

# Improving of Antitumor Immunity and Therapeutic Efficacy of Cancer Vaccines and Adoptive Immunotherapies Using Monoclonal Antibodies

**Review Article**

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**Abstract**

In the past two decades, immunotherapy has become a novel therapeutic modality for cancer patients. In this therapeutic modality, the immune system of patient's body is augmented to acquire the ability of recognition and destruction of tumor/cancer cells. Cancer immunotherapy is divided into two forms: passive immunotherapy and active immunotherapy. In passive immunotherapy monoclonal antibodies or ex vivo-proliferated/activated effector immune cells, especially T cells, are used to destroy malignant cells.

Active immunotherapy is performed using various approaches, such as tumor specific/associated antigens and antigen-loaded dendritic cell vaccines, to generate patient's immune responses against tumor/cancer cells. Recently, some approaches of immunotherapy have been approved by U.S. FDA for use in patients with advanced cancers. However, anticancer efficacy of most immunotherapeutic strategies should be improved to obtain satisfactory results in cancer patients. In this paper, we discuss the application of monoclonal antibodies targeting the cell surface molecules related with the antitumor responses of effector immune cells and their beneficial effects on cancer vaccines and other anticancer therapies.

**Keywords:** Cancer; Immunotherapy; Cancer vaccine; Monoclonal antibody; Immune responses

**Abbreviations:** U.S. FDA: United States Food and Drug Administration; IL: Interleukin; TCR: T Cell Receptor; GITR: Glucocorticoid Induced TNF Receptor Family-Related Protein; TGF- $\beta$ : Transforming Growth Factor- $\beta$ ; TNFRSF-4: Tumor Necrosis Factor Receptor Super Family Member 4; TNF: Tumor Necrosis Factor; Bcl-X<sub>L</sub>: B Cell Lymphoma-Extra Large; Bcl-2: B Cell Lymphoma-2; CTLA-4: Cytotoxic T Lymphocyte Associated Antigen-4; PD-1: Programmed Death-1; Foxp3: Fork-head Box Protein P3; NY-ESO-1: New York Esophageal Squamous-Cell Carcinoma-1; NK: Natural Killer; NKT: Natural Killer T; PD-L: PD-Ligand; MART-1: Melanoma Antigen Recognized By T Cell-1; BCG: Bacillus Calmette-Guerrin

**Introduction**

At present, immunotherapy is a standard therapy for some types of cancer. Immunoadjuvants, monoclonal antibodies, and anticancer vaccines are used in cancer patients. IL-2 is a major cytokine that has been used as an immunoadjuvant in some cancer patients, especially patients with metastatic melanoma [1]. However, toxicity and little therapeutic responses limit its use in cancer patients. In a few studies, vaccination with tumor specific/associated antigens and immunogenic vectors, including melanoma cancer antigen gp100 (gp209-2M) and gp209-2M-expressing fowlpox viral vector, have been successfully used to increase antitumor immune responses [2,3]. In general, cancer vaccines did not induce notable toxicity. However, vaccination of patients with cancer antigens showed limited successes [4-6] and their efficacy was lower than 5%.

In primary studies in 1980s, tumor infiltrating lymphocytes were found to have antitumor activities. In mice, tumor

infiltrating lymphocytes showed potent antitumor effects after in vitro proliferation [7]. Tumor infiltrating lymphocytes from human melanoma tumors were reported to be able to recognize autologous tumor cells in a MHC-restricted manner [8]. Adoptive immunotherapy with autologous tumor infiltrating lymphocytes in combination with exogenous IL-2 induced therapeutic responses (30%) in patients with melanoma [9]. Tumor-reactive tumor infiltrating lymphocytes were also isolated and expanded from other types of cancer, including renal cell carcinoma and glioma [10,11]. However, this therapeutic approach did not have appropriate efficacy in most types of cancer. Effector T cells were also expanded from tumor draining lymph nodes [12,13]. In our study, tumor draining lymph node cells did not show appropriate antitumor activity (unpublished data).

Generation of tumor antigen-specific lymphocytes by vaccination with peptide vaccines such as gp100 did not lead to promising therapeutic antitumor responses [14]. In addition, immunotherapy with transgenic lymphocytes expressing tumor antigen-specific TCRs in mice bearing transgenic tumors expressing the cognate antigen demonstrated that high frequencies of tumor-specific cytotoxic lymphocytes are not sufficient for prevention of tumor growth [15,16]. Thus, generation of tumor-specific T cells via vaccination is not adequate for elimination of established tumors.

Tumor-specific T cells have been reported in tumor tissues, tumor draining lymph nodes, and the peripheral blood of cancer patients. But, tumor-specific T cells compose a little proportion of lymphocyte pool in cancer patients. For example, lower than 1% of peripheral blood lymphocytes and 2-15% of tumor infiltrating lymphocytes were reported to be tumor-specific T cells in human

melanomas [17]. Polyclonal activation of lymphocytes by anti-CD3 and anti-CD28 antibodies as well as IL-2, which are commonly used for ex vivo proliferation of lymphocytes, leads to expansion of both tumor-specific and non-specific lymphocytes and also up-regulation of CD25 on lymphocytes. More importantly, increased levels of regulatory T cells have been observed after polyclonal activation of T cells in the presence of IL-2 [18].

Antigen-specific stimulation of T cells can enhance the number of tumor-specific T cells [19]. Vaccination with tumor antigen-pulsed dendritic cells induced antigen-specific T cells, both in vitro and in vivo. In several murine tumor models, prophylactic dendritic cell vaccines showed suitable efficacy in prevention of tumor growth. However, most therapeutic dendritic cell vaccines were unable to reject established tumors or induce long-lasting delay in tumor growth [20]. These findings indicate that improving the antitumor efficacy of ex vivo expanded lymphocytes, tumor antigen vaccines, and dendritic cell vaccines are necessary.

### Augmenting of antigen-specific responses of antitumor effector immune cells

Triggering of antigen-specific immune responses of effector immune cells is a complex process and needs signaling through several co-stimulatory molecules. On the other hand, immune responses are carefully regulated through various inhibitory mechanisms to prevent autoimmunity and deleterious effects of immune responses on healthy tissues.

Several mechanisms are recruited by tumor/cancer cells to suppress antitumor activity of effector immune cells, including altered expression of MHC class I molecules, expression of Fas ligand, expression of inhibitory molecules such as B7-H1 (PD-L1), production of immunosuppressive soluble agents, as well as the immunosuppressive activity of immunoregulatory cells such as regulatory T cells and myeloid derived suppressor cells [21]. T cells that recognize tumor antigens in the absence of co-stimulatory signals become anergic or may be deleted [22]. Signaling through inhibitory molecules also results in suppression of antitumor activity of effector immune cells. Indeed, lack of signaling of co-stimulatory molecules and/or signaling through inhibitory molecules is an important reason of impaired tumor immunosurveillance in cancer patients. Agonistic/antagonistic monoclonal antibodies targeting these cell surface molecules can be beneficial for augmentation of antitumor immunity. These antibodies have also potential to improve therapeutic efficacy of adoptive immunotherapy and cancer vaccines.

Two decades ago, monoclonal antibodies have been used to enhance antitumor immune responses. In murine tumor models, targeting of several co-stimulatory/inhibitory molecules on the cell surface of effector immune cells by monoclonal antibodies led to increased antitumor immunity [23-26]. Based on satisfactory results from these preclinical studies in mice, a number of clinical trials were performed using monoclonal antibodies targeting cell surface co-stimulatory/inhibitory molecules. At present, some of these antibodies are approved by U.S. FDA for use in cancer therapy. Antagonistic anti-CTLA-4 monoclonal antibody is the earliest antibody that approved by U.S. FDA for use in patients with cancer in 2011.

Several agonistic antibodies for triggering co-stimulatory signals and antagonistic antibodies for blocking inhibitory

molecules on the cell surface of immune cells as well as tumor/cancer cells and tumor stromal cells have been used in various murine tumor models and cancer patients. Some of these antibodies showed beneficial effects on antitumor immunity.

### Agonistic monoclonal antibodies

**Anti-GITR monoclonal antibody:** GITR is expressed on regulatory T cells and other T cell subsets. GITR can deliver a co-stimulatory signal to naïve CD4+ T cells and CD8+ T cells, especially when TCR stimulation is weak [27]. GITR engaging with agonistic antibodies induced cytokine production and proliferation of T cells in vitro [28-29]. In addition, agonistic anti-GITR monoclonal antibodies have been reported to block suppressive activity of regulatory T cells [30,31]. In preclinical studies, Agonistic anti-GITR monoclonal antibody showed antitumor effects in various murine tumor models [32-34]. Anti-GITR monoclonal antibody increased antitumor efficacy of melanoma specific DNA vaccine such as vaccine-induced CD8+ T cell responses in a murine melanoma tumor model [35].

In another murine melanoma tumor model, vaccination with dendritic cells engineered to secrete anti-GITR antibodies had therapeutic effects [36]. Anti-GITR monoclonal antibody in combination with anti-PD-1 monoclonal antibody induced potent antitumor immunity. Importantly, combinational anti-GITR-anti-PD-1 antibody therapy together with chemotherapy (cisplatin or paclitaxel) further increased the antitumor immunity [37]. In patients with head and neck squamous cell carcinoma, regulatory T cells (CD25<sup>high</sup>) infiltrating tumor tissue expressed GITR, IL-10, and TGF- $\beta$ , but, peripheral blood regulatory T cells did not express GITR, IL-10, and TGF- $\beta$ . These GITR expressing tumor infiltrating regulatory T cells showed more suppressive activity than that peripheral blood regulatory T cells [38]. These findings suggest that administration of agonistic anti-GITR monoclonal antibodies as a monotherapy or in combination with other cancer therapy modalities may have beneficial effects.

**Anti-OX40 monoclonal antibody:** OX40 (CD134, TNFRSF4), another member of TNF receptor family is expressed on T cells and acts as a co-stimulatory molecule [39]. This molecule is transiently expressed on T cells upon TCR stimulation. The maximum expression level of OX40 is 48 hours after TCR stimulation and its expression is impeded 72-96 hours later [40]. OX40 ligand is expressed on antigen presenting cells including dendritic cells, macrophages, and B cells as well as endothelial cells after their activation [41,42]. OX40-OX40 ligand interaction leads to production of Th1 cytokines and up-regulation of anti-apoptotic proteins such as Bcl-X<sub>L</sub> and Bcl-2 [43-44].

Agonistic anti-OX40 monoclonal antibodies enhanced antitumor immune responses in several murine tumor models. Anti-OX40 monoclonal antibody increased CD8+ T cell infiltration to tumor tissue and decreased immunosuppression in the tumor [45]. OX40 engagement could deplete or block suppressive activity of regulatory T cells and augmented antitumor immunity [46,47]. Anti-OX40 monoclonal antibody together with chemotherapy (cyclophosphamide) led to apoptosis of regulatory T cells at tumor sites and produced potent antitumor immunity capable of regressing established B16 melanoma tumor [48]. Anti-OX40 monoclonal antibody together with radiotherapy resulted in therapeutic antitumor immunity against lung cancer [49].

Agonistic anti-OX40 monoclonal antibody in combination with antagonistic anti-CTLA-4 monoclonal antibody induced potent effector T cells with antitumor activity in mice [50]. Agonistic anti-OX40 monoclonal antibody in combination with antagonistic anti-PD-1 monoclonal antibody synergistically produced protective antitumor immunity against murine ovarian tumor [51].

Administration of antibodies targeting other cell surface co-stimulatory molecules such as CD28 did not show promising results. In a phase I clinical trial, agonistic anti-CD28 monoclonal antibody (TGN142) induced cytokine-release syndrome in healthy volunteers due to strong activation of T cells and subsequent release of plentiful amount of pro-inflammatory cytokines [52].

### Antagonistic (Blocking/Depleting) monoclonal antibodies

**Anti-CTLA-4 monoclonal antibody:** CTLA-4 is a transmembrane protein expressed on the cell surface of T cells within 24-48 hours after T cell activation. CTLA-4 downregulates immune responses of T cells. This molecule is also expressed constitutively on regulatory T cells [53]. CTLA-4 is structurally homologous to CD28 and competes with CD28 in attachment to CD80 and CD86. In comparison with CD28, CTLA-4 has very more affinity and avidity to CD80 and CD86 molecules and confers an inhibitory signal to T cell [54]. Indeed, CTLA-4 has a crucial role in modulation of activation of naïve T cells and memory T cells. Increased frequencies of CD4+CD25+ T cells expressing high levels of Foxp3 and CTLA-4 were reported in the lymph nodes of patients with B cell non-Hodgkin's lymphoma [55].

In preclinical studies, CTLA-4 blockade was effective in some murine tumor models including glioma, sarcoma, ovarian carcinoma, and bladder carcinoma, but, was ineffective in other tumor types such as breast, prostate, and colorectal tumors [56]. In a phase I pilot study in 2002, for the first time, administration of a single dose of 3mg/kg of Ipilimumab (MDX010, BMS-734016), a human monoclonal antibody against CTLA-4, to patients with inoperable melanoma resulted in durable partial responses in two of 17 patients [57].

In other study, CTLA-4 blockade using anti-CTLA-4 monoclonal antibodies led to cancer regression as well as induction of autoimmunity in patients with metastatic melanoma [58]. Latterly, in several phase II clinical studies, Ipilimumab was used to increase antitumor immunity in patients with metastatic melanoma. Increased patient's survival was observed in some patients treated with Ipilimumab [59-62]. In a phase III clinical trial in patients with advanced melanoma, patients treated with Ipilimumab (10mg/kg) and Dacarbazine showed significantly more survival rate than patients treated with Dacarbazine alone [63]. Administration of Ipilimumab after curative surgery also enhanced significantly overall survival in patients with recurrent advanced melanoma [64].

In a phase II clinical trial, administration of Ipilimumab resulted in some clinical effects in patients with metastatic renal cell carcinoma [65]. Ipilimumab also produced objective responses in patients with prostate cancer [66,67]. In contrast, in a phase III clinical trial, administration of Ipilimumab, when compared to placebo, did not increase overall survival in patients with castration-resistant metastatic prostate cancer pretreated with docetaxel and single dose radiotherapy [68]. Similarly, Ipilimumab

did not produce clinical responses in patients with metastatic pancreatic adenocarcinoma [69]. Combinational therapy with chemotherapy and Ipilimumab had moderated efficacy in patients with non-small cell lung cancer [70]. In a phase II clinical study, Tremelimumab, another human monoclonal antibody against CTLA-4, did not show obvious clinical effects in 45 patients with treatment-refractory colorectal cancer [71]. Drug-related adverse effects were observed in some patients treated with Ipilimumab which were usually manageable. However, a few deaths (less than 1%) were observed after treatment with anti-CTLA monoclonal antibody. In a phase III clinical trial, five patients (1%) died due to the adverse effects of Ipilimumab [64].

In some studies, CTLA-4 blockade has been resulted in improved immune responses to tumor specific/associated antigens. In patients with prostate cancer, CTLA-4 blockade led to decreased levels of Prostate-specific antigen [66]. In patients with melanoma treated with Ipilimumab, patients who had high serum levels of antibodies against NY-ESO-1 and NY-ESO-1-specific CD8+ T cells showed more clinical responses to Ipilimumab [72]. However, this correlation between response to Ipilimumab and appearance of anti-NY-ESO-1 antibodies in patient's sera was not observed in another study [73].

Ipilimumab has also been used in combination with cancer vaccines in patients with metastatic melanoma [74,75]. In a phase III clinical trial in patients with progressive metastatic melanoma pretreated with chemotherapy or IL-2, administration of Ipilimumab with or without a gp100 peptide vaccine improved overall survival, when compared to peptide vaccine alone. Overall survival rates in treated groups, including Ipilimumab, Ipilimumab together with gp100 vaccine, and gp100 vaccine alone, were 10.1 months, 10 months, and 6.4 months, respectively [60].

**Anti-PD-1 monoclonal antibody:** PD-1 (CD279) is expressed on the cell surface of T cells, B cells, NK cells, NKT cells, activated monocytes, and dendritic cells. Interaction of PD-1 with its ligands PD-L1 and PD-L2 triggers an inhibitory signaling in T cells which leads to downregulation of Bcl-X<sub>L</sub> expression and T cell differentiation. On the other hand, signaling through PD-L1 and PD-L2 alters cytokine production and maturation of dendritic cells [76]. These inhibitory signaling pathways help to avoid deleterious effects of immune responses during infection or inflammation. However, these signals can also impair antitumor immune responses [77]. Thus, blocking these pathways may improve antitumor immunity.

Nivolumab (BMS-936558), a human IgG4 anti-PD-1 monoclonal antibody, has been used in several studies to block PD-1 signaling. In a phase I clinical trial in patients with advanced solid tumors, including non-small cell lung cancer, melanoma, prostate cancer, renal cell carcinoma, and colorectal carcinoma (n=236), administration of Nivolumab led to clinical responses in patients with non-small cell lung cancer (18%), melanoma (28%), and renal cell carcinoma (27%). Drug-related adverse events were tolerable [78]. PD-1 blocking resulted in lower toxicities than CTLA-4 blockade. But, pneumonia was reported in 1.5% of patients treated with Nivolumab [79]. In 39 patients with metastatic melanoma, colorectal cancer, castration-resistant prostate cancer, non-small cell lung cancer, renal cell carcinoma, anti-PD-1 monoclonal antibody (MDX-1106) was well tolerated and induced durable complete response in one



patients with colorectal cancer, two partial responses in patients with melanoma and renal cell carcinoma, and significant tumor regressions in two patients with melanoma and non-small cell lung cancer [80]. In patients with hematopoietic malignancies (n=17), PD-1 blocking using anti-PD-1 monoclonal antibody CT-011, a human IgG1 monoclonal antibody against PD-1, produced clinical responses in 33% of patients. One patient with follicular lymphoma completely treated [81]. In previously untreated patients with metastatic melanoma, administration of Nivolumab was associated with significant improved overall survival and progression-free survival when compared to Dacarbazine [79].

Administration of Pembrolizumab (MK-3475), a human IgG4 monoclonal antibody against PD-1, led to long-lasting therapeutic responses in 34% of patients with advanced melanoma. Pretreatment with Ipilimumab or IL-2 did not affect the activity of Pembrolizumab in these patients [82]. Pembrolizumab was also associated with durable antitumor activity in patients with melanoma (one patient with complete response and three patients with partial response), Merkel cell carcinoma (one patient with complete response), and stable disease in patients (15 patients) with other malignancies [83]. New findings indicate that Pembrolizumab is a suitable choice for treatment of Ipilimumab-refractory melanoma [84]. In patients with resected metastatic melanoma (n=33), Nivolumab in combination with a multi-peptide vaccine (gp100, MART-1, and NY-ESO-1 with Montanide ISA 51 VG) was well tolerated and produced immunologic activity with promising survival [85].

In 2014, U.S. FDA approved Keytruda (Pembrozomide) for use in patients with advanced or un-resectable melanoma who are no longer responding to other therapies. Recently, U.S. FDA also approved Opivido (Nivolumab) for the treatment of patients with previously treated metastatic squamous non-small cell lung cancer.

**Anti-PD-L1 monoclonal antibody:** PD-L1 (B7-H1) is expressed on a variety of hematopoietic and non-hematopoietic cells and PD-L2 is expressed on dendritic cells, macrophages, B cells, and mast cells. Expression of these molecules is upregulated in inflammation [86]. More importantly, expression of PD-L1 and, to some extent, PD-L2 is reported in various types of tumor/cancer including ovarian cancer, breast cancer, cervical cancer, colon cancer, non-small cell lung cancer, glioblastoma, pancreatic cancer, gastric cancer, melanoma, and urothelial cancer, as well as hematopoietic malignancies such as Hodgkin's lymphoma, B cell lymphoma, T cell lymphoma, multiple myeloma, acute myeloid leukemia, chronic lymphocytic leukemia, and adult T cell leukemia/lymphoma. Expression of PD-L1 was correlated with disease prognosis in some cancer patients [87-90]. On the other hand, PD-1 has been reported to be expressed at high levels on tumor-specific T cells [91,92]. Thus, interaction of PD-1 on T cells with PD-L1 expressed on tumor cells and immune cells can hamper immune responses of T cells [76].

In patients with urothelial bladder carcinoma, expression of PD-L1 was high in tumor tissue of patients who did not show therapeutic responses to BCG vaccine [93]. These findings indicate that PD-1-PD-L signaling pathways can be an important immunosuppressive mechanism at tumor sites. In a multicenter

phase I clinical trial, anti-PD-L1 monoclonal antibody BMS-936559, a human IgG4 monoclonal antibody against PD-L1, was administered to 217 patients with advanced cancers, including non-small cell lung cancer (n=75), melanoma (n=55), colorectal cancer (n=18), renal cell carcinoma (n=17), ovarian cancer (n=17), pancreatic cancer (n=14), gastric cancer (n=7), and breast cancer (n=4). Anti-PD-L1 monoclonal antibody produced objective responses in patients with melanoma (17%), renal cell carcinoma (12%), and non-small cell lung carcinoma (10%). One patient with ovarian cancer also showed objective response. Drug-related toxicities were lower than that induce by CTLA-4 blockade. Furthermore, pneumonia was not observed in patients treated with this antibody [94]. In a phase I clinical study, administration of anti-PD-L1 monoclonal antibody (MPDL3280A) led to clinical activity in patients with metastatic urothelial bladder carcinoma, and this clinical activity was correlated with PD-L1 expression on tumor infiltrating immune cells [95]. Expression of PD-L1 at tumor sites was correlated with patient's responses to anti-PD-1 monoclonal antibody therapy [96-100]. Other anti-PD-L1 monoclonal antibodies (MPDL3280A and MED14736) also produced objective responses in patients with non-small cell lung cancer, metastatic renal cell carcinoma, metastatic bladder carcinoma, and head and neck squamous cell carcinoma [100-105]. Table 1 shows recently reported clinical trials of anti-PD-1 and anti-PD-L1 monoclonal antibodies in cancer patients.

**Anti-CD25 monoclonal antibody:** Regulatory T cells constitutively express high levels of CD25 on their cell surface. Increased frequencies of regulatory T cells have been reported in most types of cancer and elevated levels of this T cell subset were associated with poor prognosis in some cancer patients. Accordingly, administration of anti-CD25 monoclonal antibody resulted in enhanced antitumor immunity [21]. Co-administration of anti-CD25 and anti-CTLA-4 monoclonal antibodies synergistically decreased suppression of cytotoxic T cells and NK cells [106]. Anti-CD25 monoclonal antibody in combination with IL-12 gene transduction led to rejection of tumors in mice. However, anti-CD25 monoclonal antibody did not affect tumor growth when used as a monotherapy [107].

Anti-CD25 monoclonal antibody can also be used in combination with adoptive immunotherapy or cancer vaccines. But, expression of CD25 is induced on T cells after activation [108] and anti-CD25 monoclonal antibody may deplete these recently activated effector T cells. Therefore, the appropriate time of anti-CD25 monoclonal antibody injection should be considered in combinational therapy of anti-CD25 antibody with adoptive immunotherapy and cancer vaccine. In several studies, depletion of CD25+ regulatory T cells before vaccination has increased vaccine-mediated antitumor immune responses. Anti-CD25 monoclonal antibody as a monotherapy and also in combination with whole tumor cell vaccine (irradiated pancreas adenocarcinoma cells) induced tumor specific immune responses [109]. Furthermore, anti-CD25 monoclonal antibody in combination with dendritic cell vaccine led to long-term immunity against experimental glioma in mice [110]. In a murine melanoma model, combinational therapy with anti-CD25 monoclonal antibody and dendritic cell-tumor fusion vaccine significantly reduced pulmonary metastasis compared to monoclonal antibody or fusion vaccine alone [111].

**Table 1:** Clinical trials in which agonistic and antagonistic antibodies targeting PD-1/ PD-L1 were employed..

Target	Antibody	Cancer Type	Patient's Number	Therapeutic Responses	Reference
PD-1	Pembrolizumab	Progressive metastatic colorectal carcinoma with or without mismatch-repair deficiency	41 patients	Objective response rate and progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair-deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch repair-proficient colorectal cancers.	101
PD-1	Nivolumab	Previously heavily treated relapsed or refractory Hodgkin's lymphoma	23 patients	Objective response was observed in 20 patients (87%), including 17% with a complete response and 70% with a partial response. Three patients (13%) had stable disease. The rate of progression-free survival at 24 weeks was 86%.	102
PD-1	Nivolumab	Advanced treatment-refractory melanoma	107 patients	Objective responses were observed in 31% of patients (33 of 107) with melanoma. Seven of 107 patients (7%) experienced stable disease lasting for 24 weeks or more. Overall survival rates of 62% at 1 year and 43% at 2 years were achieved, with a median overall survival of 16.8 months.	103
PD-1	Lambrolizumab	Advanced melanoma	135 patients	The confirmed response rate, evaluated by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was 38%.	104
PD-1	Nivolumab	Advanced melanoma, non-small cell lung cancer, castration-resistant prostate cancer, renal cell cancer, and colorectal cancer	296 patients	Among 236 patients in whom response could be evaluated, objective responses (complete or partial responses) were observed in 18% of patients with non-small cell lung cancer (14 of 76 patients), 28% of patients with melanoma (26 of 94 patients), and 27% of patients with renal cell cancer (9 of 33 patients).	78
PD-1	Nivolumab	Advanced metastatic melanoma, colorectal cancer, castrate-resistant prostate cancer, non-small cell lung cancer, and renal cell carcinoma	39 patients	Durable complete response was observed in one patient with colorectal cancer and partial responses were observed in two patients with melanoma and renal cell carcinoma. Two patients with melanoma and non-small cell lung cancer experienced significant lesional tumor regressions not meeting partial response criteria.	80
PD-L1	BMS-936559	Non-small cell lung cancer, melanoma, colorectal cancer, renal cell cancer, ovarian cancer, pancreatic cancer, gastric cancer, and breast cancer	207 patients	Durable objective Response rate of 6 to 17% and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) were observed in patients with non-small cell lung cancer, melanoma, and renal cell cancer.	94
PD-L1	MPDL3280A	Different tumor types (including locally advanced or metastatic solid tumors, and hematological malignancies)	175 patients	Complete and partial responses (evaluated by Response Evaluation Criteria in Solid Tumors, version 1.1) were observed in 32 of 175 (18%) patients with all tumor types. Complete and partial responses were observed in 11 of 53 (21%), 11 of 43 (26%), 7 of 56 (13%), and 3 of 23 (13%) of patients with non-small cell lung cancer, melanoma, renal cell carcinoma, and other tumors (including colorectal cancer, gastric cancer, and head and neck squamous cell carcinoma), respectively.	105

PD-L1	MPDL3280A	Metastatic bladder cancer	68 patients	For patients with a minimum of 6 weeks of follow-up, objective response rates were 43% (13 of 30) for patients with high level of PD-L1 expression in tumor tissues and 11% (4 of 35) for patients with low/without PD-L1 expression in tumors.	98
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## Conclusion

In cancer patients effector immune cells do not respond to cancer cells. Indeed, cancer cells recruit several mechanisms to evade from cancer immunosurveillance. These mechanisms also impede the therapeutic efficacy of cancer vaccines and adoptive immunotherapies. Augmenting of co-stimulatory signaling and modulation of inhibitory signaling in effector immune cells may induce antitumor immunity. Monoclonal antibodies that target co-stimulatory/inhibitory molecules on the cell surface of effector immune cells, tumor cells, and tumor stromal cells can be a promising approach for enhancing of antitumor immune responses. At present, some of these antibodies are approved by U.S. FDA for use in patients with some advanced cancers which are refractory to other cancer therapy modalities. Agonistic/antagonistic monoclonal antibodies can be used in combination with cancer vaccines and adoptive immunotherapies, and even with conventional cancer therapies, to improve their therapeutic efficacy.

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