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REVIEW

Immune Checkpoint Blockade in Cancer Immunotherapy: Mechanisms, Clinical Outcomes, and Safety Profiles of PD-1/PD-L1 Inhibitors

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Abstract

Programmed cell death protein 1 (PD-1) and its ligand PD-L1 are critical for the regulation of T cell exhaustion and activity suppression. Tumor cells expressing immune checkpoints including PD-L1 escape monitoring of T cells from the host immune system. Checkpoint inhibitors are highly promising therapies that function as tumor-suppressing factors via modulation of tumor cell–immune cell interactions as well as boosting T cell-mediated anti-tumor immunity. Notably, PD-1 or PD-L1 monoclonal antibody (mAb) has demonstrated promising therapeutic effects in clinical studies of many types of cancer. These mAbs have caused significant tumor regression with impressive anti-tumor response rates as well as a favorable safety profile in cancer patients. Furthermore, the combination of PD-1/PD-L1 mAbs with other types of anti-tumor agents has also developed to boost the anti-tumor responses and enhance therapeutic effects in cancer patients. This review clarifies the mechanisms of PD-1/PD-L1-mediated anti-cancer immune responses and some clinical studies of mAbs targeting PD-1/PD-L1. The challenges and future of PD-1/PD-L1 blockade therapy are also discussed.

Keywords Immune checkpoints · PD-1 · PD-L1 · Monoclonal antibody · Immunotherapy

Abbreviations

PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
mAbs	Monoclonal antibodies
Tregs	Regulatory T cells
APCs	Antigen-presenting cells
CTLA-4	Cytotoxic T-lymphocyte protein 4
NSCLC	Non-small cell lung cancer
IFN-γ	Interferon-γ
TNF-α	Tumor necrosis factor-α
IL-2	Interleukin-2
DC	Dendritic cells
NK	Natural killer
SHP-2	Src homology 2
PI3K	Phosphatidylinositol 3-kinase
MHC	Major histocompatibility complex
CRC	Colorectal cancer
CRPC	Castrate-resistant prostate cancer
RCC	Renal cell cancer
ORR	Objective response rate
BRAF	Proto-oncogene B-Raf

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Introduction

In tumor microenvironments, tumors exploit a wide range of immune escape mechanisms to escape immune destruction, including induction of an immunosuppressive microenvironment and suppression of cytotoxic T-lymphocyte effector functions (Gajewski et al. 2013). Immunotherapy strategies are designed to activate anti-tumor responses and reverse tumor immune suppression (Zarour 2016). One of

the most effective strategies is activating T cell-mediated anti-tumor responses, which is based on the regulation of the balance between co-stimulatory and co-inhibitory signals (Krogsgaard and Davis 2005). These signals are also called immune checkpoints, which are important for regulating self-tolerance, preventing autoimmunity, and protecting the host from tissue damage (Mellman et al. 2011; Sharma and Allison 2015; Topalian et al. 2015). The immune checkpoints include the receptors expressed by effector T cells and the regulatory T cells (Tregs) as well as their respective ligands expressed by antigen-presenting cells (APCs) and/or tumor cells, thereby assisting the invasion of the anti-tumor immune response. Immune checkpoints regulate immune cell activities and proliferation, thereby maintaining tolerance to self-antigens and ensuring the immune responses avoid chronic inflammation. However, in the tumor microenvironment, tumor cells express inhibitory receptors and block functions of effector T activity via impairing the ability of tumor-specific T lymphocytes and triggering the expression of immune checkpoints.

Monoclonal antibodies (mAbs) blocking immune checkpoint receptors have emerged as promising therapeutics. For example, mAbs against immune checkpoints including programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) have been widely applied to restore the function of effector T cells and enhance their anti-tumor abilities by blocking tumor cell triggered inhibitory signals in tumor-specific T cells (Fig. 1). Furthermore, mAbs with high specificity have also been shown to disrupt the function of immune checkpoints by blocking ligand-receptor interactions. Importantly, mAbs targeting immune checkpoints have demonstrated promising results in animal xenograft models as well as cancer patients in clinical studies, suggesting their potential as therapeutic candidates for cancer immunotherapy.

A series of immune checkpoints has been identified over the past few decades (Gajewski et al. 2013; Keir et al. 2006, 2008; Krummel and Allison 1995; Nishimura et al. 1999; Ocana-Guzman et al. 2016; Sledzinska et al. 2015). There has been a particular focus on cytotoxic T-lymphocyte protein 4 (CTLA-4) and PD-1 immune checkpoints, which are co-inhibitory molecules that regulate the immune function of T cells. CTLA-4 or PD-1 blockage activates T cell-mediated anti-tumor immunity, and some studies have shown anti-tumor efficiency by CTLA-4 or PD-1 blockage in animal xenograft models including non-small cell lung cancer (NSCLC), melanoma, and other types of cancer. To the best of our knowledge, the underlying molecular mechanisms of CTLA-4 and PD-1-mediated immune responses against cancer differ. CTLA-4 regulates the proliferation of T cells at an early stage of immune responses, whereas PD-1 is responsible for the proliferation of T cells at a later stage.

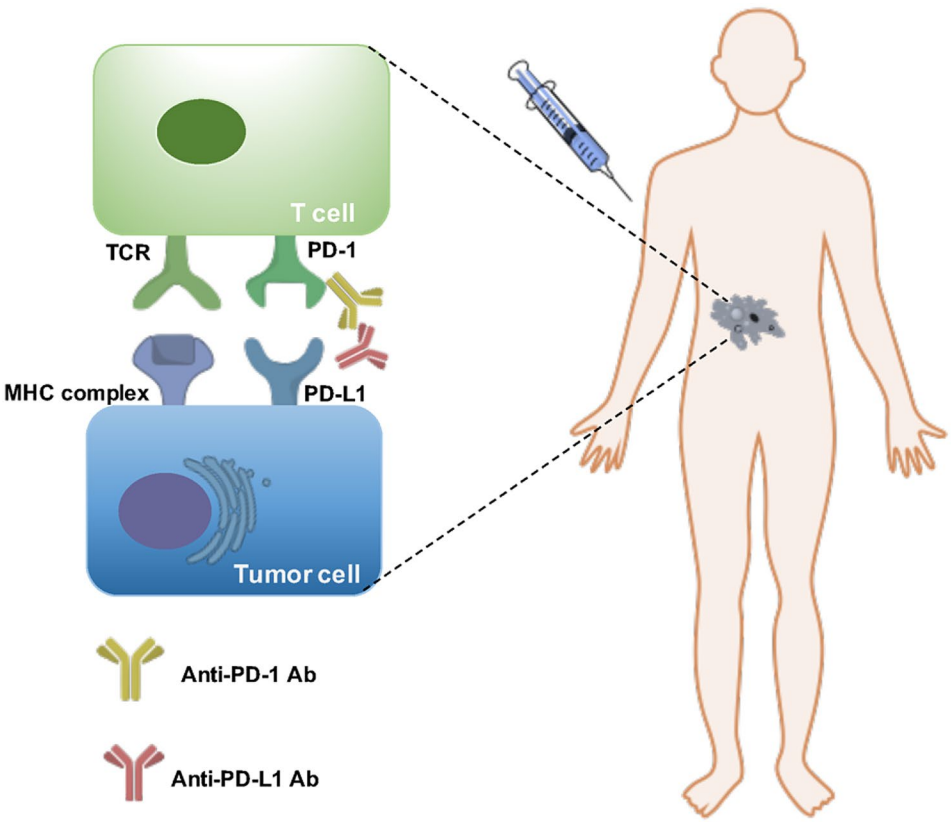

Fig. 1 Diagram demonstrating the applications of anti-PD-1 and anti-PD-L1 mAbs in cancer immunotherapy

Additionally, by competitively binding CD80/CD86, which is a ligand for CD28, CTLA-4 also inhibits the activation of T cells. PD-1 inhibits the proliferation and survival of T cells by interacting with PD-L1, impacting the production of cytokines including interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ (Blank et al. 2004; Dong et al. 2002; Iwai et al. 2002; Leach et al. 1996).

Based on the understanding of the molecular mechanisms of CTLA-4 and PD-1 for the regulation of T cells, mAbs targeting CTLA-4 and PD-1 have been developed and approved for cancer immunotherapy. For instance, ipilimumab, the first anti-CTLA-4 mAb, was approved by the US Food and Drug Administration (FDA) in 2011. It is used to block CTLA-4 and induce sustained anti-tumor responses (Hodi et al. 2010). Additionally, some mAbs targeting PD-1 and PD-L1 have also been approved for cancer immunotherapy and demonstrated good therapeutic effects for a wide range of cancers (Brahmer et al. 2010; Hamid et al. 2013; Powles et al. 2014a; Zou et al. 2016). mAbs that target the PD-1 receptor include pidilizumab, nivolumab, pembrolizumab, PDR001, MEDI0680, and AMP-224. A combination of PD-1/PD-L1 blockage therapy with other anti-cancer drugs has also been widely investigated. In this review, the structures and interactions of PD-1 and PD-L1, molecular mechanisms of PD-1 and PD-L1-mediated anti-cancer immune responses, some clinical trials of mAbs targeting PD-1 and PD-L1, and current challenges and the future of PD-1 and PD-L1 blockage therapy are discussed.

Structures of PD-1 and PD-L1 and Their Roles in Cancer Immunotherapy

Structure and Interactions of PD-1 and PD-L1

PD-1, a member of the B7-CD28 receptor family, is a 55 kDa monomeric type I surface transmembrane glycoprotein (Chen 2004; Xia et al. 2016). It is composed of an extracellular IgV domain, a transmembrane domain, and an intracellular cytoplasmic domain (Butte et al. 2007; Viricel et al. 2015). PD-L1, a 40 kDa type I transmembrane protein, is composed of two side-by-side domains and extracellular IgV and IgC domains (Dong et al. 1999). Compared with PD-1, PD-L1 lacks intracellular signaling. The first murine Apo-PD-1 extracellular domain structure (PDB ID: 1NPU) was discovered by Zhang et al. (2004) as shown in Fig. 2a. Cheng et al. (2013) reported a human Apo-PD-1 extracellular domain structure that was identified by NMR. Lázár-Molnár et al. (2017) established the human Apo-PD-1 extracellular crystal structure (PDB ID: 3RRQ) though X-rays as shown in Fig. 2b. Figure 2c shows the overlap of 1NPU and 3RRQ. For PD-L1, several human Apo-PD-L1 extracellular crystal structures have been reported with high resolution (Chen et al. 2010; Lin et al. 2008; Zak et al. 2015; Zhang et al. 2017). The structures of two (PDB ID: 3FN3 and 5C3T) are shown in Fig. 2d, e and their overlap is shown in Fig. 2f.

Before human PD-1/PD-L1 crystal structures were identified (Zak et al. 2015), the crystal structures of murine PD-1 with human PD-L1 were used to elucidate PD-1 and PD-L1's interactions (Lin et al. 2008). However, human and murine PD-1 share only 64% of amino acid sequence identity, and amino acid sequence identity between human and murine PD-L1 is 77% (Konstantinidou et al. 2018), indicating that interactions between murine PD-1 and human PD-L1 are different from human PD-1/PD-L1 interactions. Figure 3a shows the crystal structure of human PD-1/PD-L1 (PDB ID: 4ZQK). Between the human Apo-PD-1 structure (PDB ID: 3RRQ) and human PD-1 (PDB ID: 4ZQK), an obvious structural arrangement of PD-1 can be observed (Fig. 3b). In addition, interaction analysis demonstrated that three hotspot pockets were identified that are responsible for the binding affinity between human PD-1 and PD-L1 (Fig. 3c).

Mechanism of PD-1- and PD-L1-mediated Immune Responses

The PD-1/PD-L1 axis is a desirable target for cancer immunotherapy due to its higher efficiency, selectivity, lower toxicity, and broader spectrum of anti-tumor activities (Larkin et al. 2015a; Robert et al. 2015). PD-1 and its ligands including PD-L1 and PD-L2 regulate the inhibition and exhaustion of T cells. PD-L1 is broadly expressed in hematopoietic and non-hematopoietic cells, whereas PD-L2 is inducibly expressed in dendritic cells (DCs), macrophages, memory B cells, and bone-marrow-derived mast cells. Interestingly, when compared with PD-L2, the high expression of PD-L1 is more closely associated with tumor growth and metastasis as supported by several clinical studies. However, the high expression of PD-L2 is associated with a decrease in survival time but no statistical significance, indicating that the PD-1/PD-L1 axis is a more desirable target for cancer immunotherapy than the PD-1/PD-L2 axis (Fernandes and Brabek 2017).

PD-1 is widely expressed in B cells, T cells, and natural killer (NK) cells (Nurieva et al. 2006), while PD-L1 is expressed in DCs, macrophages, and tumor cells (Latchman et al. 2001). By binding with PD-1, PD-L1 triggers co-inhibitory signals and inhibits the function of T cells by modulating the T cell receptor (TCR)-meditated signaling pathways and counterbalancing the activation of co-stimulatory signals. Emerging evidence has also identified new functional roles of the PD-1/PD-L1 signaling axis (Alsaab et al. 2017; Wei et al. 2018).

The primary function of PD-1 is to inhibit the activation of TCR signaling. Therefore, cells highly expressing PD-L1,

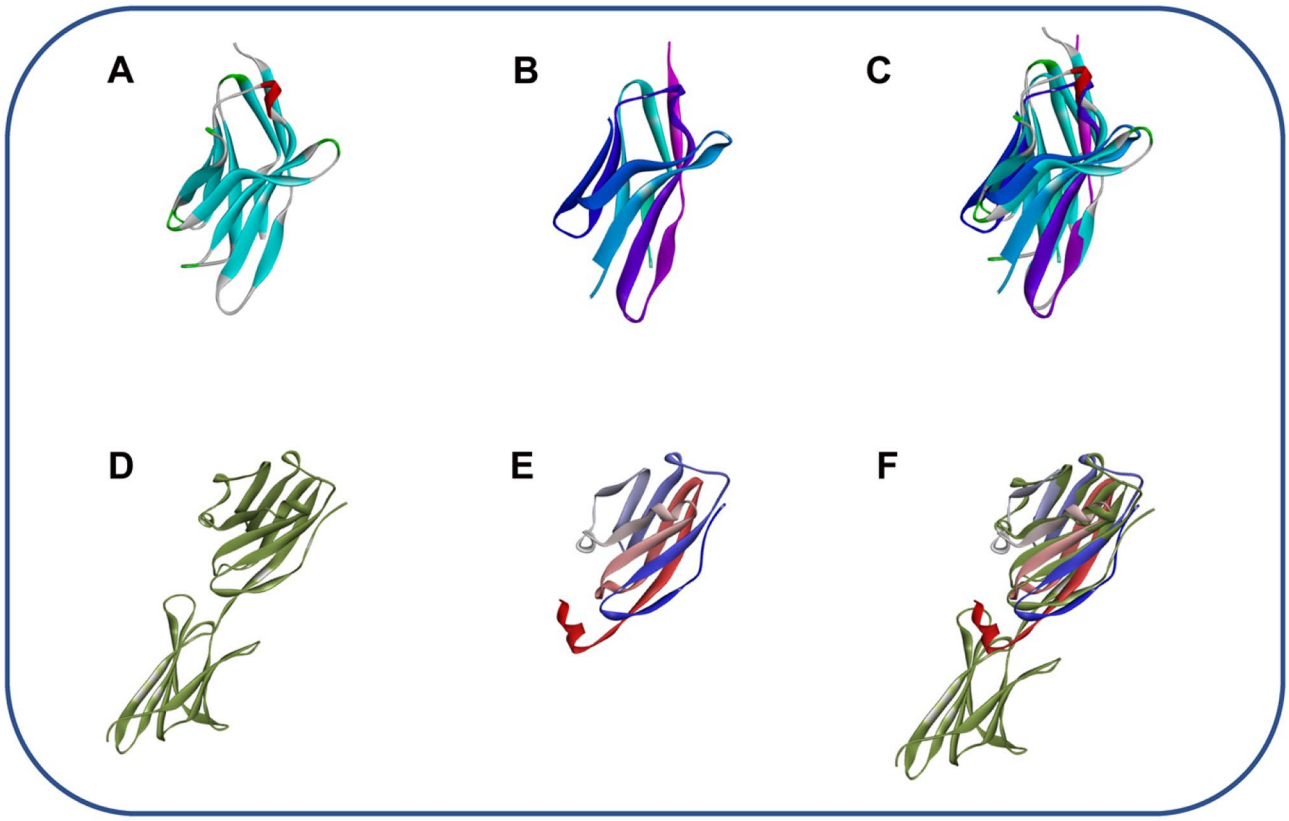

Fig. 2 The structures of murine and human PD-1 and PD-L1. **a** The structure of the murine PD-1 extracellular domain (1NPU). **b** The structure of the human PD-1 extracellular domain (3RRQ). **c** The overlap of 1NPU and 3RRQ. **d** The structure of the human PD-L1 extracellular domain including both V-type and C2-type domains (3FN3). **e** The structure of the murine PD-L1 extracellular V-type domain (5C3T). **f** The overlap of 3FN3 and 5C3T

including APCs and tumor cells, interact with PD-1 overexpressed T cells, leading to dysfunction of T cells. TCR signaling is induced by the interactions between TCR on T cells and MHC-peptide loading complex on APCs. However, the activation of PD-1 inhibits the phosphorylation of the TCR signaling intermediates, leading to the termination of TCR signaling and inhibition of T cell proliferation (Patsoukis et al. 2012). PD-1 directly inhibits Ras, an enhancer of T cell inactivation (Patsoukis et al. 2012). There are two signaling motifs in the cytoplasmic tail of PD-1, the intracellular immunoreceptor tyrosine-based switch motif (ITSM) and the immunoreceptor tyrosine-based inhibitory motif (Chemnitz et al. 2004; Sheppard et al. 2004). By binding with PD-L1, ITSM is phosphorylated and recruits Src homology 2-containing tyrosine phosphatase (SHP-2), thereby inhibiting the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway (Hofmeyer et al. 2011; Parry et al. 2005; Yokosuka et al. 2012). PI3K/Akt signaling pathway blockage downregulates the mechanistic target of rapamycin and inhibits protein synthesis and cell growth. PI3K/Akt signaling pathway blockage also inhibits the degradation of transcription factor FoxO1, which in turn enhances the expression of PD-1 (Staron et al. 2014). Recent studies indicate that CD28 is also a primary target of PD-1-induced attenuation of T cell signaling. These studies utilized a cell-free membrane reconstitution model to examine functional relationships during T cell activation and reveal that PD-1 leads to preferential dephosphorylation of CD28 rather than the TCR, via recruitment of SHP-2. This suggests that PD-1, at least in part, acts through a similar molecular mechanism of attenuating CD28-mediated co-stimulation. Interestingly, recent findings indicate that SHP-2 is not essential for responses to anti-PD-1 therapy or induction of T cell exhaustion in vivo (Wei et al. 2018). This suggests the functional redundancy of the signaling pathways downstream of PD-1. This redundancy is most likely mediated through redundant phosphatases (for example, SHP1), but alternatively could be mediated through wholly distinct mechanisms.

PD-1 activation induces a decrease in B cell lymphoma extra-large, thereby impacting cell survival and proliferation. Basic leucine zipper transcription factor expression is also regulated by PD-1 activation, thereby weakening the functions of effector T cells and resulting to their dysregulation. Another study reported that PD-1 modulates cell metabolism

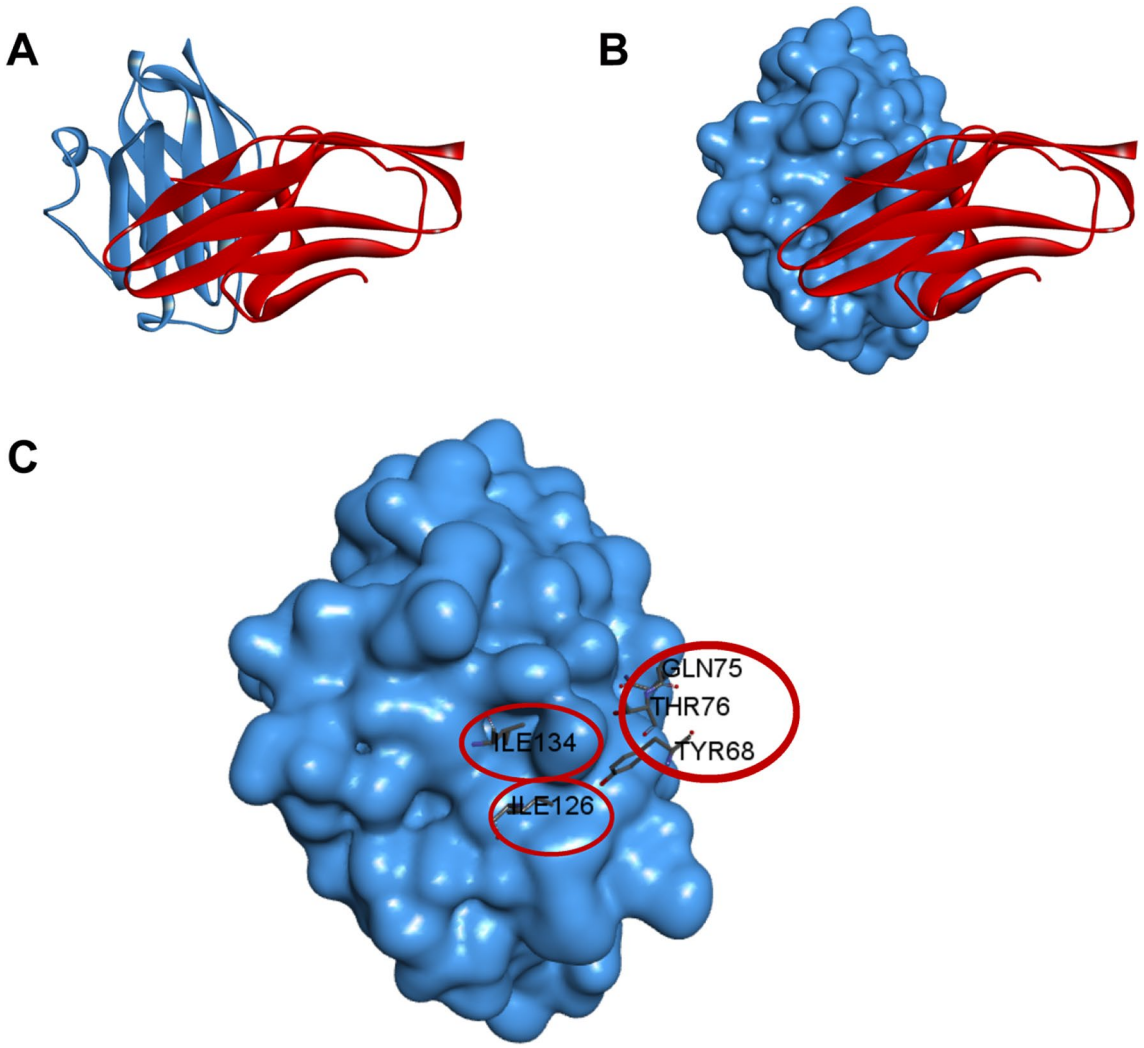

Fig. 3 The structure of human PD-1/PD-L1 complex and hotspot pockets between PD-1 and PD-L1. **a** The structure of human PD-1/PD-L1 complex (4ZQK); the red one is PD-1 and the blue one is PD-L1. **b** PD-L1 is shown at the surface and interacting with PD-1. **c** The key residues that bind with PD-L1 are shown in the sticks with residue numbers. Three hotspot pockets are shown in the red cycles

by inhibiting glycolysis and promoting fatty acid oxidation (Patsoukis et al. 2015). The downstream effects mediated by PD-1/PD-L1 binding cause a decrease in several inflammatory cytokines including IL-2, TNF-α, and IFN-γ (Barber et al. 2006; Freeman et al. 2000; Latchman et al. 2001). Recent research reported that macrophage expression of PD-L1 may lead to the active eviction of T cells from the tumor microenvironment (Alsaab et al. 2017). This suggests that in addition to regulating T cell activation and cytolytic capacity, PD-1 signaling may also regulate T cell tracking and migration.

PD-1 overexpression results in T cell exhaustion in mice and humans infected with chronic virus, which is supported by several studies (Barber et al. 2006; Hofmeyer et al. 2011; Ka et al. 2011; Lu et al. 2014; Quigley et al. 2010; Youngblood et al. 2011). Alternatively, PD-1 is upregulated in $CD8^+$ T cells while PD-1 blockage reverses exhausted $CD8^+$ T cells (Barber et al. 2006; Pauken and Wherry 2015). Exhausted T cells also exhibit insufficient protective immunologic response (Barber et al. 2006; Blackburn et al. 2009; Day et al. 2006). Studies have reported that PD-L1 expressed in tumor cells induces Treg proliferation by regulating Akt signaling pathways (Francisco et al. 2009; Haxhinasto et al. 2008). Treg has immunosuppressive functions, and part of its mechanism is to suppress the proliferation of effector T cells (Bettelli et al. 2006). Apart from binding with PD-1, PD-L1 interacts with CD80, which is mainly expressed in activated T cells, thereby inhibiting T cell-mediated immune responses (Butte et al. 2007; Park et al. 2010). Once PD-L1 is highly expressed in tumor cells, it signals T cells, thereby impacting their survival, but the underlying mechanisms are not fully understood (Azuma et al. 2008; Dong et al. 2003).

Overall, the multiple effects initiated by PD-1/PD-L1 interactions including the inhibition of T cell proliferation, promotion of T cell exhaustion, and dampening of the functions of effector T cells lead to immune evasion of cancer cells.

mAbs targeting PD-1 and PD-L1 developed to block their binding, thereby shutting off the inhibitory signals and consequently leading to reactivation of anti-tumor immune response mediated by T cells (John et al. 2013; Mantovani 2010; Zang and Allison 2007). Numerous clinical studies have demonstrated that PD-1 and PD-L1 blockage therapies show promising anti-tumor activities for various cancer types (Ansell et al. 2015; Brahmer et al. 2010, 2012; Herbst et al. 2014; Le et al. 2015; Lipson et al. 2013; Powles et al. 2014a; Topalian et al. 2012). Herein, we discuss immune checkpoint blockage of PD-1 and PD-L1.

Immune Checkpoint Blockage of PD-1

mAbs target PD-1 by blocking PD-1/PD-L1 interactions, which in turn enhances the functions of effector T cells and simultaneously promotes the proliferation of T cells (Wong et al. 2007). In general, PD-1 inhibitors competitively bind to PD-1 and block PD-1/PD-L1 interactions, thereby inhibiting PD-1-mediated downstream events including the activation of NK cells and cytotoxic T cells. PD-1 inhibitors also regulate negative signals on the T cell surface and promote the activation and proliferation of T cells. In addition to the inhibitory effect on the immune checkpoint, PD-1 inhibitor AMP-224 also has antineoplastic activities. Currently, mAbs targeting PD-1 include pidilizumab, nivolumab, pembrolizumab, spartalizumab, MEDI0680, and AMP-224 (Table 1).

Pidilizumab

Pidilizumab (CT-011 and MDV9300) is the first humanized immunoglobulin (Ig) G1 mAb against PD-1. Pidilizumab has broader clinical activities for various cancer types including B cell lymphoma, colorectal cancer, hematologic malignancies, melanoma, and solid tumors.

In a phase I clinical trial, pidilizumab therapy was well tolerated and its total clinical benefit rate was approximately 33% in patients with hematologic malignancies including Hodgkin lymphoma, myeloid leukemia, and lymphocytic leukemia (Berger et al. 2008). In this study, the administration of pidilizumab (0.2–6.0 mg/kg) was well tolerated in patients with advanced hematologic malignancies. The median half-life of pidilizumab is up to 410 h, and an elevation of blood $CD4^+$ lymphocytes is observed up to 21 days after pidilizumab therapy. We speculate that the clinical benefits may be related to the durable tumor-specific immune response induced by pidilizumab. The safety profile and clinical activities are supported by two phase II studies, in which a 55% overall response rate was observed in patients after autologous hematopoietic stem cell transplantation. Pidilizumab therapy also demonstrated safety profiles in these clinical studies (Armand et al. 2013; Westin et al. 2014). These results may be due to the lower dose and less frequent administration of pidilizumab. For instance, in one clinical trial of patients with relapsed follicular lymphoma, pidilizumab was dosed at 3 mg/kg intravenously every 4 weeks (Westin et al. 2014). Another phase II study initiated by Atkins et al. (2014) evaluated anti-tumor activity and the safety profile of pidilizumab in patients with metastatic melanoma. Overall, 45% of patients did not respond to pidilizumab therapy, although pidilizumab therapy was well tolerated and improved substantial survival in heavily pretreated patients (Atkins et al. 2014). Additionally, pidilizumab therapy was well tolerated in patients with diffuse intrinsic pontine glioma, demonstrating that pidilizumab might be a drug candidate for diffuse intrinsic pontine glioma therapy (Fried et al. 2018). Fried et al. (2016) evaluated the effects of pidilizumab on children with diffuse intrinsic pontine glioma. This was the first study conducted on pediatric patients. Administration of pidilizumab was well tolerated in 9 of 13 patients during the study period. However, two patients experienced grade 3 adverse events. Other adverse events included fatigue (50%), anorexia (17%), and hypophosphatemia (17%) but none were significant. However, the sample cohort was relatively small, limiting support of the final conclusions. Some phase III clinical trials of pidilizumab in other types of cancers are still underway.

Nivolumab

As a humanized IgG4 antibody targeting PD-1, nivolumab (BMS-936558) blocks interactions between PD-1 and its ligands including PD-L1 and PD-L2. In 2014, nivolumab was approved by the FDA for the treatment of refractory unresectable melanoma. In 2015, the FDA approved nivolumab for the treatment of NSCLC after progression on a platinum-based chemotherapy regimen (Brahmer et al. 2015). To date, nivolumab therapy has been approval for many cancers including advanced renal cancer, colorectal cancer, hepatoma, head and neck squamous cell carcinoma, and advanced urothelial cancer.

In the first phase I clinical trial, nivolumab therapy demonstrated therapeutic effects and favorable safety profiles in patients with metastatic melanoma, colorectal cancer (CRC), castrate-resistant prostate cancer (CRPC), NSCLC, and renal cell cancer (RCC). Although nivolumab was well tolerated with anti-tumor activity, one patient with metastatic melanoma experienced severe inflammatory colitis after nivolumab therapy following five doses (1 mg/kg) administered over 8 months (Brahmer et al. 2010). In this study, anti-tumor activity of nivolumab is most likely through immunologic mechanisms, because non-hematologic tumors

Table 1 Summary of FDA-approved PD-1 and PD-L1 inhibitors

Agent name	Antibody type	Target	Phase	Cancer types
Pidilizumab	IgG1	PD-1	Phase I/II	Glioma; hepatoma
			Phase II	Acute myeloid leukaemia; CRC; diffuse large B cell lymphoma; follicular lymphoma; malignant melanoma; multiple myeloma; pancreatic cancer; prostate cancer; renal cell carcinoma
Nivolumab	IgG4	PD-1	Phase I/II	Haematological malignancies; lymphoma; rectal cancer
			Phase II	Acute myeloid leukaemia; adrenocortical carcinoma; biliary cancer; bronchopulmonary dysplasia; cervical cancer; cholangiocarcinoma; CNS cancer; diffuse large B cell lymphoma; nasopharyngeal cancer; oropharyngeal cancer; pancreatic cancer; penile cancer; peripheral T cell lymphoma; prostate cancer; soft tissue sarcoma; solid tumors; testicular cancer; thyroid cancer; uterine cancer; uveal melanoma
			Phase II/III	Non-Hodgkin's lymphoma
			Phase III	Bladder cancer; breast cancer; fallopian tube cancer; glioblastoma; multiple myeloma; ovarian cancer; peritoneal cancer
Pembrolizumab	IgG4	PD-1	Phase I	Adenocarcinoma; gliosarcoma
			Phase I/II	Chronic lymphocytic leukaemia; haematological malignancies; leiomyosarcoma; mantle-cell lymphoma; precursor cell lymphoblastic leukaemia-lymphoma; T cell lymphoma
			Phase II	Acute myeloid leukaemia; adenoid cystic carcinoma; bone cancer; cholangiocarcinoma; follicular lymphoma; germ cell and embryonal neoplasms; glioblastoma; glioma; inflammatory breast cancer; lymphoma; meningeal carcinomatosis; meningioma; neuroendocrine tumors; non-Hodgkin's lymphoma; osteosarcoma; penile cancer; rectal cancer; sarcoma; soft tissue sarcoma; thymoma; thyroid cancer; uveal melanoma
			Phase III	Breast cancer; fallopian tube cancer; gastrointestinal cancer; mesothelioma; multiple myeloma; nasopharyngeal cancer; ovarian cancer; peritoneal cancer; prostate cancer
Spartalizumab	IgG4	PD-1	Phase I	Acute myeloid leukaemia; lymphoma; multiple myeloma; ovarian cancer; renal cancer; renal cell carcinoma; squamous cell cancer
			Phase I/II	Gastrointestinal stromal tumours; liver cancer
			Phase II	Breast cancer; CRC; diffuse large B cell lymphoma; gastric cancer; nasopharyngeal cancer; NSCLC; solid tumors
			Phase III	Malignant melanoma
MEDI0680	IgG4κ	PD-1	Phase I/II	B cell lymphoma
AMP-224	PD-L2 extracellular domain with IgG1 Fc	PD-1	None	
BMS-936559	IgG4	PD-L1	Discontinued	
Atezolizumab	Fc-engineered IgG1κ	PD-L1	Phase I	Haematological malignancies; multiple myeloma; non-Hodgkin's lymphoma
			Phase I/II	Acute myeloid leukaemia; follicular lymphoma; glioblastoma; pancreatic cancer
			Phase II	Anal cancer; chronic lymphocytic leukaemia; cutaneous T cell lymphoma; diffuse large B cell lymphoma; endometrial cancer; gastric cancer; gynaecological cancer; mantle-cell lymphoma; marginal zone B cell lymphoma; oesophageal cancer; soft tissue sarcoma; solid tumors; thyroid cancer
			Phase III	Bladder cancer; cervical cancer; CRC; fallopian tube cancer; head and neck cancer; liver cancer; malignant melanoma; mesothelioma; ovarian cancer; peritoneal cancer; renal cell carcinoma

Table 1 (continued)

Agent name	Antibody type	Target	Phase	Cancer types
Durvalumab	Fc-engineered IgG1	PD-L1	Phase I	Gastrointestinal cancer; lymphoproliferative disorders; thyroid cancer; vulvo-vaginal cancer
			Phase I/II	Chronic lymphocytic leukaemia; cutaneous T cell lymphoma; haematological malignancies; lung cancer; lymphoma; malignant melanoma; non-Hodgkin's lymphoma; peripheral T cell lymphoma; renal cancer
			Phase II	Acute myeloid leukaemia; Brain metastases; cholangiocarcinoma; CRC; diffuse large B cell lymphoma; endometrial cancer; gallbladder cancer; gastric cancer; germ cell and embryonal neoplasms; glioblastoma; mesothelioma; multiple myeloma; myelodysplastic syndromes; neuroendocrine tumors; oesophageal cancer; oropharyngeal cancer; prostate cancer; sarcoma; soft tissue sarcoma
			Phase II/III	Breast cancer; gynaecological cancer; pancreatic cancer
			Phase III	Biliary cancer; bladder cancer; cervical cancer; fallopian tube cancer; head and neck cancer; liver cancer; ovarian cancer; peritoneal cancer; renal cell carcinoma; solid tumors
Avelumab	IgG1	PD-L1	Phase I	Acute myeloid leukaemia; follicular lymphoma; liver cancer; meningioma
			Phase I/II	Liposarcoma; lymphoma; oropharyngeal cancer; pancreatic cancer
			Phase II	Bladder cancer; endometrial cancer; fallopian tube cancer; gastrointestinal cancer; germ cell and embryonal neoplasms; glioblastoma; haemangiosarcoma; intestinal cancer; leiomyosarcoma; nasopharyngeal cancer; neuroendocrine tumors; Oesophageal cancer; osteosarcoma; penile cancer; peripheral T cell lymphoma; peritoneal cancer; prostate cancer; small cell lung cancer; squamous cell cancer; thymoma
			Phase III	Breast cancer; diffuse large B cell lymphoma; gastric cancer; head and neck cancer; NSCLC; ovarian cancer; solid tumors

do not express PD-1. Importantly, tumor regressions were seen in CRC and NSCLC patients, indicating that the capacity of nivolumab to enhance anti-tumor immunity extends beyond the tumor types of melanoma and RCC. Another phase I study evaluated nivolumab in patients with melanoma, NSCLC, and RCC but no responses were observed in patients with CRC or CRPC. Additionally, severe adverse effects were observed in 15% of patients and 6% of patients discontinued therapy (Antonia et al. 2014; Topalian et al. 2012).

In a phase II clinical trial, nivolumab therapy was administered to patients with metastatic renal cell carcinoma and a 20–22% objective response rate (ORR) and an 18.2- to 25.5-month prolonged overall survival rate were observed (Motzer et al. 2015b). In this study, a total of 168 patients were randomly treated with nivolumab at doses of 0.3, 2, or 10 mg/kg intravenously once every 3 weeks. Interestingly, no dose–response relationship was observed as measured by the survival rate. Overall, nivolumab therapy demonstrated a manageable safety profile in all groups, consistent with some phase I clinical trials. Similarly, another phase II clinical trial showed that nivolumab therapy demonstrated a 21% ORR and a 35% 3-year overall survival rate in patients with advanced RCC (McDermott et al. 2015). Nivolumab also has therapeutic effects for hepatoma patients with a manageable adverse event profile supported by a prolonged 6-month overall survival rate after nivolumab therapy (Hamanishiet al. 2015). In addition to a wide spectrum of cancer types, nivolumab therapy also shows promising activities compared with other traditional chemotherapies. For instance, in a phase III trial of patients with refractory melanoma, nivolumab therapy demonstrated a higher ORR than chemotherapy (32% vs. 11%) (Rexer 2015). In other phase III trials for NSCLC, advanced squamous cell lung cancer, advanced RCC, and recurrent head and neck squamous cell carcinoma, nivolumab therapy demonstrated better survival benefits than some traditional therapies (Brahmer et al. 2015; Borghaei et al. 2015; Motzer et al. 2015a). For instance, in advanced NSCLC patients, the median overall survival was 9.2 months with nivolumab vs. 6.0 months with docetaxel. Moreover, the safety profile of nivolumab was more favorable than that of docetaxel. Importantly, the survival benefit of nivolumab therapy was observed independent of tumor PD-L1 expression levels (Brahmer et al. 2015).

Pembrolizumab

As a humanized IgG4 mAb against PD-1, pembrolizumab (MK-3475) has drawn considerable attention in recent years. In 2014, pembrolizumab was initially approved by the FDA for the treatment of refractory unresectable melanoma. In 2017, pembrolizumab was further approved for the treatment

of unresectable or metastatic solid tumors with mismatch repair deficiency (Syn et al. 2017). Notably, this was the first anti-cancer drug approved by the FDA based on tumor genetics. In 2018, pembrolizumab was approved by the FDA for the treatment of advanced cervical cancer and refractory or relapsed primary mediastinal large B cell lymphoma.

In a phase I trial, evaluating the safety and anti-tumor activity of pembrolizumab in patients with primary mediastinal B cell lymphoma, the ORR was 41% (7/17) and 13 out of 16 patients (81%) showed decreases in target lesions. Additionally, 11 patients (61%) experienced drug-related adverse events (mostly grade 1–2) and no treatment-related deaths were observed (Zinzani et al. 2017). In another phase I clinical trial, pembrolizumab was used for the treatment of ten patients with advanced solid tumors. Pembrolizumab was administered as an intravenous infusion at 2 or 10 mg/kg every 2 weeks until unacceptable toxicity. Therefore, it did not have a definite maximum-tolerated dose (Patnaik et al. 2015). The response rate across all cohorts was 38% and adverse events (grade 3 or 4) were reported in 13% of patients. This study also determined the PD-L1 expression levels in tumor tissue. However, the anti-tumor activities of pembrolizumab were independent of tumor PD-L1 expression levels. This may have been due to the limited number of patients. An expansion clinical trial was further applied to evaluate the anti-tumor activities of pembrolizumab in 173 patients with malignant melanoma previously treated with ipilimumab or inhibitors for proto-oncogene B-Raf (BRAF) and/or mitogen-activated protein kinase. Pembrolizumab therapy (2 or 10 mg/kg every 3 weeks) was well tolerated with no drug-related deaths. The ORR (41/157) was 26% and adverse events (grade 3 or 4) were reported in five patients (Robert et al. 2014). In addition to its therapeutic effects against melanoma, pembrolizumab also demonstrated promising activities in Hodgkin lymphoma. In a phase I clinical trial, pembrolizumab therapy achieved 65% ORR in relapsed or refractory Hodgkin lymphoma (Armand et al. 2016). In the subsequent phase II clinical trial, pembrolizumab therapy achieved 69% ORR and adverse events (grade 3 or 4) were reported in 4.4% of patients (Chen et al. 2017). Except for its safety profile, pembrolizumab demonstrated superior overall survival than ipilimumab (55% vs 43%) in a phase III clinical trial of patients with advanced melanoma (Schachter et al. 2017). This study conducted a head-to-head comparison of pembrolizumab vs ipilimumab for advanced melanoma. A total of 834 patients were enrolled and randomly assigned to receive pembrolizumab every 2 weeks ($n=279$), pembrolizumab every 3 weeks ($n=277$), or intravenous ipilimumab every 3 weeks ($n=278$). The 24-month overall survival rate was 55% in the 2-week group, 55% in the 3-week group, and 43% in the ipilimumab group. These data support that the use of pembrolizumab is more beneficial for advanced melanoma. The difference may be due to their different mechanisms. Two additional phase III clinical trials of pembrolizumab for the treatment of patients with advanced hepatocellular carcinoma or metastatic head and neck cancer are ongoing (Abou-Alfa et al. 2018; Cohen et al. 2015).

Spartalizumab

Spartalizumab (PDR001) is another humanized anti-PD-1 IgG4 mAb with a subnanomolar affinity with PD-1. The first clinical trial of spartalizumab treated advanced solid tumors. Spartalizumab was well tolerated with a safety profile similar to other anti-PD-1 antibodies. A total of 58 patients were treated with Spartalizumab and only one developed grade 3 autoimmune colitis (Naing et al. 2016a). Additionally, spartalizumab maintained patients with anaplastic thyroid cancer in a stable stage for 7 months in another phase I study. Spartalizumab was also used in an expansion cohort of anaplastic thyroid cancer and a 27% overall disease control rate was achieved. Spartalizumab also had a favorable safety profile as no unexpected side effects were reported (Wirth et al. 2018). Spartalizumab was consistently well tolerated and demonstrated a manageable safety profile in another phase I/II clinical trial of advanced melanoma and NSCLC. It is worth noting that the ORR was higher in PD-L1 positive patients in certain tumor types including melanoma and NSCLC (Lin et al. 2018). Overall, these data support the potential anti-tumor activities of spartalizumab. The therapeutic effects of spartalizumab in other types of cancer have not yet been determined. Spartalizumab demonstrated synergistic anti-tumor effects with other agents in a clinical trial.

MEDI0680

MEDI0680 (AMP-514) is a humanized IgG4κ antibody that blocks the binding between PD-1 and PD-L1/PD-L2. The isotype information on MEDI0680 is not yet available. In 2016, the first phase I clinical trial of MEDI0680 was conducted in patients with advanced solid tumors to assess its safety profile and anti-tumor activity and define its highest tolerable dose (Naing et al. 2016b). In 51 patients, 9 (18%) had an objective response including 1 (2%) complete response (renal cancer) and 14 (28%) had stable disease as their best response. No unexpected adverse events were observed. These results suggested that MEDI0680 has preliminary signs of efficacy with an acceptable safety profile. Naing et al. (2019) conducted a phase I study of MEDI0680 in patients with advanced solid malignancies. In 58 patients, eight had objective responses (14%) including five with kidney cancer and three with melanoma. MEDI0680 showed a manageable safety profile as no treatment-related deaths were observed and most adverse effects were mild to moderate. This study also showed that MEDI0680 therapy

enhanced $CD4^+$ and $CD8^+$ T cell proliferation in tumors and promoted plasma IFN-γ (Naing et al. 2019). Another phase I clinical trial of MEDI0680 in patients with advanced malignancies is ongoing (Infante et al. 2015).

AMP-224

AMP-224 was the first anti-PD-1 fusion protein composed of the extracellular domain of PD-L2 and the Fc region of human IgG1. By binding with PD-1 on chronically stimulated T cells, AMP-224 triggers cytotoxic T cell activation and immune response against tumors. AMP-224 exhibits distinctive safety and efficacy compared to other PD-L1 inhibitors because of different components and mechanisms. In 2013, the first clinical trial showed that AMP-224 was well tolerated up to 30 mg/kg in patients with advanced solid tumor. A total of 42 patients were treated with AMP-224 at doses of 0.3, 1, 3, 10, or 30 mg/kg intravenously at day 1 and day 15. No drug-related inflammatory adverse events were identified and one patient at 30 mg/kg AMP-224 developed flu-like symptoms. This study also demonstrated that AMP-224 specific inhibits population of $PD\text{-}1^+$ CD4 and $PD\text{-}1^+$ CD8 T cells in a dose-dependent manner (LoRusso et al. 2013). Another pilot study demonstrated that AMP-224 has a manageable safety profile in colon cancer patients with radiation therapy. A total of 17 patients were enrolled and intravenously administered 10 mg/kg AMP-224 at day 1. However, no objective responses were observed in this study. This may have been due to the lower efficacy of one single injection of AMP-224 and the relatively small sample size (Duffy et al. 2016). The therapeutic effects of AMP-224 in other types of cancer have not yet been determined.

Immune Checkpoint Blockage of PD-L1

Pre-clinical studies have shown that the expression of PD-L1 on tumor cells suppresses T cell activation and promotes tumor cell escape from the host immune system (Dong et al. 2002; Hirano et al. 2005). Binding of PD-L1 to its receptor inhibits T cell migration, proliferation, secretion of cytotoxic mediators, and restriction of cell killing. Therefore, the blockage of PD-L1 with specific mAbs provides an alternative method of activating T cell-mediated immune response. Anti-PD-L1 antibodies specifically disturb PD-1/PD-L1 interactions but do not block PD-1/PD-L2 interactions, which makes anti-PD-L1 antibodies less toxic as PD-1/PD-L2 interactions are important for maintaining peripheral tolerance. Four anti-PD-L1 mAbs are currently approved. Herein, we briefly discuss current clinical trials of anti-PD-L1 mAbs including BMS-986559, atezolizumab, durvalumab, and avelumab (Table 1).

BMS-936559

BMS-936559 (MDX-1105) is a human IgG4 mAb against PD-L1. Pre-clinical studies have demonstrated the anti-tumor activities of BMS-936559 in animal tumor models. Phase I trials of BMS-936559 were conducted in 207 patients with different refractory malignancies, including melanoma ($n = 55$), NSCLC ($n = 75$), colorectal ($n = 18$), ovarian ($n = 17$), renal cell ($n = 17$), pancreatic ($n = 14$), and breast cancer ($n = 4$). The patients were intravenously administered BMS-936559 at doses of 0.3, 1, 3, or 10 mg/kg on days 1, 15, and 29 in a 6-week cycle. Patients received BMS-936559 for up to 16 cycles until an unacceptable toxic effect was reported. The median duration of therapy was 12 weeks. Fifteen patients had objective responses (14%) including nine with melanoma, two with renal cancer, five with NSCLC, and one with ovarian cancer. Grade 3 or 4 adverse effects occurred in 9% of patients. Overall, BMS-936559 was well tolerated and the ORR was 6–17% in patients with different cancers; however, no response was found in patients with CRC or pancreatic cancer (Brahmer et al. 2012). Additionally, two clinical trials (NCT01455103 and NCT01452334) were withdrawn prior to enrollment (Li et al. 2016).

Atezolizumab

Atezolizumab (MPDL3280A and RO5541267) is human Fc-engineered anti-PD-L1 antibody. In 2015, atezolizumab was approved by the FDA for the treatment of NSCLC. In 2016, it was approved by the FDA for the treatment of urothelial carcinoma. However, in another phase III clinical trial, atezolizumab failed as the second-line treatment for urothelial carcinoma. In 2019, it was approved by the FDA for the treatment of advanced triple-negative breast cancer. Overall, atezolizumab was well tolerated in several clinical studies as no unexpected side effects were reported. In a phase I clinical trial, atezolizumab was well tolerated for several advanced solid tumors with no maximum-tolerated dose including CRC, melanoma, RCC, NSCLC, and gastric cancer. The median duration of therapy was 127 days. The ORR was 39% in patients with $PD\text{-}L1^+$ tumors, whereas patients with $PD\text{-}L1^-$ tumors had an ORR of 13%. Grade 3 or 4 adverse effects including hepatitis, rash, and colitis occurred in 39% of patients (Herbst et al. 2013). In another phase II clinical trial, 119 patients received ≥ 1 dose of atezolizumab. The median duration of therapy was 15 weeks. Grade 3 or 4 treatment-related effects occurred in 19 patients and one grade 5 treatment-related effect was observed. Interestingly, atezolizumab achieved higher ORR in patients with PD-L1-positive tumors than in patients with PD-L1-negative tumors (18% vs. 15%) (Balar et al. 2017). These results supported that atezolizumab therapeutic efficiency is associated

with PD-L1 expression. Atezolizumab also showed anti-tumor activities in metastatic urothelial bladder cancer. A total of 31 urothelial bladder cancer patients were treated with atezolizumab for a median duration of 43 days. The ORR was 26% and grade 3 or 4 treatment-related adverse effects occurred in 3.2% of patients (Powles et al. 2014b). Some clinical trials of atezolizumab to explore its anti-tumor activities in other tumors are ongoing.

Durvalumab

Durvalumab (MEDI4736) is an Fc-optimized humanized anti-PD-L1 IgG1κ mAb. It was approved by the FDA for the treatment of bladder cancer patients who had progressed after treatment with platinum. Anti-tumor activity of durvalumab is associated with PD-L1 expression. In a phase I/II open label study of patients with urothelial bladder cancer, a total of 61 patients (40 with PD-L1$^+$ and 21 with PD-L1$^-$) were enrolled. A 44.6% ORR in the PD-L1-positive group was achieved after treatment with durvalumab compared to a 0% ORR in the PD-L1-negative group (Massard et al. 2016). Grade 3 or 4 treatment-related adverse effects occurred in three patients. These results supported the promising anti-tumor activities of durvalumab in PD-L1$^+$ patients with a manageable safety profile. In another phase I clinical trial of patients with NSCLC or melanoma, durvalumab therapy showed an ORR of 23% in a PD-L1$^+$ group and a 14% ORR in all patients. Only grade 1 or 2 treatment-related adverse effects occurred in 43% of patients. A phase III clinical trial of patients with locally advanced NSCLC is ongoing (Brahmer et al. 2014).

Avelumab

Avelumab (MSB0010718C) is a humanized IgG1 antibody directly against PD-L1. It was approved by the European Medicines Agency (EMA) for the treatment of gastric cancer in 2017. The FDA and EMA also approved it in 2017 for the treatment of Merkel cell carcinoma, a highly aggressive skin cancer (Kim 2017).

The anti-tumor activities of avelumab were investigated in a large-scale clinical trial in which more than 1,700 patients were recruited with different types of tumors including head and neck cancer, gastric cancer, bladder cancer, adrenocortical cancer, renal cancer, ovarian cancer, melanoma, breast cancer, and NSCLC. Avelumab was well tolerated in different cancer patients with acceptable side effects (below grade 3 adverse effects) (Boyerinas et al. 2015). Avelumab also showed anti-tumor activities in patients with metastatic urothelial cancer in a phase 1 trial. A total of 249 patients (82 patients with PD-L1$^+$ and 124 patients with PD-L1$^-$) were enrolled. The patients were intravenously administered 10 mg/kg avelumab every 2 weeks until unacceptable toxicities occurred or other protocol-specified criteria for withdrawal. The median duration of therapy was 12 weeks. The ORR was 17% including 6% complete responses and 11% partial responses. Interestingly, the ORR was 24% in patients with PD-L1$^+$ tumors, whereas patients with PD-L1$^-$ tumors had an ORR of 13% (Rao and Patel 2019). In a phase 2 trial of patients with Merkel cell carcinoma, 88 patients were enrolled and received at least one dose of avelumab by intravenous infusion every 2 weeks. Grade 3 treatment-related adverse effects occurred in 5% of patients and a 31.8% ORR was achieved indicating the potential of avelumab for the treatment of difficult malignancies (Kaufman et al. 2016). In a phase I clinical trial of advanced or metastatic breast cancer, avelumab therapy achieved only a 5.4% ORR in the entire cohort. Interestingly, among all patients with PD-L1 expression, 33.3% had polygenic risk scores. In the PD-L1 positive group, four of nine patients with triple-negative breast cancer had polygenic risk scores compared with one of 39 patients with triple-negative breast cancer who had polygenic risk scores in the PD-L1-negative group (Dirix et al. 2018). These results support that the anti-tumor activities of avelumab are associated with PD-L1 expression in tumors. Clinical trials of avelumab in patients with other types of cancers are ongoing.

Current Challenges and the Future of PD-1/PD-L1 Blockade Therapy

To date, considerable research has been devoted to cancer immunotherapy strategies based on immune checkpoint blockade. Regulation of T cell-mediated anti-tumor immune response is one of the most frequently used cancer immunotherapy strategies. The PD-1/PD-L1-mediated pathways play critical roles in suppressing T cell immunity. Therefore, mAbs targeting PD-1 or PD-L1 have been developed for the treatment of cancer and clinical trials are ongoing. According to the clinical data, many PD-1/PD-L1 mAbs have exhibited tolerance, high response rates, durable responses, and acceptable toxicity profiles. However, some obstacles persist in PD-1/PD-L1 blockade therapy including unpredicted efficacy of PD-1/PD-L1 inhibitors and the emergence of resistance to PD-1/PD-L1 blockade.

One of the major obstacles to cancer immunotherapy is unpredicted efficacy of immune checkpoint inhibitors. According to the clinical data, approximately 20–30% of cancer patients respond to PD-1 or PD-L1 inhibitors, whereas 70–90% of patients report adverse events (Fernandes and Brabek 2017). Additionally, to date, some anti-PD-1 or PD-L1 mAbs have demonstrated efficiency only in patients with specific types of cancers. One reason for variabilities in patients' responses to treatment with PD-1 or PD-L1 inhibitors is that additional immune checkpoints, such as CTLA-4, are also crucial for the regulation

of anti-cancer immune responses. Therefore, combination therapy has been used to overcome this obstacle. Indeed, the combination of various anti-tumor therapeutic agents with PD-1/PD-L1 pathway blockade has offered new therapeutic options for patients with advanced cancers. Combination therapy not only enhances the total anti-tumor responses in patients but also significantly improves the therapeutic efficiency (Larkin et al. 2015a; Postow et al. 2015; Robert et al. 2015; Wolchok et al. 2013). For instance, in a phase III clinical trial of melanoma, nivolumab combined with ipilimumab prolonged the median progression-free survival to 11.5 months compared to 2.9 months in an ipilimumab-treated group and 6.9 months in an nivolumab-treated group. However, combination therapy also leads to a higher incidence of adverse events. In a combination therapy group, a 55% rate of adverse events was reported compared to the nivolumab-treated group (16.3%) and ipilimumab-treated group (27.3%) (Larkin et al. 2015b). Therefore, exploration of various combination strategies with high efficiency and minimum toxicity might be an option for cancer immunotherapy.

The emergence of resistance to PD-1/PD-L1 blockade is another major hurdle. Although some promising clinical results have been achieved by PD-1/PD-L1 pathway blockage strategies, few patients with advanced cancers respond to single immune checkpoint blockade. It is known that tumors apply multiple strategies for immune evasion (Taube et al. 2012). Therefore, to promote an anti-tumor response in patients with no response to single PD-1/PD-L1 blockage therapy, a combination of anti-PD-1/PD-L1 mAbs with other therapeutic agents has been used. Various candidates have been applied in combination with anti-PD-1 or PD-L1 mAbs including chemotherapy drugs, small molecule compounds, and radiation drugs (Dovedi et al. 2014). For instance, in a phase II clinical trial, pidilizumab was combined with rituximab (anti-CD20 antibody) for the treatment of follicular lymphoma. A 52% complete response rate was reported and no grade 3 or 4 adverse events were observed in the combination group (Westin et al. 2014). In another clinical trial of patients with advanced solid tumors, a combination of atezolizumab with VEGF-specific mAb bevacizumab exhibited favorable anti-tumor effects with minimum toxicity (Lieu et al. 2014). Various combination strategies are still ongoing. Favorable therapeutic results achieved by these strategies will likely improve cancer immunotherapy.

Conclusion

Considerable research has been devoted to the field of cancer immunotherapy. Recovering T cell-mediated anti-tumor immunity is one of the most frequently used strategies to date. The PD-1/PD-L1 pathway plays a crucial role in the regulation of T cell activities and is the most studied immune checkpoint for cancer immunotherapy. Numerous mAbs have been developed against PD-1 or PD-L1 for cancers and some relevant clinical trials are still underway. According to the clinical data we reviewed, some PD-1/PD-L1 mAbs have exhibited good tolerance and therapeutic outcomes for some types of cancer. The toxicity profiles are also reasonable with acceptable adverse event rates. Furthermore, the combination of anti-tumor therapeutic agents targeting other pathways with PD-1/PD-L1 pathway blockade has been developed to provide a more effective therapeutic option for cancer patients. Armed with the understanding of the molecular mechanisms of immune checkpoints, cancer microenvironments, and the discovery of novel targeting immune checkpoints, cancer immunotherapy will achieve more promising results against cancer.

Taken together, we clarified the mechanisms of PD-1/PD-L1-mediated anti-cancer immune responses and some clinical studies of mAbs targeting PD-1/PD-L1. Based on the clinical data we reviewed, some PD-1/PD-L1 mAbs have demonstrated good tolerance, promising therapeutic outcomes, and acceptable toxicity profiles for some types of cancer. We believe that the combination of anti-tumor therapeutic agents targeting other pathways with PD-1/PD-L1 pathway blockade will improve cancer immunotherapy strategies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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