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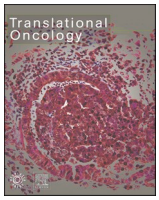

Anti-PD-1/PD-L1 therapy for colorectal cancer: Clinical implications and future considerations

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ABSTRACT

Colorectal cancer (CRC) is the third most prevalent cancer in the world. The PD-1/PD-L1 pathway plays a crucial role in modulating immune response to cancer, and PD-L1 expression has been observed in tumor and immune cells within the tumor microenvironment of CRC. Thus, immunotherapy drugs, specifically checkpoint inhibitors, have been developed to target the PD-1/PD-L1 signaling pathway, thereby inhibiting the interaction between PD-1 and PD-L1 and restoring T-cell function in cancer cells. However, the emergence of resistance mechanisms can reduce the efficacy of these treatments. To counter this, monoclonal antibodies (mAbs) have been used to improve the efficacy of CRC treatments. mAbs such as nivolumab and pembrolizumab are currently approved for CRC treatment. These antibodies impede immune checkpoint receptors, including PD-1/PD-L1, and their combination therapy shows promise in the treatment of advanced CRC. This review presents a concise overview of the use of the PD-1/PD-L1 blockade as a therapeutic strategy for CRC using monoclonal antibodies and combination therapies. Additionally, this article outlines the function of PD-1/PD-L1 as an immune response suppressor in the CRC microenvironment as well as the potential advantages of administering inflammatory agents for CRC treatment. Finally, this review analyzes the outcomes of clinical trials to examine the challenges of anti-PD-1/PD-L1 therapeutic resistance.

Introduction

Immunotherapy has gained considerable attention as a therapeutic approach for the treatment of cancer and other diseases. This method uses the patient's immune system to improve the chances of survival or slow disease progression [1–3]. The primary objective of cancer treatment is to shift the immune context from a state of tolerance to a state of reactivation or immunogenicity, to enhance the detection and accessibility of cancer antigens. Checkpoint mediators, specifically the programmed death-1 receptor (PD-1) and programmed death ligand 1 (PD-L1), play crucial roles in cancer immunotherapy. Immune checkpoint inhibitors (ICIs) stimulate the immune system to eliminate the cancer cells. Recent research has demonstrated that ICIs, including monoclonal antibodies (mAbs) and small-molecules, effectively target immune molecules to inhibit the activity of checkpoint mediators [4–6]. Consequently, there is an urgent need to develop new checkpoint molecules that enhance the visibility and accessibility of cancer antigens to improve cancer treatment.

PD-1 and PD-L1 are immune checkpoints that play vital roles in immune response regulation in humans. The PD-1 receptor is present on immune cells, including T- and B-cells, whereas PD-L1 is expressed on various types of tumor cells. Numerous studies have shown that inhibiting PD-L1/PD-1 activity can yield significant clinical efficacy in a wide range of tumors, including colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC) [7], gastric cancer, and other malignancies [8–11]. The US Food and Drug Administration (FDA) has approved several PD-1 and PD-L1 inhibitors, including pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq), and durvalumab (Imfinzi) for the treatment of various types of malignancies [12–14]. These inhibitors block the PD-1/PD-L1 pathway, thus enhancing the

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ability of the immune system to fight cancer cells. Monoclonal antibodies that target the PD-1/PD-L1 pathway have shown significant antitumor efficacy in various cancers. Therefore, inhibition of the PD-L1/PD-1 pathway could be advantageous for the successful treatment of tumors.

This review presents a succinct overview of the therapeutic application of PD-1/PD-L1 blockade in CRC using monoclonal antibodies and combination therapies. Additionally, this study examines the function of PD-1/PD-L1 as a suppressor of the immune response in the CRC microenvironment, as well as the potential advantages of administering inflammatory agents for CRC therapy. Finally, this study analyzes the outcomes of clinical trials to delve into the challenges of anti-PD-1/PD-L1 therapeutic resistance.

Mechanisms of PD-1/PD-L1 blockade

The utilization of PD-1/PD-L1 blockade as a form of immunotherapy has significantly transformed the therapeutic landscape for a multitude of cancer types [15,16]. PD-1 is a cell surface receptor that is prominently expressed on specific immune cells, such as T cells, B cells, and natural killer cells. Its primary function entails the regulation of immune responses and the prevention of unwarranted immune reactions. Conversely, PD-L1 is a protein that is expressed on the outer membrane of numerous normal cells, as well as certain cancer cells. Cancer cells have the ability to utilize the PD-1/PD-L1 pathway to evade immune surveillance [17]. Upon the interaction between PD-L1 on cancer cells and PD-1 on T cells, inhibitory signals are transmitted to the T cells, resulting in diminished T cell activity and compromised anti-tumor immune responses. This intricate interplay enables cancer cells to evade eradication by the immune system. Thus, the purpose of PD-1/PD-L1 blockade is to counteract the immune evasion mechanism employed by cancer cells.

The immune system must eliminate cancer cells because of their atypical genetic profiles and distinctive markers in order to safeguard the body. However, when immune responses are excessively suppressed or tolerance is heightened, cancer cells are often misidentified as self-cells. Under normal physiological conditions, antigen-presenting cells (APCs) present pathogen-derived antigens on their surfaces to T cells, which are subsequently distributed throughout an organism. In the immune response, the T-cell receptor (TCR) on CD4+ helper T cells and CD8+ cytotoxic T cells is initially activated upon binding to the antigen presented by the major histocompatibility complex (MHC) on the surface of APCs, as illustrated in Fig. 1. However, T-cell activation requires secondary signals from co-stimulatory receptors, as depicted in Fig. 1. The interaction between these receptors and their respective ligands on APCs facilitates the transmission of activated or tolerant signals to T cells.

Immune checkpoint molecules effectively regulate T-cell function by activating (co-stimulatory molecules) or inhibiting signals (co-inhibitory molecules). Co-stimulatory molecules can regulate multiple functions of T cells, including activation, proliferation, differentiation, and survival. T-cell co-stimulatory molecules, including CD27, CD28, inducible T cell co-stimulator (ICOS), CD40, CD30, OX40, and 4–1BB, provide essential co-stimulatory signals through interactions with accessory molecules CD80 or CD86 and ICOS ligand (ICOSL) on APC [18]. In addition, T cells possess co-inhibitory molecules, including cytotoxic T lymphocyte antigen 4 (CTLA-4), PD-1, TIM-3, and LAG-3 [19]. CTLA-4 functions as a central checkpoint in lymphoid organs by binding to B7-1/B7-2 on APCs, whereas PD-1 is a peripheral checkpoint that interacts with its ligands (PD-L1/L2, B7-H1/CD274, or B7-DC/CD273) on targets such as cancer cells [20,21]. Immune checkpoint molecules, including PD-1, CTLA4, TIM-3, and LAG-3 can be used to predict and treat various types of cancers, including breast cancer, ovarian cancer, and lung cancer [22]. PD-1 is expressed on the T cell surface during activation and induces T-cell exhaustion. Furthermore, PD-1 is expressed on various other immune cells, including B cells, lymphocytes, and natural killer cells (NKs) [23,24]. However, it primarily affects CD8+ T cells, which are crucial for tumor cell defense. Under normal physiological conditions, the primary function of PD-1 is to transmit suppressive signals to T-cells during an immunological response by inhibiting casein kinase 2 (CK2) activity. This inhibition prevents the phosphorylation of the regulatory domain of PTEN,

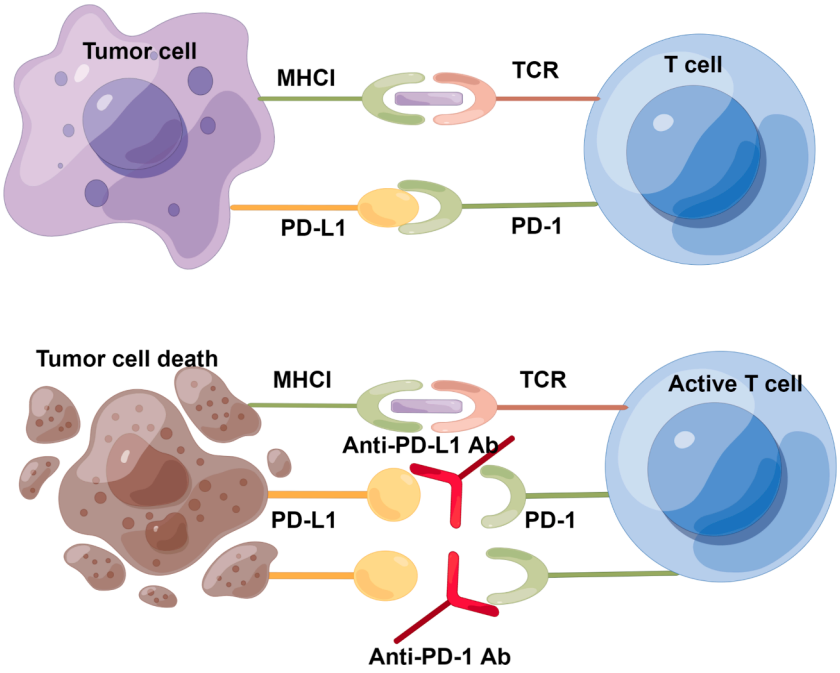

Fig. 1. Diagram depicting the anticancer mechanism of PD-1/PD-L1 inhibitors. Tumor cells escape from the anti-tumor activity of T cells by the binding of PD-L1 to the PD-1 receptor. PD-1 or PD-L1 antibodies block the binding of PD-L1 on tumor cells to PD-1 receptors on T cells, which allows T cells to induce the immune response against tumor cells. MHCI, Major histocompatibility complex I; TCR, T cell receptor; PD-L1, Programmed death-ligand 1; PD-1, Programmed death-receptor 1; Ab, antibody.

resulting in the cessation of phosphoinositide 3-kinase (PI3K) activity, inhibition of cyclin-dependent kinase (CDK), and regulation of T cell surface receptor expression levels.

Tumor necrosis factor alpha (TNF-α) and interleukin-17 (IL-17) promote the expression of PD-L1 in tumor and immune cells [25], leading to the suppression of tumor immunity [26]. Immunohistochemical studies have revealed that metastatic CRCs have a higher incidence of PD-L1 expression than primary tumors [27]. Nevertheless, the efficacy of anti-PD-1/PD-L1 therapy varies across malignancies and patients, and numerous mechanisms have been identified to impede tumor immunity during tumorigenesis [28–31]. Recently, it has been observed that ncRNAs, specifically lncRNAs, play a significant role in the regulation of the PD-1/PD-L1 pathway during carcinogenesis [32]. A notable example is the upregulation of lncRNA NEAT1 in tumor cells, which is associated with an increase in infiltrating macrophages and microglia, and subsequently leads to the enhanced expression of TNFα and other inflammatory cytokines [29]. Furthermore, recent studies have confirmed the significance of m6A modification in the regulation of the PD-1/PD-L1 axis, thereby influencing immune response and strategies for immunotherapy [28]. Notably, METTL3 has been found to enhance the expression of chemokines with pro-tumorigenic properties such as CXCL1, CXCL5, and CCL20, while also destabilizing PD-L1 mRNA in an m^6A-dependent manner [33]. However, it is worth mentioning that NSCLC patients with low expression of METTL3 have shown improved prognosis when undergoing anti-PD-1 therapy [33]. Beside these pathways, the interferon receptor pathways, PI3K/AKT, and HMGA1-dependent pathway have all been linked to constitutive PD-L1 expression in cancer (Fig. 2) [31,34]. Wei et al. [31] reported a significant upregulation of PD-L1 expression in CRC stem cells (CSCs), CSC-enriched tumor-spheres, and chemo-resistant CRC cells. The researchers also identified a direct interaction between the PD-L1 receptor and HMGA1. PD-L1 is upregulated by HMGA1, which in turn activates HMGA1-dependent pathways such as PI3K/AKT and MAPK/ERK/JNK [35,36]. These pathways promote the expansion of CSCs [31]. Additionally, chromosomal alterations have been found to upregulate PD-L1 expression. Genetic alterations in the 9p24.1 locus have been found to upregulate the expression of PD-L1 and PD-L2 in tumor cells [37,38]. The adaptive immunological resistance observed in various types of cancers is associated with the interaction between PD-1 and PD-L1, which affects the usage of metabolic substrates and ultimately results in T cell exhaustion. This mechanism enables tumor cells to evade the immune system and trigger apoptosis in activated T-cells. Consequently, PD-1/PD-L1 blockade effectively enhances immune cell-mediated anti-tumor activity [39].

PD-1/PD-L1 activity in the CRC microenvironment

Antibodies targeting co-inhibitory T-cell receptors, such as PD-1 (CD279), bind to their ligands PD-L1 (CD274 or B7-H1) and PD-L2 (CD273 or B7-DC) [40,41]. The PD-1/PD-L1 axis serves as an immune checkpoint that is frequently upregulated in various tumors and their microenvironments. The modulation of the immune response against cancer cells is critically dependent on PD-1/PD-L1 immune checkpoint proteins. In CRC, PD-L1 is frequently expressed by tumor and immune cells in the tumor microenvironment [42]. Inducing PD1/PD-L1 expression in CRC can lead to the inhibition of T-cell activity and impair the immune system's capacity to combat cancer.

PD1/PD-L1 expression in CRC can be induced by multiple factors, including small extracellular vesicles (sEV), inflammatory cytokines, and oncogenic pathways [8,42–44]. For instance, CRC-derived sEV can stimulate M2 macrophage polarization and increase PD-L1 expression via the PTEN/AKT and SCOS1/STAT1 pathways, thereby promoting CRC progression [42]. Furthermore, inhibiting CRC-generated sEV--miRNAs that specifically target PD-L1 in tumor-associated macrophages (TAMs) has been proposed as a novel strategy for the treatment of CRC and for improving the efficacy of anti-PD-L1 therapy in CRC [42]. Inflammatory signaling upregulates the expression of the PD-1/PD-L1 immune checkpoint [45]. In contrast, the IL-17 pathway, which includes IL-17A, IL-17C, and IL-17F, reduces the expression of PD-1/PD-L1 and CD8+ T cell infiltration in breast cancer [46].

Recent research has demonstrated that targeting the PD-1/PD-L1 pathway can improve outcomes in patients with advanced CRC, particularly tumors with microsatellite instability (MSI) or DNA mismatch repair deficiency (dMMR) [47,48]. Additionally, administration of aPD-L1NP-PTPN6 inhibited the proliferation, invasion, and migration of CRC cells by suppressing MAPK/ERK signaling in tumor-bearing mice. This resulted in prolonged survival compared to other treatment options [49]. Tumor counts in azoxymethane

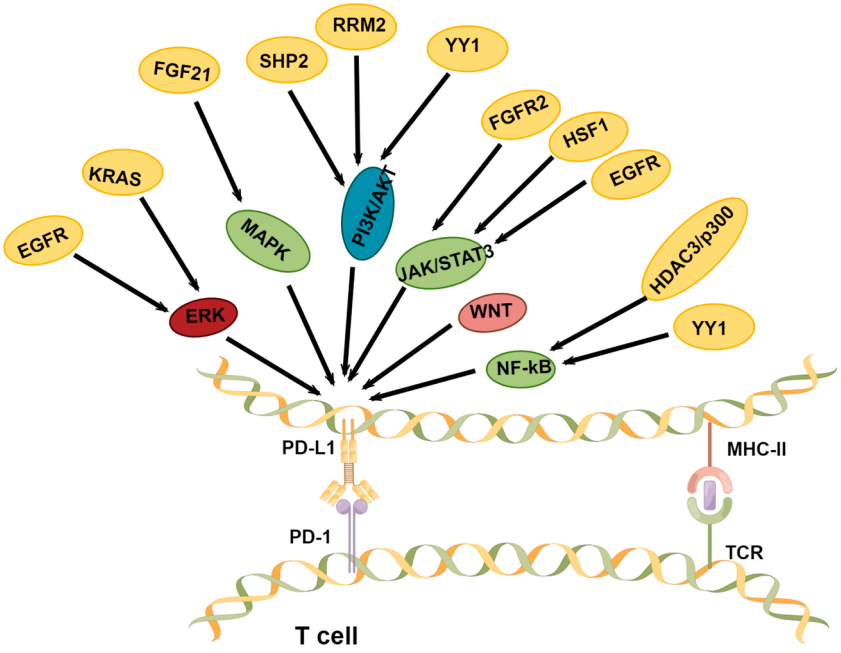

Fig. 2. Various pathways regulation of PD-1/PD-L1 expression. PI3K/AKT pathway, MAPK pathway, JAK/STAT pathway, WNT pathway, NF-κB pathway and ERK pathway promote the expression of PD-1/PD-L1 axis.

(AOM)/dextran sulfate sodium (DSS)-treated mice were specifically reduced by the administration of an anti-PD1 antibody, which inhibits PD-1 signaling [50]. These tumors exhibit a higher mutational burden and frequency of neoantigens, rendering them more susceptible to immune recognition. Therefore, PD-1/PD-L1 blockade stimulates T-cell activity and boosts the immune response against cancer cells.

Previous studies have shown that the PD-1/PD-L1 pathway is a crucial regulator of the immune response to cancer cells in the CRC microenvironment (Fig. 3) [51]. Targeting this pathway has shown promise as a therapeutic strategy for CRC, particularly in patients with MSI or dMMR tumors [49]. However, further investigation is necessary to fully comprehend the complex interactions in the tumor microenvironment and to optimize the implementation of the PD-1/PD-L1 blockade in CRC management.

Monoclonal antibodies in CRC treatment

PD-1/PD-L1

Various strategies have been employed to improve the overall survival of patients with CRC. These strategies involve combining traditional cytotoxic drugs and targeted therapies, such as cetuximab or panitumumab targeting the epidermal growth factor receptor (EGFR) [52,53], or bevacizumab targeting the vascular endothelial growth factor receptor (VEGFR) in mCRC [54].

Additionally, researchers have explored alternative therapies, including probiotics, anti-inflammatory agents, and gold-based drugs to mitigate the negative effects of combination therapies [55]. Owing to the limitations of currently available treatment modalities, novel therapeutic agents, such as immune checkpoint inhibitors, have been developed. Antibodies, recombinant ligands, and receptors can be used to target various immune response modulator pathways. Combination therapy is also a viable treatment approach.

Ipilimumab was the first checkpoint inhibitor approved by the FDA for the treatment of metastatic melanoma. This monoclonal antibody inhibits CTLA-4 receptor activity. Moreover, inhibition of PD-1 and other immune checkpoint proteins has revealed additional strategies to enhance immune responses against tumors. Specifically, anti-PD-1 therapy impedes the interaction between PD-L1-expressing tumor cells and PD-1-expressing T cells. One significant benefit of anti-PD-1 or anti-PD-L1 therapy is its potential to enhance the effectiveness of conventional cancer treatments while minimizing side effects [56]. Surprisingly, cutaneous toxicities have emerged as the most prevalent immune-related adverse event associated with anti-PD-1 blockade therapies [57,58].

Anti-PD-1 antibodies have been effective in treating various types of cancers, including melanoma, renal cell carcinoma, prostate cancer, non-small cell lung cancer (NSCLC), and CRC [59]. A phase I clinical trial (NCT00441337) was conducted to evaluate the safety, tolerability, efficacy, and pharmacokinetics of the monoclonal antibody nivolumab (BMS-936558; MDX-1106) in 39 patients with advanced solid tumors. Four dose cohorts of nivolumab (0.3, 1, 3, and 10 mg/kg) were administered to 14 patients diagnosed with mCRC. In a phase 3 trial (NCT03143153), Doki et al. (year) found that combining nivolumab with chemotherapy as a first-line treatment for 970 patients with advanced esophageal squamous cell carcinoma resulted in significantly prolonged overall survival compared to chemotherapy alone [60]. In a phase 3 clinical trial (NCT02632409), Bajorin et al. evaluated the effectiveness of nivolumab in the treatment of 353 patients with muscle-invasive urothelial carcinoma. The findings indicated that adjuvant nivolumab significantly improved survival rates in the intention-to-treat population compared to placebo [61]. Previous studies have suggested that elevated PD-L1 (B7-H1) levels in patients with cancer may be associated with unfavorable prognoses [62], This finding highlights the potential significance of PD-L1 as a predictive marker for cancer treatment. Nivolumab exhibited good tolerability, with no instances of anti-human antibody development observed even after repeated dosing [42]. Notably, a full response was reported in a patient with dMMR CRC and PD-L1 expression (B7-H1) in tumor cells, highlighting the potential of PD-L1 expression and dMMR genotype as predictive biomarkers for treatment response [63]. Based on these findings, the presence of PD-L1-expressing tumors may facilitate exploration of the efficacy of nivolumab in advanced cancers.

The efficacy of nivolumab in the treatment of patients with

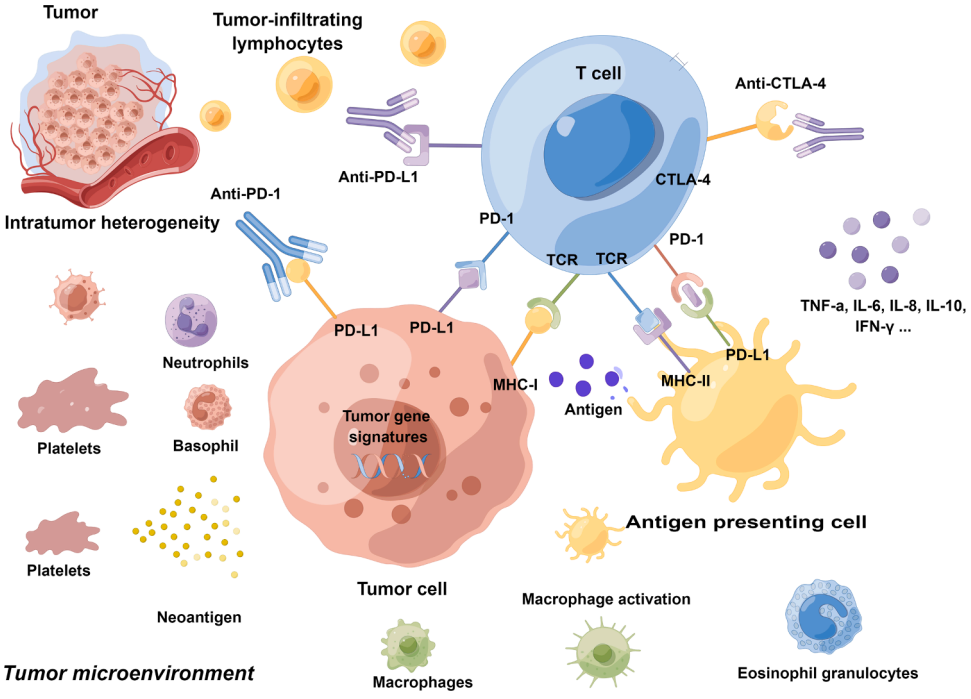

Fig. 3. Tumor microenvironment and biomarkers for immunotherapy. PD-1, programmed cell death protein 1; PD-L1, programmed deathligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; TCR, T cell receptor; MHC-I, Major histocompatibility complex class I; MHC-II, Major histocompatibility complex class II.

metastatic dMMR or MSI-H CRC was evaluated in a phase II open-label clinical trial (NCT02060188) conducted across 31 sites in eight countries. The study findings indicated that patients with dMMR/MSI-H metastatic CRC who received prior treatment experienced improved disease control and longer-lasting responses. Among the 74 patients included in this study, 51 achieved disease control for at least 12 weeks. Additionally, eight patients showed responses lasting 12 months or longer. The Kaplan-Meier estimate for the 12- month response rate was 86 % (95 % CI 62–95) [64]. Two parallel clinical trials were conducted to evaluate the efficacy and safety of nivolumab in patients with treatment-resistant anal squamous cell carcinoma and malignant solid tumors including CRC. The findings revealed that nivolumab was well tolerated up to 20 mg/kg and had no dose-limiting toxicities at lower doses. These results suggest that nivolumab is a promising therapeutic agent for patients with CRC. Furthermore, a phase II clinical trial (NCT02060188) was conducted to assess the efficacy of nivolumab and ipilimumab combination therapy in patients with metastatic, microsatellite instability-high (MSI-H) and non-MSI-H CRC [65]. First-line treatment with the combination for MSI-H/dMMR mCRC demonstrated good tolerance and significant clinical improvement [65]. Based on the findings of this study, the FDA has approved the use of nivolumab, either as a monotherapy or in combination with ipilimumab, for the treatment of patients with MSI-H/dMMR mCRC. A comparative analysis of the CheckMate 142 cohorts revealed that the combination of nivolumab and low-dose ipilimumab showed a more favorable benefit-risk profile than nivolumab alone for the treatment of second-line MSI-H/dMMR mCRC [66]. This study presents the first report of a novel dual immuno-oncology (I-O) combination treatment in this patient population, using nivolumab in combination with low-dose ipilimumab as first-line therapy for patients with MSI-H/dMMR mCRC [66].

A phase I clinical trial conducted on a cohort of 32 patients with advanced solid tumors, including colon and rectal adenocarcinoma, involved intravenous administration of pembrolizumab (MK-3475), a monoclonal antibody targeting PD-1 receptors, at doses of 1, 3, or 10 mg/kg to patients with a history of treatment for metastatic disease. The results of the trial demonstrated that pembrolizumab, administered at a dose range of 2–10 mg/kg every 2 weeks, was well tolerated and exhibited antitumor activity in various solid tumors [67].

Another study, designated as the multi-cohort phase III KEYNOTE-048 trial (NCT02358031), assessed the safety and overall response rate of pembrolizumab in a cohort of 882 patients with PD-L1 positive head and neck squamous cell carcinoma (HNSCC). Of these patients, 128 exhibited a PD-L1 combined positive score (CPS) of < 1, whereas 373 had a CPS ranging from 1 to 19. However, the sample size of the PD-L1 CPS 1 subgroup was inadequate for a formal analysis. In previous studies, both pembrolizumab monotherapy and combined chemotherapy regimens have shown efficacy in treating patients with PD-L1 CPS 1 tumors [68]. The findings suggest that pembrolizumab exhibits a positive safety profile and efficacy for the treatment of patients with recurrent HNSCC expressing PD-L1. Furthermore, a multi-cohort study comprising 20 patients with advanced colorectal carcinoma expressing PD-L1 demonstrated a favorable safety profile for pembrolizumab, with antitumor activity in a single patient with MSI-H CRC [69]. These findings further support the hypothesis that PD-L1 expression can predict the response to pembrolizumab.

Immunotherapy has recently been shown to be effective in the treatment of various solid tumors. Specifically, monoclonal antibodies targeting PD-L1, such as pembrolizumab, MPDL-3280 A or atezolizumab, MEDI-4736 or durvalumab, and MSB-0010718C or avelumab, have shown promise in achieving durable clinical responses in patients with a variety of tumor types, including CRC [70], hepatocellular carcinoma [71], non-small cell lung cancer [72], and gastrointestinal cancer [73]. Pembrolizumab, a humanized anti-PD-L1 monoclonal antibody, has been approved as a first- and second-line treatment for several types of cancers, including CRC, melanoma, lung cancer, and head and neck squamous cell carcinoma [74–77]. Durvalumab (anti-PD-L1) therapy significantly improved progression-free survival (PFS) and overall survival (OS) in a recent study of patients with unresectable stage III NSCLC who did not progress after concomitant chemoradiation [78,79]. Patients with relapsed thymoma showed antitumor activity following PD-L1 inhibition in a phase I dose-escalation trial of avelumab (anti-PD-L1, NCT01772004), despite a high frequency of immune-related adverse events [80]. Immunotherapy has shown promise in the management of several tumors; however, its impact on mCRC remains limited. Only a small proportion of patients with mCRC exhibiting MMR gene abnormalities responded well to immunotherapy. For instance, the monoclonal antibody atezolizumab, which targets PD-L1, has been shown to enhance progression-free survival in previously untreated patients with mCRC [81].

Increased immune cell infiltration during PD-1 targeting treatment has been linked to increased antitumor activity in tumors expressing PD-L1 and MSI. However, anti-PD-L1 therapy has demonstrated greater efficacy in combination therapies for CRC, possibly because of variations in PD-1 and PD-L1 expression within the tumor microenvironment. PD-L1 is frequently expressed in tumor cells and tumor-infiltrating immune cells in certain types of cancer, such as melanoma and breast cancer. In contrast, in other tumors such as CRC and gastric carcinoma, PD-L1 expression is limited to tumor-infiltrating immune cells rather than tumor cells [8]. These observations have significant implications for the development of immune-targeted therapies for CRC treatment.

PD-1/PD-L2

PD-L2 binds to the PD-1 receptor on T cells, resulting in T cell exhaustion and immune evasion. Clinical trials involving patients with CRC have linked PD-L2 expression with poor prognosis and chemotherapy resistance. Despite the lack of approved PD-L2-specific targeted therapies for CRC, several ongoing clinical trials are currently investigating the safety and efficacy of these treatments. A phase I trial was conducted to evaluate the efficacy of the anti-PD-L2 antibody, BMS-986156, in combination with the anti-PD-1 antibody nivolumab, in patients with advanced solid tumors, including CRC [66]. Furthermore, a phase I/II study is currently investigating the combination of the PD-L2 inhibitor CA-170 and the anti-PD-1 antibody pembrolizumab for patients with advanced solid tumors, including CRC [82]. Collectively, these trials provide evidence that PD-L2 may serve as a promising therapeutic target.

Currently, a multitude of clinical trials are being conducted to evaluate the efficacy of PD-1/PD-L1 inhibitors in the context of CRC. These trials are also exploring the potential synergistic effects of combining PD-1/PD-L1 inhibitors with other targeted therapies or chemotherapy. It is anticipated that the results of these trials will provide further elucidation regarding the potential benefits of PD-L2-targeted therapies for the treatment of CRC.

Combination of PD-1 inhibitors and mAbs for cancer therapy

The concomitant use of PD-1 inhibitors and mAbs holds promise as a potential strategy for cancer immunotherapy. PD-1 inhibitors, classified as immunotherapy drugs, function by blocking the PD-1 receptor on T cells, thereby impairing their ability to attack cancer cells. In contrast, mAbs are synthetic molecules designed to selectively bind to specific targets on cancer cells, such as receptors or proteins, thereby stimulating an immune response against cancer.

The combined administration of PD-1 inhibitors and monoclonal antibodies (mAbs) can have a synergistic effect on the immune response against cancer. Certain mAbs can enhance the recruitment of immune cells to the tumor site, whereas PD-1 inhibitors can impede the ability of cancer cells to suppress the immune response. A notable example of an effective combination therapy is the use of pembrolizumab, a PD-1 inhibitor, in conjunction with ipilimumab, a monoclonal antibody, for the

treatment of advanced melanoma [83]. The considered therapeutic approach has shown superior effectiveness compared to monotherapy with either agent, resulting in improved outcomes. PD-1 inhibitors, when combined with anti-CD40 or anti-CD137, have shown significant synergistic effects in various cancer models, such as cholangiocarcinoma, breast cancer, and colon cancer [84,85]. Furthermore, tumor antigen-releasing treatments, such as radiotherapy and chemotherapy, have been shown to increase responsiveness to anti-PD-1 therapies [86–88].

Ongoing research is exploring additional combinations of PD-1 inhibitors and mAbs for the treatment of various cancers, including lung cancer, bladder cancer, and lymphoma. However, it is imperative to acknowledge that adverse effects may arise with any cancer therapy, and a comprehensive assessment of the advantages and disadvantages of combination therapy must be conducted on a case-by-case basis for each patient.

Administration of inflammatory agents for CRC therapy

IL-15 is considered a promising immunotherapeutic agent because of its ability to stimulate the activation, proliferation, cytotoxicity, and survival of CD8+ T and NK cells [89]. The IL-15 super-agonist mutant, N-803, has demonstrated efficacy in inducing antitumor immune responses against various tumors, including HCC and CRC [90–92]. To evaluate the impact of IL-15 on immune responses, a metastatic murine CT26 colon carcinoma model was treated with a combination of anti-PD-L1, anti-CTLA4, and IL-15. The combination resulted in a notable increase in the cytotoxicity of cytotoxic T lymphocytes and IFNγ secretion, a reduction in PD-1 surface expression on CD8+*T* cells and IL-10 secretion, and prolonged survival of murine metastatic colon tumors [93]. Furthermore, the administration of CD80-Fc to PD-L1+ CT26 colon carcinoma *in vivo* has been shown to impede tumor progression and enhance tumor-infiltrating T cells [94].

Irradiated t-haNK cells expressing PD-L1 effectively suppressed the growth of engrafted tumors in NSG mice with triple-negative breast, lung, and bladder cancers [95]. Co-administration of PD-L1 t-haNK cells with N-803 and anti-PD-1 antibodies effectively suppressed tumor growth in C57BL/6 mice with engrafted oral cavity squamous carcinoma tumors [95]. These findings suggest that IL-15 has potential as an immunotherapeutic agent that can effectively synergize with anti-PD-1 to enhance suppression of tumor immune activity.

IL-17a, a unique cytokine, is exclusively produced by specific immune cells, such as T helper 17 (Th17) cells. It plays a critical role in the inflammation and immune responses against certain pathogens, particularly fungi. IL-17a has been correlated with an unfavorable prognosis in patients with cancer, specifically CRC [8]. L-17a may regulate PD-1 expression in T cells by enhancing PD-L1 expression via the p65/NRF1/miR-15b-5p axis. This mechanism promotes resistance to anti-PD-1 therapy in patients with MSS CRC [8,96]. Concurrent inhibition of IL-17a and PD-1 has been shown to be effective in CT26 and MC38 tumors, characterized by increased cytotoxic T lymphocytes and reduced myeloid-derived suppressor cells [8,96]. Additionally, concomitant administration of an IL-17a monoclonal antibody and PD-1 blockade delayed the progression of 4-nitroquinoline-1-oxide (4NQO)-induced precancerous and cancerous lesions and increased the survival rate in a mouse model of oral carcinogenesis [97]. Nagaoka et al. [98] conducted a preclinical investigation to evaluate the efficacy of personalized immunotherapy using a combination of anti-IL-17 and anti-PD-1 mAbs in eliminating YTN16 gastric cancers. The results of this study suggest that IL-17a could serve as a potential therapeutic target for enhancing the efficacy of cancer treatment in humans.

Clinical trials and challenges

Despite the existence of various therapeutic protocols, CRC continues to be a significant contributor to neoplastic mortality [99,100]. Consequently, multiple trials have been initiated to incorporate the latest category of checkpoint immune inhibitors, which specifically target PD-1/PDL-1 complexes, into the therapeutic regimen for patients with FIGO stage III or IV or relapsed CRC. Immune checkpoint inhibition has shown significant potential for the treatment of cancer, surpassing traditional therapies for CRC. The FDA has approved several monoclonal antibodies that specifically target PD-1/PD-L1 for the treatment of various cancers (Table 1). However, not all patients experience favorable outcomes with these agents (Table 2). Preclinical and clinical trial data suggest that only 20–50 % of patients receive benefits from anti-PD-1/PD-L1 therapy in diverse cancer types. Resistance to anti-PD-1/PD-L1 immunotherapy is a crucial factor in the poor prognosis and treatment failure of CRC patients undergoing anti-PD-1/PD-L1 therapy [101]. Additionally, our understanding of the impact of exceeding the PD-L1-positive level, antigen load or mutational load within the tumor, and genetic factors affecting the efficacy and resistance of anti-PD-1/PD-L1 therapy remains limited.

PD-1/PD-L1 blockade has been extensively studied in clinical trials, and its effectiveness has been demonstrated in various cancer types. The effectiveness of PD-1/PD-L1 inhibitors was assessed through a meta-analysis encompassing 91 clinical trials, spanning phases I to III, across various cancer types [102]. This comprehensive analysis demonstrated that the combination of PD-1/PD-L1 inhibitors with chemotherapy yielded a significantly higher objective response rate compared to immunotherapy alone [102]. Furthermore, the utilization of the aforementioned combination resulted in a significant reduction in the length of response [102]. For instance, in specific scenarios, pembrolizumab may be administered to patients with MSI-H, dMMR, solid tumors, and limited alternative treatment options, which aimed to assess the effectiveness of PD-1 blockade in solid tumors [103], revealing the sensitivity of MSI-H and dMMR tumors to immune checkpoint blockade. The application of PD-1/PD-L1 blockade in immunotherapy broadens the scope of clinical effectiveness beyond immunogenic tumor classifications, such as melanoma and renal-cell cancer, to encompass treatment-resistant, metastatic non-small-cell lung cancer. Additionally, PD-1/PD-L1 blockade has the potential to facilitate the establishment of immunological memory. Following treatment, T cells that have effectively identified and eradicated cancer cells can endure within the organism, offering enduring safeguard against tumor relapse. Nevertheless, it is imperative to acknowledge that there persist challenges and areas of continuous research in this field. Presented herein are several pivotal aspects pertaining to clinical trials and the obstacles associated with PD-1/PD-L1 blockade.

Several clinical trials have assessed the safety and effectiveness of PD-1/PD-L1 blockade as a standalone treatment or in conjunction with other therapies in various cancer types, including colorectal cancer, melanoma, lung cancer, bladder cancer, and Hodgkin lymphoma [1,7,104–106]. The combination of PD-1/PD-L1 blockade with chemotherapy, targeted therapy, or other immunotherapies aims to augment the efficacy of PD-1/PD-L1 blockade by targeting diverse mechanisms of tumor immune evasion or through synergistic effects. Certain combinations have demonstrated enhanced response rates; however, the identification of optimal combinations and treatment sequences remains an ongoing exploration. These clinical trials have yielded promising outcomes, culminating in the regulatory approval of multiple PD-1/PD-L1 inhibitors for the therapeutic management of diverse malignancies. Nevertheless, the response rates exhibit variability across distinct tumor types, and not all patients exhibit a favorable response to treatment. Ongoing research endeavors strive to comprehend the underlying factors that influence response rates and ascertain predictive biomarkers. Moreover, recent research has demonstrated that PD-L1 expression has the potential to function as biomarkers on tumor cells, with the evaluation of tumor mutational burden and immune cell infiltration being conducted to forecast the response to PD-1/PD-L1 blockade [107–109]. Despite the widespread utilization of PD-L1 expression as a biomarker, its association with treatment response is

Table 1
FDA approved immune checkpoint inhibitors that target PD-1/PD-L1 or CTLA-4 for the treatment of multiple cancers.

Organ	Cancer	The anti-PD-1/PD-L1 drug type	Patients	Phase trial	Schedule	Clinical trial
Skin	MM	Belapectin plus pembrolizumab [121]	6	First	Every 3 wk	NCT02575404
		Pembrolizumab [122]	46	First	Every 2 or 3 wk	NCT01295827
		Tebentafusp [123]	127	Second	Every 8 or 12wk	NCT02570308
	CSCC	Pembrolizumab [124]	27	Second	Every 21 days	NCT02721732
		Cemiplimab [125]	26	First	Every 3 wk	NCT02760498, NCT02383212
	BCC	Cemiplimab [126]	84	Second	Every 3 wk	NCT03132636
	MCC	Ipilimumab plus nivolumab [127]	14	First		
Lung	NSCLC	Pembrolizumab [128]	559	Third	Every 3 or 6 wk	NCT02775435
		Nivolumab [129]	350	Third	Every 3 wk	NCT02998528
		Cemiplimab [130]	710	First	Every 3 wk	NCT03088540
		Atezolizumab [130,131]	2503, and 307	Third, and second	Every 2–4 or 12wk.	NCT02367781, NCT02657434, NCT03836066.
		Ipilimumab and Nivolumab [132]	227	Third	Every 2 or 6 wk	NCT02477826
		Durvalumab plus tremelimumab [133]	58	Second	Once every 28 days	NCT03373760
	SCLC	Atezolizumab [134]	403	Third	Every 6 or 9 wk	NCT02763579
Liver	HCC	Atezolizumab plus Bevacizumab [135,136]	336	Third	Every 3 wk	NCT03434379, NCT03434379.
		Cabozantinib plus atezolizumab [137]	837	Third	Every 3 wk	NCT03755791
		Atezolizumab and/ or bevacizumab [138]	104	First	Every 3 wk	NCT02715531
Gastrointestinal	mCRC	Atezolizumab and/ or cobimetinib [139]	273	Third	Every 2 wk	NCT02788279
		Capecitabine and Bevacizumab and/ or Atezolizumab [140]	133	Second	Every twice daily	NCT02873195
		FOLFOXIRI and bevacizumab alone or plus atezolizumab [141]	201	Second	Every 8 wk	NCT03721653
		Atezolizumab and cobimetinib [142]	152	First	Every once daily	NCT01988896
		Vemurafenib plus cetuximab plus 5-FU/LV [143]	60	First	Every 2 wk	NCT02291289
Liver	HCC	Lenvatinib Plus Pembrolizumab [144]	104	First	Every 6 or 9 wk	NCT03006926
		Pembrolizumab [145,146]	169, 413	Second, Third	Every 3 wk	NCT02702414, NCT02702401
Breast	BC	Pembrolizumab [147]	784	Third	Every 3 wk	NCT03036488
		Camrelizumab [148,149]	46, 40	Second	Every 6 or 12 wk, Every 2 wk	NCT04303741, NCT03394287
Head and neck	HNSCC	Pembrolizumab plus cetuximab [150]	33	Second	Every 3 wk	NCT03082534
		Belapectin plus pembrolizumab [121]	6	First	Every 3 wk	NCT02575404
Urological	RCC	Avelumab plus axitinib [151]	866	Third	Every 2 wk	NCT02684006
		NKTR-214 plus Nivolumab [152]	38	First	Every 3 wk	NCT02983045
		Nivolumab plus ipilimumab [153]	46	Second	Every 4 wk	NCT02996110
		Cabozantinib versus everolimus [154]	267	Third	Every 2–12 wk	NCT01835158
	mUC	Ramucirumab and pembrolizumab [155]	24	First	Every 3 wk	NCT02443324
		Pembrolizumab [156,157]	542 and 1010	Third	Every 3 wk	NCT02256436, NCT02853305
		Nivolumab [61]	353	Third	Every 2 wk	NCT02632409
		Atezolizumab [158]	809	Third	Every 3 wk	NCT02450331
		Avelumab [159]	700	Third	Every 2 wk	NCT02603432
Gynecological	CC	Socazolimab [160]	104	First	Every 2 wk	NCT03676959
		Pembrolizumab [161,162]	617, 18	Third, Second	Every 3 wk	NCT03635567, NCT03192059
	EC	Pembrolizumab [162]	25	Second	Every 3 wk	NCT03192059
Lymphoma	CHL	Pembrolizumab [163]	151	Third	Every 3 wk	NCT02684292
		Brentuximab vedotin plus nivolumab [164]	59	Second	Every 3 wk	NCT03057795
	PMBL	Brentuximab vedotin plus nivolumab [165]	30	Second	Every 3 wk	NCT02581631
		Pembrolizumab [166]	21, 53	First, Second	–	NCT01953692, NCT02576990

Abbreviation:5-FU/LV, 5-fluorouracil/leucovorin; BC, breast cancer; BCC, basal cell carcinoma; CC, Cervical cancer; CHL, classical Hodgkin lymphoma; CSCC, cutaneous squamous cell carcinoma; EC, Endometrial cancer; HCC, Hepatocellular Carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; mCRC, metastatic colorectal cancer; MM, metastatic melanoma; mUC, metastatic urothelial carcinoma; NSCLC, Non-small cell lung cancer; PMBL,Primary mediastinal B-cell lymphoma; RCC, renal cell cancer; SCLC, Small-Cell Lung Cancer.

not unequivocal. Furthermore, there exists a necessity to identify alternative dependable biomarkers in order to enhance the selection of patients who are more likely to derive therapeutic benefits.

Recent research has demonstrated that the inhibition of PD-1/PD-L1 signaling pathway can lead to immune-related adverse events (irAEs) [110,111], wherein the immune system mistakenly targets healthy tissues. These adverse events can manifest in different organs and systems, exhibiting a spectrum of severity. Timely identification and effective management of irAEs are imperative to ensure patient well-being. Additionally, PD-1/PD-L1 blockade may induce therapy resistance while also eliciting notable responses in select individuals [105,112]. Moreover, tumor cells have the ability to acquire strategies to elude immune surveillance [113], such as modifying antigen presentation or enhancing alternative immune checkpoints [114]. Nevertheless, the utilization of PD-1/PD-L1 inhibitors and other immunotherapies can be financially burdensome, posing a challenge in certain healthcare systems. Endeavors are currently underway to enhance affordability and accessibility, aiming to provide fair and equal treatment for all patients.

Numerous studies have indicated that elevated PD-1/PD-L1 expression is indicative of a favorable prognosis. However, it is important to acknowledge that tumors can acquire resistance to drugs by adaptively increasing PD-L1 expression during therapy. The correlation between

Table 2
demonstrates that patients exhibit potential outcomes when treated with anti-PD-1/PD-L1 agents.

Cancer types	PD-1/PD-L1 dosages	Side effects	Outcome	Clinical trial
CRC, and ovarian, pancreatic and breast cancers	BMS-936,559: 03–10 mg/kg, every 14 days for 6 weeks	Grade 3 or 4 toxic effects in 9 % of patients.	ORR: 1/17 ovarian cancer	NCT00729664 [40]
Melanoma	Pembrolizumab (200 mg) plus ipilimumab 1 mg/kg once every 3 weeks for four doses, followed by pembrolizumab monotherapy.	Grade 3–4 drug-related adverse events occurred in 27 % of patients.	The median progression-free survival: 5.0 months; The median overall survival: 24.7 months. The median duration of response: 16.6 months.	NCT02743819 [104]
NSCLC	Tremelimumab (75 mg) plus durvalumab 1500 mg once every 28 days for four cycles then durvalumab alone every 28 days.	Grade ≥3 adverse events occurred in 34 % of patients.	Durvalumab plus tremelimumab had minimal activity in NSCLC patients progressing on prior anti-PD-1 therapy	NCT03373760 [133]
NSCLC without EGFR, ALK or ROS1 genomic tumor aberrations	Cemiplimab 350 mg ($n = 312$) or placebo ($n = 154$) every 3 weeks for up to 108 weeks in combination with four cycles of platinum-doublet chemotherapy	Grade ≥3 adverse events occurred with cemiplimab plus chemotherapy (43.6 % patients) and placebo plus chemotherapy (31.4 % patients).	Cemiplimab show efficacy in aNSCLC as both monotherapy and in combination with chemotherapy for both squamous and non-squamous histologies.	NCT03409614 [167]
Stage IIB or IIC melanoma	Pembrolizumab (2 mg/kg in paediatric patients) or placebo every 3 weeks for 17 cycles.	Grade 3–4 treatment-related adverse events occurred in 16 % of patients in the pembrolizumab groups versus 4 % of in the placebo group.	Pembrolizumab versus placebo as adjuvant therapy reduced the risk of disease recurrence or death with a manageable safety profile.	NCT03553836 [168]
Advanced melanoma	PD-1 inhibitors nivolumab or pembrolizumab in 20 untreated patients with advanced melanoma.	Five patients (25 %) experienced grade 3 immune-related adverse events from combination therapy.	FMT is safe in the first-line setting and warrants further investigation in combination with immune checkpoint inhibitors.	NCT03772899 [169]
Recurrent or metastatic cervical cancer	Socazolimab (5 mg/kg) every 2 weeks	–	Socazolimab has durable safety and efficacy for the treatment of recurrent or metastatic cervical cancer.	NCT03676959 [160]
Metastatic castration-resistant prostate cancer and NSCLC	Isatuximab +cemiplimab in patients with mCRPC or NSCLC	All patients experienced ≥1 treatment-emergent adverse event. Grade≥3 events occurred in 54.2 % patients with mCRPC and 60.0 % patients with NSCLC.	CD38 and PD-1 modulation by Isa+Cemi has a manageable safety profile, reduces CD38+ immune cells in the TME, and activates peripheral T cells.	NCT03367819 [170]
Advanced NSCLC	Patients received pembrolizumab (200 mg every 3 weeks) plus next-line chemotherapy.	The treatment-related adverse events were fatigue (60 %), anemia (54.3 %), and nausea (42.9 %).	Pembrolizumab plus next-line chemotherapy was associated with statistically significant higher PFS in comparison with historical controls of single-agent chemotherapy alone.	BTCRC-LUN15–029 [171]
PDAC	Nivolumab and/or sotigalimab with gemcitabine/nab-paclitaxel (chemotherapy) in PDAC patients	Two patients died due to an adverse event: acute hepatic failure on sotiga/chemo	Potential treatment-specific correlates of efficacy and may enable biomarker-selected patient populations in subsequent PDAC chemoimmunotherapy trials.	NCT03214250 [172]
Metastatic pMMR CRC	Patients received regorafenib combined with nivolumab.	Grade 3/4 treatment-related adverse events were hypertension (16 %), rash (10 %) and anaemia (6 %)	Regorafenib plus nivolumab can be well tolerated with limited anticancer activity in metastatic pMMR CRC.	NCT03712943 [173]
	Patients received pembrolizumab and maraviroc (core period, 8 cycles), followed by pembrolizumab monotherapy.	The feasibility rate was 94.7 %, with one grade 4 hyperglycemia and no additional ≥ grade 3 treatment-related toxicities.	Therapy with pembrolizumab and maraviroc was feasible and showed a beneficial toxicity pattern.	NCT03274804 [77]
Naïve melanoma, RCC), microsatellite stable, CRC, and ovarian cancer.	Patients received the combination of ziv-aflibercept (at 2–4 mg/kg) plus pembrolizumab (at 2 mg/kg) administered intravenously every 2 weeks with expansion cohorts	Grade ≥3 adverse events occurred in 19/33 patients (58 %), the most common being hypertension (36 %) and proteinuria (18 %).	he combination of ziv-aflibercept and pembrolizumab demonstrated an acceptable safety profile with antitumor activity in solid tumors.	NCT02298959 [174]
Advanced rectal cancer	Patients received neoadjuvant sintilimab monotherapy (200 mg by intravenous infusion) every 21 days.	Only one (6 %) patient had a grade 3, 4 adverse event.	Anti-PD-1 monotherapy is effective and tolerable for patients and could potentially spare some patients from radical surgery.	NCT04304209 [175]

Abbreviation: GPs, ginseng polysaccharides; PDAC, pancreatic ductal adenocarcinoma; MTD, maximum tolerated dose; FMT, Fecal microbiota transplantation.

PD-L1 levels and therapeutic efficacy is not proportional, necessitating the development of optimal treatment strategies [115]. In light of these considerations, we assert that the detection of PD-L1 expression plays a crucial role in PD-1 blockade therapy. Firstly, it is imperative to assess PD-L1 expression to determine the suitability of PD-1 blockade therapy for tumor. Additionally, monitoring dynamic changes in PD-L1 expression throughout treatment should be required to detect. Furthermore, the resistance to PD-1 blockade is cause by the exosome secretion of PD-L1. This resistance is not only attributed to the upregulation of PD-L1 expression but also to the direct interaction between PD-L1 exosomes and anti-PD-L1 antibodies. PD-L1 exosomes derived from tumor and immune cells have the ability to impede tumor advancement by facilitating antigen presentation and modulating immune response. Nevertheless, the current research primarily concentrates on the influence of exosomes on tumor progression, thus necessitating a more comprehensive investigation of exosomes [116]. In order to facilitate precision medicine and effectively monitor changes in PD-L1 expression, there is a pressing need for improved detection methods [117]. Furthermore, it is crucial to continuously monitor the dynamic expression of PD-L1 on the cell membrane and exosomes. Additionally, recent findings have revealed that certain molecular targets employed in cancer treatment have an impact on the effectiveness of immunotherapy, thereby contributing to the emergence of resistance to PD-1/PD-L1 blockade therapy. Numerous inflammatory factors, such as TNF-a, IFN-γ, IL-6, IL-17, and EGF, exert a significant influence on the PD-1/PD-L1 pathway, aligning with the notion that inflammation fosters tumorigenesis rather than metastasis. These inflammatory factors possess the capability to impact tumor immune evasion, thereby presenting novel targets for synergistic immunotherapy [118]. Neoantigen vaccines, a prominent area of research in immunotherapy, have been

employed to identify and select highly exogenous neoantigens by sequencing the complete exons of tumor cells, thereby stimulating immune responses [119]. These neoantigens have also been combined with PD-1/ PD-L1 blockade therapy with good effects [120].

To summarize, the utilization of PD-1/PD-L1 blockade has revolutionized the field of cancer treatment, prompting ongoing investigations to enhance its efficacy, ascertain prognostic biomarkers, drug resistance, and investigate combination strategies. It is imperative to address the obstacles associated with biomarkers, immune-related adverse events, and therapy accessibility to fully capitalize on the advantages offered by PD-1/PD-L1 blockade in cancer patients.

Conclusions

Immunotherapeutic agents targeting various immune checkpoints offer improved therapeutic options with limited toxicity to normal tissues. Previous studies have demonstrated that combining multiple therapies and concurrently inhibiting immune checkpoints can result in therapeutic synergy and development of long-lasting antitumor immunity. These combined therapies have the potential to improve the clinical outcomes of patients with cancer. Moreover, favorable patient outcomes can be achieved through immune checkpoint inhibition, which involves the use of targeted antibodies that bind to the inhibitory immune receptors. Overall, these therapeutic modalities have the potential to elicit a more effective response compared to traditional treatment approaches.

Based on the CRC classification, diverse responses to immunotherapeutic interventions and distinct prognoses are expected. Notably, subtypes CMS1 and CMS4 are characterized by increased infiltration of CD8+ and CD68+ macrophages, rendering them susceptible to PD-1 immune checkpoint blockade. Furthermore, CMS1 tumors exhibit T-lymphocyte interactions and express PD-1 on their cell surfaces, thereby enhancing the efficacy of monoclonal antibody-based therapies targeting PD-1 and PD-L1. A combination of chemotherapy and immunotherapy has the potential to be highly effective. Non-targeted immunotherapies that do not account for the specific mechanisms by which tumors activate the immune system are unlikely to be effective for certain CRC subtypes, such as CMS2. Failure to consider the immunological characteristics of specific subtypes of CRC may result in significant delays and reduced survival rates, even with the use of monoclonal antibody-based therapies, which can be costly.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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