Oncology Annual Meeting data suggest that PD-1/PD-L1 inhibitors may lead us into a new era for the treatment of gastric cancer[16]. Herein, we review the mechanisms of PD-1/PD-L1 blockade therapy, summarize the present knowledge of PD-1/PD-L1 inhibitors to reveal their efficacy and safety in stomach cancer or gastroesophageal junctional cancer, and highlight the possible combination of conventional therapy with PD-1/PD-L1 checkpoint inhibitors.

**MECHANISM OF ACTION OF PD-1/PD-L1** **BLOCKADE THERAPY**

PD-1, a transmembrane receptor on T cells, was initially identified from apoptotic T cell hybridomas through a subtractive method and has become known as a predominant negative regulator of antitumor T cell effector function when engaged by its ligand PD-L1, which is expressed on the surface of cells within tumors[17]. PD-1 bears its name from its earliest description that it was expressed as a receptor involved in cell death[18]. As a significant member of the B7/CD28 costimulatory molecule superfamily, PD-1 is primarily expressed on the surface of activated T and B cells. Both PD-L1 (also known as B7-H1) and PD-L2 (also known as B7-DC) are ligands of PD-1, and they are essential members of the costimulatory molecules in the B7 family[19,20]. PD-L1 is usually expressed in antigen-presenting cells (APCs), such as macrophages and DCs; however, in the presence of inflammatory factors, such as interferon (IFN) or interleukin 4 (IL-4), PD-L1 is also expressed in epithelial and skin cells[21]. PD-L2 has more exclusive expression than PD-L1 in APCs[22,23]. The binding of PD-1 to its ligands functions as an immune checkpoint and regulates the host’s costimulatory or inhibitory signals to exert effects on T lymphocytes, thereby modulating the magnitude and duration of T lymphocyte responses.

Under physiological conditions, the combination of PD-1/PD-L1 produces an inhibitory signal to prevent the host from developing autoimmune disease. However, when an inflammatory response occurs in the host, the binding of PD-1 prevents the spread of inflammation, thus localizing tissue damage and preventing the excessive inflammatory reaction. Furthermore, within the background of the tumor microenvironment, antitumor T cells continuously recognize cognate tumor antigens from when cancer develops in the primary stage to the formation of metastatic lesions. Activation of the TCR gives rise to the production of proinflammatory cytokines, including IFN-γ, which is the most potent driver of reactive PD-L1 expression[22,24]. Moreover, the chronic expression of IFN-γ in the microenvironment induces the elevated expression of PD-1 on the infiltrated T cells. The recognition of PD-1 on antitumor T cells by the highly expressed PD-L1 on tumor cells not only inhibits secretion of T cell immune stimulating cytokines (IL-2, IFN-γ, and tumour necrosis factor-α) but also promotes the secretion of the immunosuppressive cytokines (IL-10), thus inhibiting T cell activation and proliferation[25]. Eventually, the tumor cells evade immune destruction. PD-1 is therefore a negative regulator of immune responses and is becoming a promising therapeutic target in cancer immunotherapy.

**PD-1/PD-L1 EXPRESSION AND ITS CORRELATION WITH CLINICOPATHOLOGIC FEATURES OR PROGNOSIS IN PATIENTS WITH GASTRIC CANCER**

A growing number of studies have been conducted to illuminate the correlation between PD-1/PD-L1 expression and clinicopathologic features or prognosis in patients with gastric cancer. Wang *et al*[26] obtained tissues from 509 patients who underwent gastrectomy, and all tissues were collected and analyzed in the form of a tumor microarray (TMA). In that study, the authors found that a positive PD-L1 status was correlated with high CD3+ and CD8+ T cell invasion. Positive expression of PD-L1 and CD8+ T cells was associated with long OS time in stomach cancer patients, but there were no significant differences noted between the groups with high and low PD-1 and CD3 expression. These results suggest that PD-L1 expression and a high density of CD8+ T cells may serve as prognostic indicators in patients with advanced gastric cancer. Moreover, in a cellular and specimen-based study, Amatatsu *et al*[27] investigated PD-L1 mRNA expression in three gastric cancer cell lines and 124 blood specimens from patients with gastric cancer by qRT-PCR assays. It was demonstrated that a high level of PD-L1 expression significantly correlated with deep tumor invasion, distant metastasis, and advanced stage (*P* = 0.001, *P* < 0.001, and *P* < 0.001, respectively). In terms of diagnostic performance, surprisingly, the area under the ROC curve for predicting patients with distant metastasis was 0.772. The sensitivity and specificity of PD-L1 mRNA expression for predicting distant metastasis were 0.814 and 0.667, respectively. In addition, compared with patients with low PD-L1 expression, patients with high PD-L1 expression had a significantly lower 5-year survival rate (84.1% *vs* 50.0%, *P* < 0.0001). Univariate and multivariate analyses of survival revealed that PD-L1 expression was significantly associated with postoperative survival (*P* < 0.0001) and could be selected as an independent prognostic factor (*P* = 0.024). Similarly, in a study that involved 465 patients, Boger *et al*[28] reported that the immunohistochemical analysis results of a TMA exhibited a close relationship between the protein expression of PD-L1 and some important prognostic clinicopathological factors, including depth of tumor invasion, distant metastasis, and UICC stage. These findings imply that the assessment of PD-L1 expression has potential clinical application for monitoring tumor properties and progression in patients with stomach cancer. Moreover, the cancer genome atlas (TCGA) classifies gastric cancer into the following four molecular subtypes: (1) Epstein-Barr virus (EBV)-positive; (2) microsatellite instability (MSI); (3) chromosomal instability; and (4) genomically stable[29]. Identification of these subtypes offers a roadmap for patient stratification, and trials of targeted therapies also provide the necessary molecular tools to realize individualized treatment in cancer. A total of 15 eligible studies that included 3291 patients were selected for a meta-analysis[30], which showed that PD-L1 expression was associated with OS in gastric cancer (HR = 1.46, 95%CI: 1.08 ± 1.98; *P* = 0.01). The authors also found that EBV infection-positive (EBV+) and MSI tumors are more likely to express PD-L1 than the other types of gastric cancer tumors, which is consistent with the results of previous reports[31-34]. This result may provide evidence that gastric cancer patients, especially those with the subtypes of EBV+ and MSI tumors, may be prime candidates for PD-1 blockade therapy. Nevertheless, an original study from Japan showed that EBV-positive gastric cancer cells that express high levels of PD-L1 inhibited T-cell proliferation, and the IFN-γ signaling pathway played an important role in the expression of PD-L1[35].

However, the heterogeneous expression of PD-L1 within primary tumor sites is one of the critical obstacles to the clinical treatment of PD-1/PD-L1 checkpoint blockades[36]. The KEYNOTE-010 study suggested that the level of PD-L1 expression could act as a useful molecular tool to distinguish responders from nonresponders in PD-1/PD-L1 immunotherapy[37]. As mentioned above, the status of PD-L1 expression in blood specimens or tissue specimens is not only associated with clinicopathological features, prognosis, and diagnostic performance but is also associated with the therapeutic effects of PD-1/PD-L1 checkpoint blockades.

**CLINICAL EFFECTS OF PD-1/PD-L1 INHIBITORS IN GASTRIC CANCER**

PD-1/PD-L1 checkpoint blockades have dramatically transformed the landscape for conventional treatments in patients with gastric cancer. At present, there are five anti-PD-1 or anti-PD-L1 antibodies approved by the FDA for approximately 11 cancer indications[17]; these approved antibodies include two antibodies for PD-1, nivolumab and pembrolizumab, and three antibodies for PD-L1, atezolizumab, avelumab, and durvalumab. These drugs are still in the early stages of clinical research. The current PD-1 inhibitors are mainly used for the treatment of melanoma, non-small-cell lung cancer (NSCLC), and urothelial cancer. Based on the efficacy of PD-1 blockers in NSCLC and melanoma patients, PD-1/PD-L1 inhibitors will hopefully continue to expand their range of applications. Clinical trials with PD-1/PD-L1 antibodies have been initiated in multiple studies. These studies investigated the efficacy and safety of PD-1/PD-L1 antibodies in the treatment of melanoma, urinary tract cancer, digestive tract tumors, and malignant gliomas. Here, we focus on the treatment of gastric or gastroesophageal junctional cancer with PD-1/PD-L1 inhibitors.

The KEYNOTE-012 study[38], a multicenter phase Ib trial using the anti-PD-1 antibody pembrolizumab, included 162 patients with recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction cancer. The PD-L1 positive rate in these patients was 40%. All 39 patients were treated with pembrolizumab at 10 mg/kg once every 2 wk for 24 mo, and the endpoints included trial completion (24 mo), complete remission (CR), cancer progression, or the occurrence of unacceptable toxic effects. The results showed that the objective response rate (ORR) was 22.2% (95%CI: 10.1%-39.2%), the rate of grade 3 or 4 treatment-related adverse events (TRAES) was 13%, the median progression-free survival (PFS) time was 1.9 mo (95%CI: 1.8-3.5), and the median OS time was 11.4 mo. At the six month follow-up, the PFS rate was 24%, the OS rate was 69%, and nearly 53% patients experienced tumor shrinkage to some degree. Moreover, no patients withdrew from the trial due to immune-related adverse reactions. Although this trial did not include a control group, the side effects were still in the acceptable range, and these results warranted further study in phase II and III trials. CheckMate-032[39] was a multicenter phase I/II cohort study that treated advanced gastric cancer patients with nivolumab. This trial enrolled 59 patients diagnosed with advanced and metastatic (A/M) gastric or gastroesophageal junction cancer, and the positive rate of PD-L1 expression in all patients was 38%. All patients were prescribed 3 mg/kg of nivolumab every 2 wk until unacceptable toxicity effects occurred. The results showed that the ORR was 14%, the OS was 5 mo (95%CI: 3.4-12.4), and the 12-mo OS rate was 36%. Moreover, no treatment-related deaths occurred in this study, and all adverse reactions were controllable. The analysis of the classified data demonstrated that the ORRs in the PD-L1-positive and PD-L1-negative patients were 27% and 12%, respectively. Nivolumab had improved efficacy in the PD-L1-positive patients than in the PD-L1-negative patients. In a randomized controlled phase III trial published in *Lancet*, 493 participants were randomized into a nivolumab-treated group and a placebo-treated group. The OS in the two groups was 5.26 mo and 4.14 mo, respectively (HR: 0.63; 95%CI: 0.51-0.78; *P* < 0.0001); in comparison, the OS for the PD-L1-positive patients in the treatment and control groups was 5.22 mo and 3.82 mo, respectively (HR: 0.51; 95%CI: 0.21-1.25). The 12-mo OS rate in the treatment group was significantly higher than that in the control group (26.2% *vs* 10.9%). Although most of these clinical trials did not list positive PD-L1 expression as one of the inclusion criteria, the results did provide solid evidence that, compared with conventional therapy, PD-1/PD-L1 inhibitors brought new hope for gastric cancer patients with highly expressed PD-L1.

The tumor microenvironment is complicated and interacts with multiple signaling pathways, both of which jointly regulate the initiation and progression of cancers and even the responses to specific therapies. Studies have demonstrated that there are a variety of signaling pathways involved in cancer immunotherapy and that these pathways may interact with each other[40]. Acquired resistance after a period of response is one of major problems with checkpoint blockade therapy as well[41]. Therefore, it is often difficult to achieve the desired clinical effects with the long-term application of PD-1/PD-L1 inhibitors or single-agent treatment. To maximize the benefits of cancer therapy, the combination of different immunotherapies or immunotherapy with conventional therapies such as radiotherapy, chemotherapy, and oncogene-targeted therapy, has been shown to alter the immunosuppressive tumor microenvironment and enhance the ability to eliminate cancers, which is the future direction for cancer therapy[42].

A clinical trial was designed based on the foundation of the CTL-4 and PD-1 pathways having coinhibitory roles after preclinical studies showed evidence of synergy in syngeneic mouse models. In this trial, the patients were treated with a combination of ipilimumab and nivolumab to block CTLA-4 and PD-1, respectively[42]. The data showed that in the single treatment group, the time to progression (TTP) was 6.9 mo, and the ORR was 57.6%, while in the combination treatment group, the TTP was 11.5 mo, and the ORR was 57.6%[43]. Furthermore, KEYNOTE-059[44] was a phase II cohort clinical trial that studied pembrolizumab alone or in combination with cisplatin/5-FU among advanced gastric cancer patients. The data showed that the PD-L1 positive rate in the 25 enrolled patients was 64%, the ORR was 60% (95%CI: 38.7~78.9), the ORR of PD-L1-positive patients was 68.8%, the ORR of PD-L1-negative patients was 37.5%, the PFS was 6.6 mo (95%CI: 5.9-10.6), and the OS was 13.8 mo. Despite the fact that there were no adverse events related to death, the rate of grade III-IV TRAES remained high (76%) and included diarrhea, dysgeusia, thyroid disorders, and nausea. Clearly, the coinhibitory group benefitted more than the single inhibitory or traditional therapy group. On the basis of improving safety and efficacy, minimizing the adverse event rate is a major problem that is needed to address in combination treatments.

Several studies have demonstrated that the PD-L1 positive rate in gastric cancer tissues was over 40%[45-47]. We have noted that according to the molecular characteristics of gastric cancer, the TCGA divided stomach cancer into four molecular subtypes in 2014. The EBV-positive type accounts for 9% of all gastric cancers and displays recurrent PIK3CA mutations, extreme DNA hypermethylation, and high expression of PD-L1/2[29]. This classification provides a theoretical basis for the simultaneous treatment of PD-L1 inhibitors and anti-EB virus therapy. Furthermore, CD40 is one of the critical costimulatory molecules in the antitumor treatment immune response, but the effects of CD40 monoclonal antibody from clinical trials were unsatisfactory[48]. One explanation for this phenomenon is that the expression of PD-L1 on the surface of tumor cells was also elevated with the use of a CD40 agonist. Therefore, when conducting research to illuminate the mechanism of costimulatory molecules, blocking the PD-L1 pathway is of great importance. In addition, numerous studies have revealed that dysregulation of the Wnt/β-catenin signaling pathway occurred in more than 70% of gastric cancer patients[49]. Activation of the Wnt/β-catenin signaling pathway is not only involved in the physiological processes of proliferation, invasion, metastasis, and drug resistance[50-52] but is also negatively correlated with T cell invasion within many tumors such as colorectal cancer[53], melanoma[54], ovarian cancer[55], and prostate cancer[56]. In contrast, the inhibition of the Wnt/β-catenin signaling pathway significantly suppressed proliferation and metastasis both *in vitro* and *in vivo*[57]. These studies suggest that Wnt/β-catenin signaling pathway inhibitors may stimulate immune cells and enhance T cell infiltration in tumors, allowing tumors to respond to immunotherapy. It is apparent that more novel studies are needed to identify potential therapeutic targets to promote the exploration and realization of the potency of combination therapy.

**CONCLUSION**

Although considerable progress has been made in cancer therapy and the treatment of cancers has entered the new era of immunotherapy, the efficacy and safety of PD-1/PD-L1 inhibitors in advanced gastric cancer patients still need to be further explored by in-depth research in clinical settings. First, most of the clinical trials were primarily limited to early stage I or II disease, and the number of PD-L1-positive patients in the treatment group remained relatively low, which prevents gathering enough direct and potent evidence to validate the curative effects. Second, given the results of the clinical trials up to now, TRAES may become one of the critical factors that thwarts the future application of PD-1/PD-L1 blockade therapy. Identifying and understanding the mechanism of adverse events are of great importance in preventing the occurrence of side effects. Third, after the safety and efficacy of cancer immunotherapy have been validated, the next question is how to select the best treatment method for specific patients. According to the comprehensive molecular characterization of gastric adenocarcinoma, the single-cell sequencing technique would help researchers to recognize different subtypes, discriminate responders, and design the best treatment strategy for patients, allowing individualized cancer therapy to become a reality. Thus, it is essential to list PD-L1-positive gastric cancer patients in the inclusion criteria, minimize the rate of adverse events, and use molecular tools to identify specific patient subpopulations in the research of cancer immunotherapy.

The efficacy of the combination of PD-1/PD-L1 blockade therapy with other traditional therapies remains to be fully elucidated. Combination therapy provides a new direction for research and is a new aspect of cancer immunotherapy. The combination of radiation and anti-PD-1/PD-L1 therapy is as an example of this new area. Ahmed *et al*[58] retrospectively reviewed patients who received stereotactic radiosurgery (SRS) for melanoma brain metastases (BM). The patients were treated with SRS before, during, or after nivolumab therapy. Their results demonstrated that when compared with SRS alone, the combination therapy was better tolerated with no unexpected neurotoxicity. In addition, these patients had superior out-of-field BM control and OS compared with those who received the current standard treatment for melanoma[58]. Although no prospective trials have been published, there are currently several cumulative trials evaluating the safety and efficacy of PD-1/PD-L1 inhibitors combined with radiation therapy in various malignancies[59]. Preliminary reports from some of these trials have shown promising outcomes[60,61]. Consequently, efforts still need to be made in the exploration of combination therapy, new molecular targets, or already identified targets. Based on the recent successes of the field of immunotherapy, continuing to incorporate knowledge from mechanistic basic science research is essential to achieving therapeutic success.

**REFERENCES**

1 **Rangel-Sosa MM**, Aguilar-Córdova E, Rojas-Martínez A. Immunotherapy and gene therapy as novel treatments for cancer. *Colomb Med* (Cali) 2017; **48**: 138-147 [PMID: 29213157 DOI: 10.25100/cm.v48i3.2997]

2 **Couzin-Frankel J**. Breakthrough of the year 2013. Cancer immunotherapy. *Science* 2013; **342**: 1432-1433 [PMID: 24357284 DOI: 10.1126/science.342.6165.1432]

3 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

4 **Drake CG**, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. *Adv Immunol* 2006; **90**: 51-81 [PMID: 16730261 DOI: 10.1016/S0065-2776(06)90002-9]

5 **Houot R**, Schultz LM, Marabelle A, Kohrt H. T-cell-based Immunotherapy: Adoptive Cell Transfer and Checkpoint Inhibition. *Cancer Immunol Res* 2015; **3**: 1115-1122 [PMID: 26438444 DOI: 10.1158/2326-6066.CIR-15-0190]

6 **Khalil DN**, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. *Nat Rev Clin Oncol* 2016; **13**: 273-290 [PMID: 26977780 DOI: 10.1038/nrclinonc.2016.25]

7 **Papaioannou NE**, Beniata OV, Vitsos P, Tsitsilonis O, Samara P. Harnessing the immune system to improve cancer therapy. *Ann Transl Med* 2016; **4**: 261 [PMID: 27563648 DOI: 10.21037/atm.2016.04.01]

8 **Robert C**, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**: 2521-2532 [PMID: 25891173 DOI: 10.1056/NEJMoa1503093]

9 **Choi YJ**, Kim N. Gastric cancer and family history. *Korean J Intern Med* 2016; **31**: 1042-1053 [PMID: 27809451 DOI: 10.3904/kjim.2016.147]

10 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

11 IARC working group on the evaluation of carcinogenic risks to humans: some industrial chemicals. Lyon, 15-22 February 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **60**: 1-560 [PMID: 7869568]

12 **Plummer M**, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer* 2015; **136**: 487-490 [PMID: 24889903 DOI: 10.1002/ijc.28999]

13 **Zong L**, Abe M, Seto Y, Ji J. The challenge of screening for early gastric cancer in China. *Lancet* 2016; **388**: 2606 [PMID: 27894662 DOI: 10.1016/S0140-6736(16)32226-7]

14 **Orditura M**, Galizia G, Sforza V, Gambardella V, Fabozzi A, Laterza MM, Andreozzi F, Ventriglia J, Savastano B, Mabilia A, Lieto E, Ciardiello F, De Vita F. Treatment of gastric cancer. *World J Gastroenterol* 2014; **20**: 1635-1649 [PMID: 24587643 DOI: 10.3748/wjg.v20.i7.1635]

15 **Wagner AD**, Syn NL, Moehler M, Grothe W, Yong WP, Tai BC, Ho J, Unverzagt S. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2017; **8**: CD004064 [PMID: 28850174 DOI: 10.1002/14651858.CD004064.pub4]

16 **Bilgin B**, Sendur MA, Bülent Akıncı M, Şener Dede D, Yalçın B. Targeting the PD-1 pathway: a new hope for gastrointestinal cancers. *Curr Med Res Opin* 2017; **33**: 749-759 [PMID: 28055269 DOI: 10.1080/03007995.2017.1279132]

17 **Ribas A**, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018; **359**: 1350-1355 [PMID: 29567705 DOI: 10.1126/science.aar4060]

18 **Ishida Y**, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J* 1992; **11**: 3887-3895 [PMID: 1396582 DOI: 10.1002/j.1460-2075.1992.tb05481.x]

19 **Gunturi A**, McDermott DF. Potential of new therapies like anti-PD1 in kidney cancer. *Curr Treat Options Oncol* 2014; **15**: 137-146 [PMID: 24504486 DOI: 10.1007/s11864-013-0268-y]

20 **Hawkes EA**, Grigg A, Chong G. Programmed cell death-1 inhibition in lymphoma. *Lancet Oncol* 2015; **16**: e234-e245 [PMID: 25943068 DOI: 10.1016/S1470-2045(15)70103-8]

21 **Villasboas JC**, Ansell S. Checkpoint Inhibition: Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Inhibitors in Hodgkin Lymphoma. *Cancer J* 2016; **22**: 17-22 [PMID: 26841012 DOI: 10.1097/PPO.0000000000000164]

22 **Baumeister SH**, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory Pathways in Immunotherapy for Cancer. *Annu Rev Immunol* 2016; **34**: 539-573 [PMID: 26927206 DOI: 10.1146/annurev-immunol-032414-112049]

23 **Tarhini AA**, Zahoor H, Yearley JH, Gibson C, Rahman Z, Dubner R, Rao UN, Sander C, Kirkwood JM. Tumor associated PD-L1 expression pattern in microscopically tumor positive sentinel lymph nodes in patients with melanoma. *J Transl Med* 2015; **13**: 319 [PMID: 26419843 DOI: 10.1186/s12967-015-0678-7]

24 **Garcia-Diaz A**, Shin DS, Moreno BH, Saco J, Escuin-Ordinas H, Rodriguez GA, Zaretsky JM, Sun L, Hugo W, Wang X, Parisi G, Saus CP, Torrejon DY, Graeber TG, Comin-Anduix B, Hu-Lieskovan S, Damoiseaux R, Lo RS, Ribas A. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. *Cell Rep* 2017; **19**: 1189-1201 [PMID: 28494868 DOI: 10.1016/j.celrep.2017.04.031]

25 **Ribas A**. Adaptive Immune Resistance: How Cancer Protects from Immune Attack. *Cancer Discov* 2015; **5**: 915-919 [PMID: 26272491 DOI: 10.1158/2159-8290.CD-15-0563]

26 **Wang Y**, Zhu C, Song W, Li J, Zhao G, Cao H. PD-L1 Expression and CD8+ T Cell Infiltration Predict a Favorable Prognosis in Advanced Gastric Cancer. *J Immunol Res* 2018; **2018**: 4180517 [PMID: 30003113 DOI: 10.1155/2018/4180517]

27 **Amatatsu M**, Arigami T, Uenosono Y, Yanagita S, Uchikado Y, Kijima Y, Kurahara H, Kita Y, Mori S, Sasaki K, Omoto I, Maemura K, Ishigami S, Natsugoe S. Programmed death-ligand 1 is a promising blood marker for predicting tumor progression and prognosis in patients with gastric cancer. *Cancer Sci* 2018; **109**: 814-820 [PMID: 29345842 DOI: 10.1111/cas.13508]

28 **Böger C**, Behrens HM, Mathiak M, Krüger S, Kalthoff H, Röcken C. PD-L1 is an independent prognostic predictor in gastric cancer of Western patients. *Oncotarget* 2016; **7**: 24269-24283 [PMID: 27009855 DOI: 10.18632/oncotarget.8169]

29 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

30 **Gu L**, Chen M, Guo D, Zhu H, Zhang W, Pan J, Zhong X, Li X, Qian H, Wang X. PD-L1 and gastric cancer prognosis: A systematic review and meta-analysis. *PLoS One* 2017; **12**: e0182692 [PMID: 28796808 DOI: 10.1371/journal.pone.0182692]

31 **Cho J**, Chang YH, Heo YJ, Kim S, Kim NK, Park JO, Kang WK, Lee J, Kim KM. Four distinct immune microenvironment subtypes in gastric adenocarcinoma with special reference to microsatellite instability. *ESMO Open* 2018; **3**: e000326 [PMID: 29636988 DOI: 10.1136/esmoopen-2018-000326]

32 **De Rosa S**, Sahnane N, Tibiletti MG, Magnoli F, Vanoli A, Sessa F, Chiaravalli AM. EBV⁺ and MSI Gastric Cancers Harbor High PD-L1/PD-1 Expression and High CD8⁺ Intratumoral Lymphocytes. *Cancers* (Basel) 2018; **10**: pii: E102 [PMID: 29614789 DOI: 10.3390/cancers10040102]

33 **Derks S**, Liao X, Chiaravalli AM, Xu X, Camargo MC, Solcia E, Sessa F, Fleitas T, Freeman GJ, Rodig SJ, Rabkin CS, Bass AJ. Abundant PD-L1 expression in Epstein-Barr Virus-infected gastric cancers. *Oncotarget* 2016; **7**: 32925-32932 [PMID: 27147580 DOI: 10.18632/oncotarget.9076]

34 **Ma C**, Patel K, Singhi AD, Ren B, Zhu B, Shaikh F, Sun W. Programmed Death-Ligand 1 Expression Is Common in Gastric Cancer Associated With Epstein-Barr Virus or Microsatellite Instability. *Am J Surg Pathol* 2016; **40**: 1496-1506 [PMID: 27465786 DOI: 10.1097/PAS.0000000000000698]

35 **Sasaki S**, Nishikawa J, Sakai K, Iizasa H, Yoshiyama H, Yanagihara M, Shuto T, Shimokuri K, Kanda T, Suehiro Y, Yamasaki T, Sakaida I. EBV-associated gastric cancer evades T-cell immunity by PD-1/PD-L1 interactions. *Gastric Cancer* 2018 [PMID: 30264329 DOI: 10.1007/s10120-018-0880-4]

36 **McLaughlin J**, Han G, Schalper KA, Carvajal-Hausdorf D, Pelekanou V, Rehman J, Velcheti V, Herbst R, LoRusso P, Rimm DL. Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer. *JAMA Oncol* 2016; **2**: 46-54 [PMID: 26562159 DOI: 10.1001/jamaoncol.2015.3638]

37 **Herbst RS**, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387**: 1540-1550 [PMID: 26712084 DOI: 10.1016/S0140-6736(15)01281-7]

38 **Muro K**, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, Eder JP, Golan T, Le DT, Burtness B, McRee AJ, Lin CC, Pathiraja K, Lunceford J, Emancipator K, Juco J, Koshiji M, Bang YJ. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016; **17**: 717-726 [PMID: 27157491 DOI: 10.1016/S1470-2045(16)00175-3]

39 **Le DT**, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Bono P, Jaeger D, Evans TRJ, De Braud FG, Chau I, Christensen O, Harbison C, Lin CS, Janjigian YY. Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study. *J Clin Oncol* 2016; **34**: 6 [DOI: 10.1200/jco.2016.34.4\_suppl.6]

40 **Homet Moreno B**, Mok S, Comin-Anduix B, Hu-Lieskovan S, Ribas A. Combined treatment with dabrafenib and trametinib with immune-stimulating antibodies for BRAF mutant melanoma. *Oncoimmunology* 2015; **5**: e1052212 [PMID: 27622011 DOI: 10.1080/2162402X.2015.1052212]

41 **Sharma P**, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell* 2017; **168**: 707-723 [PMID: 28187290 DOI: 10.1016/j.cell.2017.01.017]

42 **Postow MA**, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. *J Clin Oncol* 2015; **33**: 1974-1982 [PMID: 25605845 DOI: 10.1200/JCO.2014.59.4358]

43 **Weber JS**, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, Zhao X, Martinez AJ, Wang W, Gibney G, Kroeger J, Eysmans C, Sarnaik AA, Chen YA. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol* 2013; **31**: 4311-4318 [PMID: 24145345 DOI: 10.1200/JCO.2013.51.4802]

44 **Fuchs CS**, Ohtsu A, Tabernero J, Van Cutsem E, Wang JD, Lam B, Koshiji M, Bang YJ. Pembrolizumab (MK-3475) plus 5-fluorouracil (5-FU) and cisplatin for first-line treatment of advanced gastric cancer: Preliminary safety data from KEYNOTE-059. *J Clin Oncol* 2016; **34**: 161 [DOI: 10.1200/jco.2016.34.4\_suppl.161]

45 **Ma J**, Li JH, Qian MR, Han WL, Tian MM, Li ZS, Wang Z, He SX, Wu KC. PD-L1 expression and the prognostic significance in gastric cancer: a retrospective comparison of three PD-L1 antibody clones (SP142, 28-8 and E1L3N). *Diagn Pathol* 2018; **13**: 91 [DOI: 10.1186/s13000-018-0766-0]

46 **Lu B**, Teng X, Fu G, Bao L, Tang J, Shi H, Lu W, Lu Y. Analysis of PD-L1 expression in trophoblastic tissues and tumors. *Hum Pathol* 2019; **84**: 202-212 [PMID: 30339966 DOI: 10.1016/j.humpath.2018.10.001]

47 **Qing Y**, Li Q, Ren T, Xia W, Peng Y, Liu GL, Luo H, Yang YX, Dai XY, Zhou SF, Wang D. Upregulation of PD-L1 and APE1 is associated with tumorigenesis and poor prognosis of gastric cancer. *Drug Des Devel Ther* 2015; **9**: 901-909 [PMID: 25733810 DOI: 10.2147/DDDT.S75152]

48 **Khong A**, Nelson DJ, Nowak AK, Lake RA, Robinson BW. The use of agonistic anti-CD40 therapy in treatments for cancer. *Int Rev Immunol* 2012; **31**: 246-266 [PMID: 22804570 DOI: 10.3109/08830185.2012.698338]

49 **Ooi CH**, Ivanova T, Wu J, Lee M, Tan IB, Tao J, Ward L, Koo JH, Gopalakrishnan V, Zhu Y, Cheng LL, Lee J, Rha SY, Chung HC, Ganesan K, So J, Soo KC, Lim D, Chan WH, Wong WK, Bowtell D, Yeoh KG, Grabsch H, Boussioutas A, Tan P. Oncogenic pathway combinations predict clinical prognosis in gastric cancer. *PLoS Genet* 2009; **5**: e1000676 [PMID: 19798449 DOI: 10.1371/journal.pgen.1000676]

50 **Liu W**, Chen Y, Xie H, Guo Y, Ren D, Li Y, Jing X, Li D, Wang X, Zhao M, Zhu T, Wang Z, Wei X, Gao F, Wang X, Liu S, Zhang Y, Yi F. TIPE1 suppresses invasion and migration through down-regulating Wnt/β-catenin pathway in gastric cancer. *J Cell Mol Med* 2018; **22**: 1103-1117 [PMID: 28994231 DOI: 10.1111/jcmm.13362]

51 **Song B**, Lin HX, Dong LL, Ma JJ, Jiang ZG. MicroRNA-338 inhibits proliferation, migration, and invasion of gastric cancer cells by the Wnt/β-catenin signaling pathway. *Eur Rev Med Pharmacol Sci* 2018; **22**: 1290-1296 [PMID: 29565486 DOI: 10.26355/eurrev\_201803\_14470]

52 **Cheng C**, Qin Y, Zhi Q, Wang J, Qin C. Knockdown of long non-coding RNA HOTAIR inhibits cisplatin resistance of gastric cancer cells through inhibiting the PI3K/Akt and Wnt/β-catenin signaling pathways by up-regulating miR-34a. *Int J Biol Macromol* 2018; **107**: 2620-2629 [PMID: 29080815 DOI: 10.1016/j.ijbiomac.2017.10.154]

53 **Grasso CS**, Giannakis M, Wells DK, Hamada T, Mu XJ, Quist M, Nowak JA, Nishihara R, Qian ZR, Inamura K, Morikawa T, Nosho K, Abril-Rodriguez G, Connolly C, Escuin-Ordinas H, Geybels MS, Grady WM, Hsu L, Hu-Lieskovan S, Huyghe JR, Kim YJ, Krystofinski P, Leiserson MDM, Montoya DJ, Nadel BB, Pellegrini M, Pritchard CC, Puig-Saus C, Quist EH, Raphael BJ, Salipante SJ, Shin DS, Shinbrot E, Shirts B, Shukla S, Stanford JL, Sun W, Tsoi J, Upfill-Brown A, Wheeler DA, Wu CJ, Yu M, Zaidi SH, Zaretsky JM, Gabriel SB, Lander ES, Garraway LA, Hudson TJ, Fuchs CS, Ribas A, Ogino S, Peters U. Genetic Mechanisms of Immune Evasion in Colorectal Cancer. *Cancer Discov* 2018; **8**: 730-749 [PMID: 29510987 DOI: 10.1158/2159-8290.CD-17-1327]

54 **Spranger S**, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. *Nature* 2015; **523**: 231-235 [PMID: 25970248 DOI: 10.1038/nature14404]

55 **Jiménez-Sánchez A**, Memon D, Pourpe S, Veeraraghavan H, Li Y, Vargas HA, Gill MB, Park KJ, Zivanovic O, Konner J, Ricca J, Zamarin D, Walther T, Aghajanian C, Wolchok JD, Sala E, Merghoub T, Snyder A, Miller ML. Heterogeneous Tumor-Immune Microenvironments among Differentially Growing Metastases in an Ovarian Cancer Patient. *Cell* 2017; **170**: 927-938.e20 [PMID: 28841418 DOI: 10.1016/j.cell.2017.07.025]

56 **Linch M**, Attard G. Prostate cancers that 'Wnt' respond to abiraterone. *Ann Oncol* 2018; **29**: 290-292 [PMID: 29240904 DOI: 10.1093/annonc/mdx785]

57 **Shan Y**, Ying R, Jia Z, Kong W, Wu Y, Zheng S, Jin H. LINC00052 Promotes Gastric Cancer Cell Proliferation and Metastasis via Activating the Wnt/β-Catenin Signaling Pathway. *Oncol Res* 2017; **25**: 1589-1599 [PMID: 28337962 DOI: 10.3727/096504017X14897896412027]

58 **Ahmed KA**, Stallworth DG, Kim Y, Johnstone PA, Harrison LB, Caudell JJ, Yu HH, Etame AB, Weber JS, Gibney GT. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. *Ann Oncol* 2016; **27**: 434-441 [PMID: 26712903 DOI: 10.1093/annonc/mdv622]

59 **Shabason JE**, Minn AJ. Radiation and Immune Checkpoint Blockade: From Bench to Clinic. *Semin Radiat Oncol* 2017; **27**: 289-298 [PMID: 28577836 DOI: 10.1016/j.semradonc.2017.03.002]

60 **Segal NH**, Kemeny NE, Cercek A, Reidy DL, Raasch PJ, Warren P, Hrabovsky AE, Campbell N, Shia J, Goodman KA, Erinjeri JP, Solomon SB, Yamada Y, Saltz L. Non-randomized phase II study to assess the efficacy of pembrolizumab (Pem) plus radiotherapy (RT) or ablation in mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) patients. *J Clin Oncol* 2016; **34**: 3539 [DOI: 10.1200/JCO.2016.34.15\_suppl.3539]

61 **Sahebjam S**, Johnstone PA, Forsyth PAJ, Arrington J, Vrionis FD, Etame AB, Tran ND, Dalvi PH, Kim S, Macaulay R, Chinnaiyan P, Yu M. Safety and antitumor activity of hypofractionated stereotactic irradiation (HFSRT) with pembrolizumab (Pembro) and bevacizumab (Bev) in patients (pts) with recurrent high grade gliomas: Preliminary results from phase I study. *J Clin Oncol* 2016; **34**: 2041 [DOI: 10.1200/JCO.2016.34.15\_suppl.2041]

**P-Reviewer:** Amiri M, Chetty R, Grotz TE, Matteucci C, Tabll AA **S-Editor:** Ji FF **L-Editor:** Wang TQ **E-Editor:**

**Specialty type:** Medicine, research and experimental

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0