

# Programmed death-1/programmed death-1 ligand axis as a therapeutic target in oncology: current insights

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**Abstract:** Over the past few years, the functional modulation of immune-checkpoint pathways using monoclonal antibodies has emerged as a promising anticancer therapeutic strategy. A key mechanism utilized by tumor cells to induce immune tolerance is upregulation of the programmed death-1 (PD-1) pathway. PD-1 is a negative coregulatory receptor on T-cells and antigen-presenting cells. The PD-1 ligand (PD-L1) is expressed by several tumor types, and appears to be dynamically regulated by the immune microenvironment. Several investigational agents targeting either PD-1 or PD-L1 are under clinical development and show durable antitumor activity across several tumor types. This review summarizes the conceptual basis, safety, and clinical activity of currently available PD-1 pathway therapeutic antibodies.

**Keywords:** immunotherapy, cancer, biomarkers, immune-checkpoint inhibitors, programmed death receptor

## Introduction

The dynamic interactions between a tumor and the host immune system develop through a complex process referred to as “cancer immunoediting”. This process allows the innate immune system to recognize and eliminate tumor cells, mainly through the cytotoxic effect of natural killer, CD4-positive, and CD8-positive T-cells, as well as interferon- $\gamma$  secretion. However, cancer cells can select mechanisms to adapt to and evade the immune response through generation of an immune-suppressive microenvironment, ultimately leading to cancer progression. The tumor microenvironment contains several suppressive mechanisms, including infiltration by specific inhibitory cells, eg, T regulatory cells and myeloid-derived suppressor cells, production of soluble immunosuppressive factors/cytokines, eg, interleukin (IL)-6, IL-10, vascular endothelial growth factor, and transforming growth factor- $\beta$ , and activation of coinhibitory immune checkpoint pathways, eg, cytotoxic T-lymphocyte-associated protein (CTLA)-4 and programmed death-1 (PD-1)/PD-1 ligand (PD-L1).

The antitumor T-cell response is initiated through antigen recognition by the T-cell receptor and further modulated by costimulatory and coinhibitory signal checkpoints. Most of these checkpoints can act both at the antigen cell presentation level and in the transmission of signals from tumor to effector cells. It is increasingly recognized that upregulation of inhibitory checkpoints by cancer cells limits the effectiveness of immune surveillance. Such inhibitory pathways include: PD-1/PD-L1/PD-L2, CTLA-4/CD80/CD86, B lymphocyte and T lymphocyte attenuator/herpes virus entry mediator, lymphocyte-activation gene 3/major histocompatibility complex-II, T-cell immunoglobulin mucin-3/galectin 9, B7-H3, B7-H4, adenosine/A2A receptors, and indoleamine 2,3-dioxygenase.

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Several anticancer strategies involving immune modulatory approaches have been evaluated in recent decades, with varying degrees of success. Closer understanding of the immune brakes or inhibitory checkpoints used by tumor cells to evade the cytotoxic immune response has led to development of novel agents with unprecedented clinical potential. One such checkpoint pathway commonly upregulated in solid tumors is the PD-1/PD-L1 axis.<sup>1</sup>

## PD-1 pathway and tumor immune escape

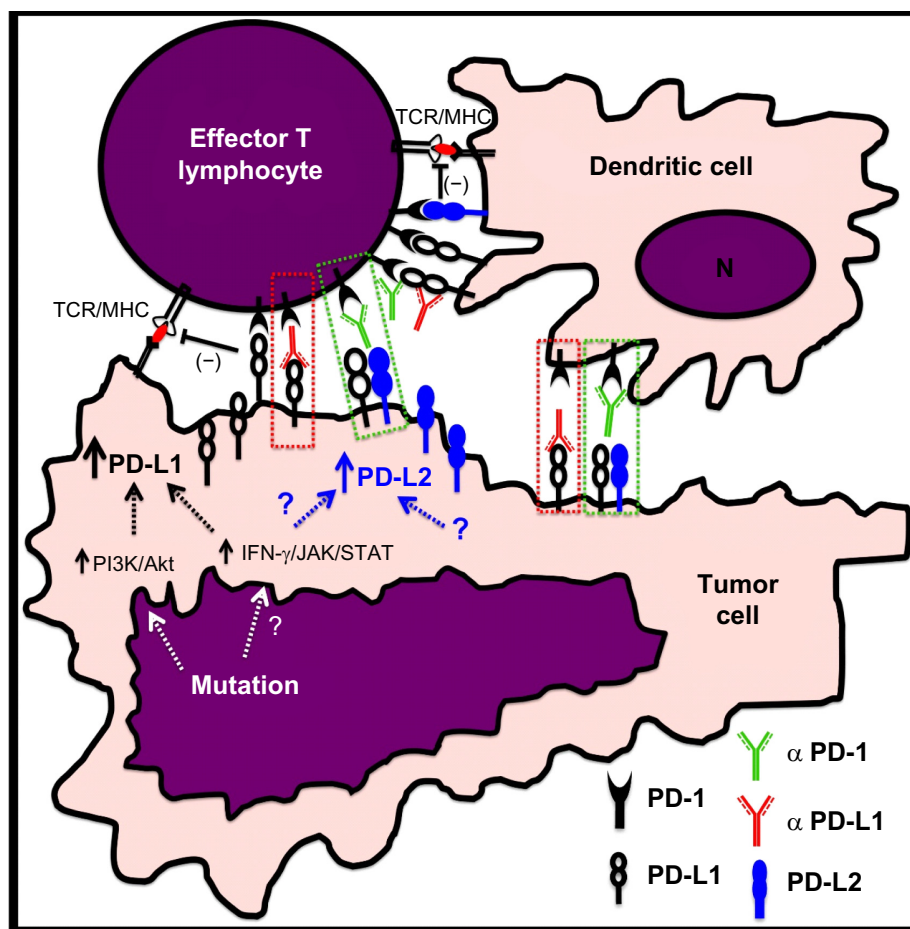
PD-1 receptor, a member of the CD28 family, is a type 1 transmembrane protein with the extracellular segment containing a single immunoglobulin (Ig)-like variable domain and the intracellular part containing an immunoreceptor tyrosine-based inhibitory motif.<sup>2</sup> PD-1 is expressed on activated T-cells, B lymphocytes, natural killer cells, dendritic cells, and activated monocytes.<sup>3,4</sup> Interaction between PD-1 and its ligands PD-L1 and PD-L2 leads to T-cell exhaustion, inactivation, and apoptosis. Exhausted T lymphocytes lose the ability to produce proinflammatory cytokines including IL-2, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ .<sup>4,5</sup> In addition, binding of PD-1 to its ligands induces cell cycle arrest by increasing P15 and P27 expression.<sup>6</sup> Expression of PD-L1 by diverse tissues mediates peripheral immune tolerance, and activation of the PD-1/PD-L1 axis limits the tissue damage after a sustained immune/inflammatory response. PD-1-expressing tumor-infiltrating lymphocytes are associated with an impaired antitumor effect and upregulation of PD-1, and PD-L1 is associated with outcome in several tumor types.<sup>7-10</sup>

To date, two PD-1 ligands from the B7 family have been characterized, ie, PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). PD-L1 is constitutively expressed in immunologically privileged sites like the placenta, retina, and tonsils,<sup>11-13</sup> as well as in macrophages and dendritic cells.<sup>4</sup> PD-L1 is upregulated in various tumors, including melanoma, high-grade glioma, and non-small cell lung cancer (NSCLC), as well as ovarian, breast, squamous cell head and neck (SCHN), and cervical carcinoma.<sup>14,15</sup>

Some investigators have reported that tumor PD-L1 expression is associated with an adverse outcome,<sup>16,17</sup> while other studies have found a favorable outcome with increased PD-L1 expression.<sup>15,18-21</sup> The performance of most commercially available antibodies against PD-L1 is unknown, and the data suggest limitations in the specificity and reproducibility of some assays that might explain the dissimilar association with outcome and limited predictive value for anti-PD-1/PD-L1 therapies.<sup>21,22</sup> In general, tumor PD-L1 positivity has been associated with a

higher likelihood of response to therapies (see below). However, clinical trials have measured tumor tissue PD-L1 using automated immunohistochemistry with different antibodies including Dako clone 28-8 (nivolumab, Bristol-Myers Squibb, New York, NY, USA), Dako clone 22C3 (pembrolizumab, Merck, Whitehouse Station, TX, USA), Spring Biosciences clone SP142 (MPDL3280A, Genentech, South San Francisco, CA, USA), and Spring Biosciences clone SP262 (MEDI4736, Astra-Zeneca, London, UK). To date, the properties and concordance between these immunohistochemistry antibodies has not been reported, and only clone SP142 has become commercially available. In addition, the scoring system used in clinical trials and the definition of PD-L1 positivity is different across studies. While some groups consider only the membranous staining of tumor cells to indicate PD-L1 positivity; others score the PD-L1 signal only in tumor-infiltrating lymphocytes. The percentages of positive cells required to consider the case as positive or negative are also dissimilar. Future studies will be required to clarify the optimal immunohistochemistry assay to predict clinical benefit.

Recent studies using validated antibodies in diverse tumor types, including melanoma, lung, SCHN, and breast carcinoma,<sup>15,20-22</sup> suggest that PD-L1 expression may actually be an indication of an ongoing interferon- $\gamma$ -mediated antitumor response resulting in adaptive resistance of the tumor by increased PD-L1 expression. These findings are supported by results obtained using antibody-independent assays to measure *in situ* PD-L1 mRNA transcripts in cancer tissues and by studies showing a positive association between PD-L1 expression and the presence of immune infiltrates.<sup>20,21,23</sup> It has been convincingly demonstrated that PD-L1 protein production is upregulated in certain cells on exposure to interferon- $\gamma$ .<sup>23</sup> In addition, PD-L1 protein expression is regulated by signal transducer and activator of transcription 3 and c-Jun,<sup>24</sup> but their expression on tumor cells is controlled by post-translational mechanisms in the tumor microenvironment.<sup>14</sup> Interaction between PD-1 on activated T-cells and PD-L1 on the surface of tumor cells leads to downmodulation of the T-cell receptor via upregulation of Casitas B-lymphoma (Cbl)-b E3 ubiquitin ligase<sup>25</sup> (Figure 1). PD-L2 expression has been found in macrophages, dendritic cells, and some neoplasms, but its role in the genesis and progression of solid tumors remains largely unexplored. Of note, PD-1 has two to six times more affinity for PD-L2 than for PD-L1,<sup>26</sup> but since PD-L2 is expected not to be commonly present in tumor cells, it has been considered as a less critical mechanism of tumor immune modulation.<sup>5</sup> Further studies screening for PD-L2 expression in various tumors using standardized assays will



**Figure 1** Modulation of the immune inhibitory PD-1/PD-L1 axis for anticancer treatment using monoclonal antibodies.

**Notes:** The diagram indicates the predicted functional interaction between tumor cells, T lymphocytes, and dendritic cells in the tumor microenvironment and highlights the two major mechanisms for PD-1/PD-L1 pathway blockade using monoclonal antibodies against PD-1 (red Ig) and PD-L1 (green Ig). After antigen recognition and activation of T lymphocytes through a TCR/MHC peptide-based interaction, cytotoxic cells become inactive by negative costimulatory signals from the PD-1/PD-L1 axis. Signaling from PI3K and interferon pathways can upregulate PD-L1 in tumor cells. The role and functional modulation of PD-L2 in the antitumor immune evasion and pharmacological blockade of the PD-1/PD-L1 axis is not well understood.

**Abbreviations:** TCR, T-cell receptor; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-1 ligand; PD-L2, programmed death-2 ligand; PI3K, phosphatidylinositol-4 5-bisphosphate 3-kinase; Ig, immunoglobulin; IFN- $\gamma$ , interferon gamma; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

be required to clarify this. The precise contribution of PD-L2 in the effect of PD-1 receptor blockade using monoclonal antibodies is yet to be determined.

Therapeutic approaches blocking the PD-1 pathway demonstrate prominent antitumor responses in preclinical models by augmenting effector T-cell function.<sup>27–30</sup> Several studies demonstrate a synergistic effect of combination of PD-1/PD-L1 blockade with other immunotherapy strategies and chemotherapy.<sup>29,31,32</sup> In vitro studies have shown that blockade of PD-1 signaling on T-cells not only enhances T-cell effector function, but also increases homing to the tumor microenvironment, T-cell proliferation, and cytotoxicity. In general, the PD-1/PD-L1 pathway plays a pivotal role in the regulation of T-cell proliferation in response to persisting antigens. In addition, PD-1/PD-L1 upregulation leads to impaired dendritic cells and depletion of activated memory B-cells.<sup>33</sup>

## PD-1 pathway-targeting agents under clinical development

There are several therapeutic antibodies targeting PD-1 or PD-L1 in clinical development (Table 1). Targeting PD-1 and PD-L1 has lasting antitumor activity in diverse tumor types and some of these compounds are in advanced clinical development. These agents have varying clinical activity and toxicity profiles (Table 2).

### PD-1 inhibitors

#### Nivolumab

Nivolumab (BMS-936558, MDX1106, ONO4538) is a fully human IgG4-blocking monoclonal antibody against PD-1. Since blockade of the axis occurs at the receptor level, nivolumab is expected to inhibit both PD-L1-mediated and PD-L2-mediated signaling (Figure 1). Its half-life is

**Table 1** General characteristics of therapeutic PD-I and PD-L1 monoclonal antibodies

Drug	Company	Isotype	Development stage
PD-I monoclonal antibodies			
Nivolumab, BMS936558, MDX1106	Bristol-Myers Squibb	Fully human IgG4	Phase III
Pidilizumab, CT011	Cure Tech	Humanized IgG1	Phase II
Pembrolizumab, MK3475	Merck	Humanized IgG4	Phase III
PD-L1 monoclonal antibodies			
BMS936559, MDX-1105	Bristol-Myers Squibb	Fully human IgG4	Phase II
MEDI4736	MedImmune	Human IgG1	Phase III
MPDL3280A, RG7446	Roche	Human IgG1	Phase III

**Abbreviations:** Ig, immunoglobulin; PD-I, programmed death-I; PD-L1, programmed death-I ligand.

dose-dependent, ranging from 12 to 20 hours. The maximum tolerated dose was not achieved in the Phase I studies using doses of 0.3, 1, 3, and 10 mg/kg. The most common adverse events associated with nivolumab are fatigue (24%), rash (12%), pruritus (10%), diarrhea (11%), decreased appetite (8%), and nausea (8%). Immune-related adverse events, including colitis, thyroiditis, hepatitis, and pneumonitis, were observed in 18% of patients.<sup>34,35</sup> Adverse events, including immune-related adverse events, were similar across dosing schedules and tumor types, and grade 3/4 toxicities were observed in 15%–20% of patients.<sup>34,36</sup> In an ongoing Phase I (CA209003) trial of nivolumab monotherapy with multiple expansion cohorts, durable responses were noted in patients with refractory advanced solid tumors, including NSCLC, renal cell carcinoma, and melanoma.<sup>34</sup> An objective response rate (ORR) was seen in 22/129 (17%) patients with NSCLC, in 33/107 (31%) subjects with advanced melanoma, and in 10/34 (29%) patients with renal cell carcinoma. Over 50% of the patients with objective responses had a durable benefit for

more than one year, and 70% retained the response (for longer than 4 months) even with discontinuation of treatment after 2 years.<sup>34</sup> In the early Phase I studies of nivolumab monotherapy, patients with PD-L1 protein expression had a 40%–70% ORR compared with <10% in patients lacking PD-L1.<sup>37</sup> In a Phase I trial of nivolumab in combination with platinum doublet therapy in NSCLC, grade 3/4 adverse events were reported in 45% of patients and were comparable with the platinum doublet alone. Grade 3/4 immune-related adverse events requiring discontinuation of nivolumab were most commonly pneumonitis and acute nephritis, and occurred in 15% of patients. The ORR for nivolumab in combination with the platinum doublet was in the range of 33%–47% across treatment arms.<sup>38</sup> Interim analysis of the combination of nivolumab and erlotinib in epidermal growth factor receptor-mutant NSCLC with acquired resistance to erlotinib showed an encouraging ORR of 19%. This combination had a low frequency (24%) of grade 3/4 adverse events.<sup>39</sup> In advanced solid tumors (NSCLC, melanoma, and renal cell

**Table 2** Clinical activity and toxicity profile of PD-I and PD-L1 inhibitors

Drug	Efficacy (ORR)	Toxicity grade $\geq 3$	Pneumonitis
PD-I inhibitors			
Nivolumab, BMS936558, MDX1106	NSCLC, 18% (with platinum doublet chemotherapy ORR 33%) Melanoma, 28% (with ipilimumab ORR 40%) Renal cell carcinoma 27%	14% with monotherapy, 49% with platinum doublet and 53% in combination with ipilimumab	3%
Pidilizumab, CT011	Melanoma, 6% Refractory DLBCL, 51% Refractory follicular lymphoma, 66% (in combination with rituximab)	0%	0%
Pembrolizumab, MK3475	NSCLC, 24% Melanoma, 38%	13%	4%
PD-L1 inhibitors			
BMS936559	NSCLC	9%	0%
MDX-1105	Melanoma		
MEDI4736	Renal cell carcinoma NSCLC, 13% SCHN, 14%	7%	0%
MPDL3280A RG7446	NSCLC, 22% Melanoma, 29% Renal cell carcinoma, 13% Bladder cancer, 43% (in PD-L1+)	13%	0%

**Abbreviations:** DLBCL, diffuse large B-cell lymphoma; NSCLC, non-small cell lung cancer; SCHN, squamous cell head and neck; PD-I, programmed death-I; PD-L1, programmed death-I ligand; ORR, objective response rate.

carcinoma), combination of nivolumab with ipilimumab, a CTLA-4 inhibitor, was feasible and provided a durable ORR regardless of PD-L1 expression.<sup>40,41</sup> Several ongoing Phase II/III trials are underway using nivolumab as a single agent and in combination with chemotherapy or additional immunotherapy in various tumors.<sup>41–44</sup>

### Pembrolizumab

Pembrolizumab (previously known as lambrolizumab or MK-3475) is a humanized monoclonal antibody (IgG4-kappa isotype) targeting the PD-1 receptor. It lacks antibody-dependent cell cytotoxicity. The half-life of the drug is around 2–3 weeks. The maximum tolerated dose was not reached in the Phase I studies at 1, 3 and 10 mg/kg dosing.<sup>45</sup> A Phase I study of MK-3475 (KEYNOTE 001 trial) was conducted in advanced refractory solid tumors including NSCLC and melanoma. Adverse events of any grade were reported in 79% of patients, 13% had grade 3–4 adverse events related to the drug. Of note, 4% of patients had drug-related pneumonitis. Hypothyroidism was reported in 8% of the patients and diarrhea in 20%.<sup>46</sup> In the reported Phase I studies of advanced malignancies, the ORR was approximately 20% in NSCLC and 50% in melanoma.<sup>47–50</sup> In patients with PD-L1 expression, the responses were significantly higher, at ~50% for NSCLC and melanoma and only ~10% in subjects with PD-L1 negative tumors. In another Phase I trial in recurrent/metastatic SCHN, 11/56 of patients had responses (ORR 19.6%) regardless of human papilloma virus status.<sup>51</sup> Pembrolizumab is currently being investigated in combination with different chemotherapy and immunotherapy regimens in various tumors.

### Pidilizumab

Pidilizumab (CT-011) is a humanized IgG1k monoclonal antibody against PD-1. A Phase I study was conducted in 17 patients with hematologic malignancies, of whom eight had acute myeloid leukemia, three had non-Hodgkin's lymphoma, three had chronic lymphocytic lymphoma, one had Hodgkin's lymphoma, one had multiple myeloma, and one had myelodysplastic syndrome.<sup>52</sup> The dose ranges evaluated were between 0.2 and 6 mg/kg. The maximal tolerated dose was not reached. The half-life was between 9 and 17 days, with linear exposure across doses. A clinical response was observed in one third of the patients. One patient with non-Hodgkin's lymphoma had a complete response and four patients achieved stable disease (two with chronic lymphocytic lymphoma, one with Hodgkin's lymphoma, and one with multiple myeloma).<sup>53</sup> A Phase II study of pidilizumab in 72 patients with diffuse large B-cell lymphoma and measurable disease after an autologous hematopoietic stem cell transplant demonstrated

a significant ORR of 51%.<sup>54</sup> Pidilizumab is also being investigated in combination with rituximab in relapsed follicular lymphoma, and was well tolerated with no grade 3–4 toxicities and clinical responses in 19/29 subjects (ORR 66%).<sup>55</sup> In a Phase II trial in advanced melanoma, the ORR was 6% with a one-year survival of 64%.<sup>56</sup>

## PD-L1 inhibitors

### MPDL3280A

MPDL3280A is a fully human monoclonal antibody with an engineered Fc portion targeting PD-L1. Therefore, PD-L2 mediated signaling is not expected to be affected by this agent (Figure 1). This change in the Fc portion is designed to avoid antibody-dependent cell cytotoxicity, thus sparing the bystander immune cells expressing PD-L1. In preliminary Phase I results for 171 patients with refractory and metastatic solid tumors, no maximal tolerated dose was observed. No treatment-related deaths were seen. Grade 3/4 treatment-related adverse events were noted in 13% of patients and only 2% had immune-related grade 3/4 adverse events. No grade 3/4 pneumonitis was seen. A total of 140 patients were evaluable for efficacy, with an ORR of 21% in all patients (22% in NSCLC, 29% in melanoma, and 13% in renal cell carcinoma), and the responses were durable. The response rates were 36% in patients with PD-L1 positive tumors and 13% in PD-L1 negative cases.<sup>57,58</sup> In an expansion cohort of patients with metastatic and refractory PD-L1 positive bladder cancer, 13/30 patients had responses (ORR 43%).<sup>59</sup> Several ongoing trials are investigating the role of MPDL3280A in solid tumors.<sup>60</sup>

### MEDI4736

MEDI4736 is an engineered human IgG1 antibody against PD-L1. It has high affinity and selectivity for PD-L1. Preliminary data from a multi-arm Phase I expansion trial in advanced solid tumors showed indications of clinical activity in various tumors.<sup>61,62</sup> This study included NSCLC, SCHN, melanoma, renal cell carcinoma, and colorectal cancer patients. The drug was well tolerated, with 7% treatment-related grade 3/4 adverse events not requiring therapy discontinuation. Early responses were noted, and a dose of 10 mg/kg every 2 weeks for 12 months was selected for further development of the drug as monotherapy and in combination with other treatments.

### BMS-936559

BMS-936559 (MDX-1105) is a humanized IgG4 monoclonal antibody against PD-L1. In a Phase I study of 207 patients with advanced refractory solid tumors using a dose range of 0.3–10 mg/kg, no maximum dose was defined.<sup>63</sup> The estimated half-life was in the range of 10–15 days. Clinical responses were seen in 9/52 (17%) in melanoma and

5/49 (10%) in NSCLC patients. Grade 3–4 treatment-related adverse events were noted in 9% of the patients. There are currently no ongoing trials with this agent.

## Final remarks and conclusion

After many years of immunotherapy showing only limited results in anticancer treatment, targeting of the PD-1/PD-L1 axis using therapeutic monoclonal antibodies has emerged as an effective strategy. Blockade of PD-1 or PD-L1 induces prominent and lasting clinical responses, with acceptable toxicity in 15%–30% of patients with advanced (and heavily pretreated) tumors. Although further work is required to understand the intimate mechanistic aspects and optimal treatment modalities, a myriad of antibodies are available, many with ongoing clinical trials. Modulation of additional costimulatory and coinhibitory checkpoints (together with PD-1/PD-L1 blockade or alone) is also ongoing and has the potential to expand the current repertoire of immunotherapy options for treating cancer in the near future.

## Disclosure

The authors report no conflicts of interest in this work.

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