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The role of antagonists of the PD-1:PD-L1/PD-L2 axis in head and neck cancer treatment

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Abstract

We review the current clinical knowledge surrounding one of the most promising immune checkpoint pathways currently investigated in head and neck squamous cell carcinoma patients, programmed cell death-1 (PD-1) and its ligands (PD-L1 and PD-L2). We review ongoing clinical trials and associated clinical responses observed with targeting the receptor, PD-1, and its ligand, PD-L1. A recent phase III clinical trial (Checkmate 141) demonstrated an improved overall survival in head and neck cancer patients treated with anti-PD-1 monotherapy as compared to standard of care for recurrent and/or metastatic disease, which raises questions on how best to incorporate immunotherapy in the context of standard of care. We discuss biomarkers of response to this class of novel drugs, which is an area of active investigation. Lastly, we project future directions in the field wherein understanding how the Fc portions of the various monoclonal antibodies may impact their clinical efficacy as well as discuss areas where our next advances may take place, such as combination strategies.

Keywords

PD-1; PD-L1; PD-L2; B7-H1; Immune checkpoint; Squamous cell carcinoma; Head and neck cancer; Immunotherapy

Introduction

The specificity and plasticity of the immune system make it an ideal tool for the treatment of cancer, with the potential to eradicate heterogeneous tumor cell populations with limited toxicity to normal tissue. The effector arm of cancer immunotherapy is regulated by both

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positive and negative co-signaling pathways – coined immunologic “checkpoints.” In healthy individuals, these effector cells are part of a remarkable system, which endows the host with the plasticity to mount a vigorous response to antigen challenge, while simultaneously limiting the extent and duration of the response, as a means to prevent autoimmunity. Unfortunately, dysregulation of these immune checkpoints can create a permissive environment for cancer development [48] and may also be usurped by cancer cells and the surrounding tumor microenvironment, thereby contributing to peripheral immune tolerance and tumor immune evasion [18].

Tumor infiltrating lymphocytes are thought to represent a host immune response directed against antigens expressed on tumor cells. Head and neck squamous cell carcinomas (HNSCC) have a relatively high mutational burden with approximately 181 somatic mutations per megabase and are also observed to have a high infiltration of immune cells, which suggests that they may be immunogenic through the expression of self-epitopes, neo-epitopes and/or virus-associated epitopes derived from oncogenic viruses, such as those from human papillomavirus (HPV) or Epstein Barr virus (EBV) [62,35]. The biologic relevance of host anti-cancer immune responses is evidenced by the fact that the degree of infiltration of CD4+ and CD8+ T cells within head and neck cancer correlates with prognosis [28,2,46,69]. However, despite the generation of effector immune cells targeting the heterogeneous cancer cell population, the cancer is able to persist and grow through adaptation and natural selection of clonal cancer cell populations that are able to evade immune recognition and clearance through mechanisms such as loss of HLA expression and/or upregulation of inhibitory immune checkpoint ligands [60,21,42,51].

To date, the best understood T cell co-signaling pathways which regulate T cell activation and proliferation are those of the CD28 and B7 superfamilies [12,13,68]. Cytotoxic T lymphocyte associated protein 4 (CTLA-4), also known as CD152, is a member of the immunoglobulin superfamily that is expressed by activated T cells and transmits an inhibitory signal to T cells. It is homologous to the T cell co-stimulatory protein, CD28, and binds to B7-1 (CD80) and B7-2 (CD86) on antigen presenting cells. CTLA-4 is constitutively expressed on regulatory T cells (Tregs) and is only upregulated in conventional T cells after activation and when bound to its ligands downregulates T cell immune responses. Another critical immune checkpoint which downregulates host immune responses and which has taken center stage in the immuno-oncology field is Programmed cell Death 1 (PD-1). PD-1 belongs to the CD28 family and is characterized as an inhibitory receptor expressed on T cells, dendritic cells (DC), natural killer (NK) cells, macrophages and B cells. In animal models of chronic viral infection and in HIV-infected humans, chronically antigen-exposed virus-reactive T cells can enter a state of “exhaustion” mediated to some extent by PD-1 expression/ligation [3,16,52,65]. Indeed, disease progression in HIV-1 infected individuals is associated with the upregulation of PD-1 on circulating HIV-specific CD8+ T cells which stands in contrast to those patients whose disease does not progress long term [76]. These PD-1 expressing T cells have impaired antiviral activity, and accumulation of exhausted virus-specific T cells correlates with an inability of the immune response to control viral replication during chronic HIV infection. Several studies have suggested a similar role for PD-1 in mediating T cell exhaustion in advanced solid cancers,

including bladder, gastric, head and neck, hodgkins lymphoma, melanoma, merkel cell, non-small cell lung, ovarian, renal cell, and triple negative breast cancer [63,29,41,50].

PD-1 mediated T cell signaling, characterized by altered cytotoxic killing, cytokine production and/or T cell proliferation, is dependent upon binding of its ligands, PD-L1 (B7-H1) or PD-L2 (B7-DC), which are upregulated in many human solid tumors, including head and neck cancers [66,18,12,13,3,5,14,70,63,42,74,73]. Tumor infiltrating CD8+ T cells in head and neck cancers have high levels of PD-1 expression and, in the setting of PD-L1 expression, these PD-1+ CD8+ T cells are functionally impaired which may facilitate tumor growth despite the presence of tumor specific CD8+ T cells in the tumor microenvironment [2,42].

The PD-1 ligands, PD-L1 and PD-L2, belong to the B7 superfamily, which also includes B7-1 (CD80), B7-2 (CD86), B7-H2, B7-H3, B7-H4 and B7-H6 [12,13]. Importantly, despite their nomenclature, PD-L1 and PD-L2 binding is not restricted to PD-1, as PD-L1 and PD-L2 bind CD80 and RGMb, respectively (Fig. 1) [49,7,72]. PD-L1 can be expressed by T cells, B cells, myeloid dendritic cells (DC) and in tissue macrophages in the lung, kidney, liver, heart and placenta [18,32]. PD-L1 expression has also been reported in the crypts of normal tonsil tissue located in Waldeyer's ring, suggesting that the tonsillar crypts may be an immune privileged site which limits host immune responses against certain foreign antigens [42].

PD-L2 expression is present primarily on antigen presenting cells, such as macrophages and dendritic cells, but can be induced on a wide variety of other immune and non-immune cells [54,73]. Despite the limited expression of PD-L1 and PD-L2 in normal tissue, they are both inducible and constitutively expressed on many solid and hematologic malignancies, including HNSCC [19,18,33, 47,71,26,45,6,4,70,58,73].

PD-1 blockade

The relevance of the PD-1:PD-L1 checkpoint in cancer immunity is highlighted by reports which demonstrate that blockade of PD-1 or PD-L1 by specific monoclonal antibodies can reverse the anergic state of tumor-specific T cells and thereby enhance antitumor immunity [18,61]. This translated to the clinic, and on September 4, 2014, the U.S. Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab, (KEYTRUDA, Merck Sharp & Dohme Corp.) for the treatment of patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication was approved based on tumor response rates and the durability of responses. This was followed in December of 2014 by U.S. FDA approval of nivolumab (OPDIVO, Bristol-Myers Squibb Company) for the treatment of previously treated unresectable or metastatic melanoma.

The roles of pembrolizumab and nivolumab in head and neck cancer therapy have also been explored. In a phase Ib trial of recurrent and/or metastatic (R/M) HNSCC (Keynote 012), PD-1 blockade with Pembrolizumab achieved a response rate of 20% at a dose of 10 mg/kg administered every 2 weeks in patients whose tumors were enriched for PD-L1 expression.

The expansion cohort of Keynote 012 included 132 patients who were not selected for tumor PD-L1 expression and the patients received a fixed dose of pembrolizumab (200 mg every 3 weeks). Of 117 patients evaluated, the overall objective response rate (ORR) was 24.8%, and when stratified by HPV status, 26.3% in HPV-negative patients and 20.6% in HPV-positive patients. Approximately 25% of patients had stable disease during therapy, for an overall disease control rate (DCR) of approximately 50%. Importantly, responses were durable, with 86% of patients still having a response at a median follow up of 5.7 months. Side effects included fatigue (15%), hypothyroidism (9.1%), decreased appetite (7.6%), and rash (7.6%). Serious side effects occurred in <10% of patients. A total of 4 patients experienced serious immune-related adverse events that included 2 patients with pneumonitis and 2 with colitis [57]. Long-term follow-up from KEYNOTE 012 demonstrated an ORR of 18% (34 of 192) in R/M HNSCC patients treated with pembrolizumab. When stratified by HPV status, there was an observed 16% ORR in HPV-negative patients and 24% ORR in HPV-positive patients. The median time to respond was 2 month (range, 2–17 months) and 24% of responders had a complete response (CR). 85% of responses lasted for more than 6 months and 71% of responses lasted for more than 12 months. Median PFS was 2 months (range, 1.9–2.1 months) and median OS was 8 months (range, 6–10 months) with a 6-month OS of 58% and a 12-month OS of 38%. Overall, Pembrolizumab demonstrated a promising ORR with durable responses [44].

Two phase III trials are ongoing with Pembrolizumab: Keynote 040 evaluates Pembrolizumab as a single agent in platinum refractory R/M HNSCC compared to standard of care chemotherapy and Keynote 048 evaluates the efficacy and safety of Pembrolizumab as monotherapy or in combination with chemotherapy relative to standard of care for the first line treatment of patients with R/M HNSCC. Approximately 780 patients will be enrolled and randomly assigned 1:1:1 to either Pembrolizumab alone, Pembrolizumab + platinum + 5-FU, or cetuximab + platinum + 5-FU.

In a randomized, phase III clinical trial (Checkmate 141), 361 patients with R/M cancer of the oral cavity, pharynx, or larynx were randomized in a 2:1 ratio to receive Nivolumab (N = 240) or investigator's choice (cetuximab, methotrexate, or docetaxel) (N = 121). All patients progressed on or within 6 months of the last dose of platinum-based therapy. Most patients received 2 systemic therapies and over 90% had received prior radiation therapy. Nivolumab was administered intravenously at 3 mg/kg every 2 weeks. Nivolumab was found to double the 1-year overall survival (OS) rates compared to investigator's choice (36%, [95% CI:28.5–43.4] versus 16.6%, [95% CI:8.6–26.8]) and reduced the risk of death by 30% in R/M HNSCC patients [27]. Median overall survival was 7.5 months (95% CI:0.51–0.96) with Nivolumab treatment as compared to 5.1 months (95% CI:4.0–6.0) with conventional chemotherapeutic agents (HR = 0.70 [95% CI:0.51–0.96] p = 0.0101). Interestingly, the benefit of Nivolumab was observed in both HPV-positive and HPV-negative HNSCC patients. In HPV-positive HNSCC patients, the median OS was 9.1 months with Nivolumab versus 4.4 months with conventional treatments (HR, 0.56; 95% CI, 0.32–0.99) and in HPV-negative HNSCC patients, the median OS was 7.5 months versus 5.8 months (HR, 0.73; 95% CI, 0.42–1.25).

The most common side effects with this class of drug are often auto-immune related and include rash, itching, cough, upper respiratory tract infections, and edema. The most serious side effects are severe immune-mediated side effects involving normal tissue, such as the lung, colon, liver, kidneys, and endocrine glands. The following immune-mediated adverse reactions occurred in less than 1% of patients treated with anti-PD1: dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures, adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis. In head and neck cancer patients, pembrolizumab was well tolerated with 6% of patients discontinuing due to a treatment-related AE but there were no treatment-related deaths [44]. Grade 3 treatment-related adverse events were observed in 13.1% of all patients receiving Nivolumab versus 35.1% of patients on standard chemotherapies [27].

PD-L1 blockade

Rather than targeting the PD-1 receptor, other groups have focused their efforts on targeting its ligand, PD-L1. Durvalumab (MEDI4736) is a selective, high affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. The Fc fragment of Durvalumab contains mutations designed to eliminate antibody-dependent cell-mediated (ADCC) and/or complement-dependent cytotoxicity (CDC), which may minimize any potential side effects of the drug. There is a low incidence of anti-drug antibody development and there is no binding to PD-L2, which may play a role in controlling inflammation in normal lung tissue and, therefore, may help to avoid PD-L2-mediated immune related toxicities.

A phase I/II global, multicenter, open-label study evaluated the safety and efficacy of Durvalumab (MEDI4736) in patients with R/M solid tumors (HNSCC, NSCLC, pancreatic adenocarcinoma, melanoma, gastroesophageal cancer, triple-negative breast cancer, hepatocellular carcinoma, and 8 additional tumor types, www.clinicaltrials.gov NCT01693562). The study employed a standard 3 + 3 dose escalation, followed by a dose expansion phase in which patients received 10 mg/kg every 2 weeks. Patient enrollment was independent of tumor PD-L1 status. Forty percent of the patients had human papillomavirus (HPV)-associated HNSCCs. As of April 2015, 62 HNSCC patients had been treated in the dose expansion phase, and ORR were higher in patients with PD-L1(+) expressing tumors (18%, 95% CI 5.2–40.3%) vs PD-L1(–) HNSCC (8%, 95% CI 1.7–21.9%). Among the 62 treated patients, DCR (CR, PR, SD for 24 weeks) and ORR were 15% and 11%, respectively [55].

There are two ongoing phase III trials with Durvalumab in R/M HNSCC patients. The EAGLE study evaluates Durvalumab (MEDI4736) as monotherapy or in combination with anti-CTLA-4 compared to standard of care chemotherapy in platinum refractory R/M HNSCC (NCT02369874). The KESTREL study also evaluates Durvalumab (MEDI4736) as either monotherapy or in combination with anti-CTLA-4 as compared to first line standard of care (EXTREME regimen) in the treatment of R/M HNSCC patients (NCT0255159). Table 1 lists all ongoing clinical trials in R/M HNSCC patients being treated with anti-PD-1 and/or anti-PD-L1 blockade.

Biomarkers of response

Understanding tumor and/or patient characteristics that might predict who will or will not respond to a particular therapy facilitates personalized patient care and allows the most efficient use of healthcare resources. In the first reported phase I study of anti-PD-1 therapy (Nivolumab), 39 patients with solid tumors refractory to conventional therapy were treated with a single dose of anti-PD-1 antibody. There was 1 durable complete response and 2 partial responses. Among 9 patient tumor biopsies studied, three of the four patients who exhibited membranous PD-L1 staining experienced tumor regression. The group reported a correlation between membranous PD-L1 expression on tumor cells and the likelihood of response to treatment [5].

Subsequently, intratumoral PD-L1 expression was evaluated in a larger cohort of patients treated with Nivolumab. Pre-treatment biopsies obtained from 42 patients were available to assess the role of intratumoral PD-L1 expression in the modulation of the PD-1: PD-L1 axis. Of the 17 patients in this study with PD-L1(–) tumors, none had an objective response; whereas, 9 of the 25 patients (36%) with PD-L1(+) expressing tumors had an objective response ($p = 0.006$) to anti-PD-1 monotherapy [55]. Correlation between response and PD-L1 expression has also been observed in R/M HNSCC [27,64,57,55].

Since clinical responses have been observed in a subset of PD-L1 negative patients undergoing treatment with PD-1 blockade, efforts are ongoing to identify additional biomarkers of response to this immunotherapeutic agent. As PD-1 binds to both PD-L1 and PD-L2, Yearley et al. investigated the expression of PD-L2 in different tumor types and evaluated the potential role it may play in predicting clinical responsiveness to anti-PD-1 therapies. The investigators developed a new assay, which was tested in human archival tumor tissue of different types of cancer and compared to standard immunohistochemistry (IHC) labeling of the same sample (range: $p = 0.0012$ to $p < 0.0001$). PD-L2 protein expression was shown to significantly correlate with levels of PD-L2 mRNA in the tumor samples, which were quantitated using Nanostring (range: $p = 0.0037$ to $p < 0.0001$) [73].

Subsequently, the group evaluated the potential relevance of PD-L2 expression in multiple solid cancer types among patients treated with Pembrolizumab and found that PD-L1 expression can be discordant with PD-L2 expression. However, in HNSCC, there was a good concordance between PD-L1 and PD-L2 protein expression. In 144 R/M HNSCC patients treated with Pembrolizumab (Keynote 012), logistic regression analysis suggested PD-L2 expression had a trend toward higher ORR after adjusting for PD-L1 expression ($p = 0.072$) and PD-L2 was positively associated with longer PFS after adjusting for the impact of PD-L1 status ($p = 0.031$). The results of the study suggested that PD-L2 status could be predictive of outcomes in Pembrolizumab treated HNSCC patients.

Currently, PD-L1 remains the most validated predictive biomarker of response to blockade of the PD-1:PD-L1 axis across multiple solid tumor types. However, the observation that not all PD-L1 positive patients respond, and that benefit has been seen in some PD-L1 negative patients, underscores the need for additional predictive biomarkers. Reports of interferon-gamma (IFN- γ) expression or inflammatory signatures, MHC Class II expression, pre-

treatment CD8+ T cell density, and PD-L1 and CD8+ T cell co-localization at the invasive margin are also demonstrating promise as biomarkers predictive of response to PD-1:PD-L1 blockade [67,37,31].

Another promising area of biomarker investigation is tumor mutational landscape and neoantigen expression. Retrospective analysis of advanced melanoma patients treated with anti-CTLA-4 mAb and NSCLC patients treated with anti-PD-1 mAb revealed that higher somatic mutational burden was significantly associated with improved clinical response [59,53]. The predictive nature of tumor mutational load was validated in a prospective phase II study with Pembrolizumab, wherein patients with mismatch repair-deficient colorectal cancer and other solid tumors had objective response rates of 40% and 71% respectively, compared to 0% response rates in mismatch repair-proficient colorectal cancer [36]. However, high mutational burden may be necessary but not sufficient to predict response to immune checkpoint blockade. In melanoma, some patients with high mutational burden did not show clinical benefit with anti-CTLA-4 blockade, and rather the presence of an immunogenic neoantigen signature was a more powerful predictor of clinical benefit [59]. While a higher burden of somatic mutations can lead to increased neoantigens, not all neoantigens are immunogenic [56].

Retrospective analysis suggests that it is not just a high burden of neoantigens expressed by tumors, but rather the presence of “clonal neoantigens”, i.e. neoantigens that are expressed by all tumor cells, that induce an immune response and predict for a greater clinical benefit from immune checkpoint blockade [43]. Interestingly, in patients with NSCLC most of the neoantigens observed were attributed to smoking induced mutations [56]. An equivalent analysis has not been done in HNSCC, however this may have implications, especially for HPV negative patients.

Future directions

The efficacy of blockade of the PD-1:PD-L1 axis across multiple solid tumors has brought with it exciting questions and future implications. One question is whether there is any difference in efficacy between currently available anti-PD-1 mAb and anti-PD-L1 mAbs, as a result of differences in receptor ligand interactions and fragment crystallizable (Fc) domains. Anti-PD-1 mAbs additionally block the interaction of PD-L2 and PD-1 and anti-PD-L1 mAbs the interaction of PD-L1 and CD80. The clinical significance of these differences is unclear, and currently there is an ongoing phase I trial investigating the combination of anti-PD-L1 and anti-PD-1 mAb (NCT02118337).

Differences also exist between the Fc portion of currently available mAbs targeting PD-1 and PD-L1, which affect interaction with Fc γ receptor (Fc γ R) expressing effector cells, and may have therapeutic implications. In mice, engagement of activating Fc γ Rs by anti-PD-1 mAb led to decreased efficacy through ADCC mediated decrease in CD8 TILs, whereas with anti-PD-L1 mAb, this same engagement led to increased efficacy through ADCC mediated depletion of myeloid cells in the tumor microenvironment [15]. Thus Fc:Fc γ R mediated ADCC may increase the efficacy of anti-PD-L1 mAbs but decrease the efficacy of anti-PD-1 mAb. While both Pembrolizumab and Nivolumab are IgG4 mAbs with low

affinity for FcγRs, most currently available anti-PD-L1 mAbs are of the IgG1 isotype and vary in their ability to induce ADCC. Further study of the effect of Fc:FcγR interaction is needed in humans. Table 2 lists the currently available mAbs and their associated characteristics.

Efficacy as single agents has launched investigation into combination with other immunotherapy agents as well as standard of care therapies including chemotherapy and radiation. As described above, anti-PD-1 and PD-L1 mAbs are already being combined with chemotherapy in R/M HNSCC. Based on preclinical data showing the immunogenic effects of radiation and synergy with anti-PD-1 or anti-PD-L1 mAb blockade [75,17], trials are ongoing and continue to be developed, incorporating these agents in the reirradiation setting and with concurrent chemoradiation as part of definitive therapy or adjuvant therapy in the locally advanced setting. These trials will begin to answer the powerful question as to how immunotherapy can be combined with chemotherapy and radiation in the upfront setting to improve outcomes. This is particularly important for HPV negative HNSCC where survival is still poor and has not improved over time [11]. Other combinations which are actively being explored in head and neck cancer include combinations with vaccines aimed to enhance T cell frequency (NCT 02432963; NCT 02626000). Other potential combinations include those which may modulate the function of immunosuppressive cells within the tumor microenvironment, such as regulatory T cells (Tregs) or myelosuppressive dendritic cells (MSDCs).

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Fig. 1.

B7 superfamily receptor-ligand interactions on T cells and antigen presenting cells. CD28 and CTLA-4 bind CD80 (B7-1) and CD86 (B7-2) [23,40,38,39,1,22,24,30,10,20]. PD-1 binds PD-L1 (B7-H1) and PD-L2 (B7-DC) [25,34,66,18]. CD80 (B7-1) also binds PD-L1 (B7-H1) [8,9,49] and RGMb binds PD-L2 (B7-DC) [72].

Table 1

Active clinical trials in recurrent/metastatic head and neck squamous cell carcinoma patients which target the PD-1:PD-L1 pathway.^a

Phase	Target	Monoclonal antibody	Company	www.clinicaltrials.gov
<i>Monotherapy</i>				
I/II	PD-1	Nivolumab (BMS-936558)	Bristol-Myers Squibb	NCT02488759
II	PD-1	Pembrolizumab (MK-3475)	University Health Network, Toronto/Merck	NCT02644369
II	PD-1	Pembrolizumab (MK-3475)	Washington University School of Medicine/Merck	NCT02296684
II	PD-1	Pembrolizumab (MK-3475)	University of Cincinnati/Merck	NCT02641093
III	PD-1	Pembrolizumab (MK-3475)	Merck	NCT02358031
III	PD-1	Pembrolizumab (MK-3475)	Merck	NCT02252042
I	PD-L1	Atezolizumab (MPDL3280A)	Genentech	NCT01375842
I	PD-L1	Avelumab (MSB0010718C)	EMD Serono/Merck	NCT01772004
II	PD-L1	Durvalumab (MEDI4736)	Astrazeneca	NCT02207530
III	PD-L1	Durvalumab (MEDI4736)	Astrazeneca	NCT02551159
<i>Combination therapy</i>				
I	PD-1	Nivolumab + cetuximab + motolimod	VentiRx Pharmaceuticals Inc	NCT02124850
I	PD-1	Nivolumab + FPA008	Five Prime Therapeutics, Inc	NCT02526017
I	PD-1	Pembrolizumab (MK-3475) + enadenotucirev	PsiOxus Therapeutics/INC Research	NCT02636036
I	PD-1	Pembrolizumab (MK-3475) + JAK1 inhibitor (INCB029110) or PI3Kdelta inhibitor (INCB050465)	Incyte Corporation	NCT02646748
I	PD-1	Pembrolizumab (MK-3475) + MGA271	MacroGenics	NCT02475213
I	PD-1	Pembrolizumab (MK-3475) + radiation	Thomas Jefferson University/Merck	NCT02318771
I	PD-1	Pembrolizumab (MK-3475) + cisplatin + radiation	Sanford Health/Merck	NCT02586207
Ib	PD-1	Pembrolizumab (MK-3475) + talimogene laherparepvec	Amgen/Merck	NCT02626000
Ib/II	PD-1	Pembrolizumab (MK-3475) + lenvatinib	Eisai Inc	NCT02501096
Ib/II	PD-1	Pembrolizumab (MK-3475) + PLX3397 (CSF1R)	Plexxikon/Merck	NCT02554812
I/II	PD-1	Pembrolizumab (MK-3475) + docetaxel	Medical University of Vienna/Merck	NCT02718820
I/II	PD-1	Pembrolizumab (MK-3475) + epacadostat (INCB025460)	Incyte Corporation/Merck	NCT02178722
I/II	PD-1	Nivolumab + epacadostat	Incyte/Bristol-Myers Squibb	NCT02327078
I/II	PD-1	Nivolumab + Varlilumab (CDX-1127, anti-CD27)	Celldex/Bristol-Myers Squibb	NCT02335918
II	PD-1	Nivolumab + stereotactic body radiotherapy (SBRT)	Memorial Sloan Kettering Cancer Center/University of Chicago	NCT02684253
II	PD-1	Pembrolizumab (MK-3475) + reirradiation	University of Maryland/Merck	NCT02289209
II	PD-1	Pembrolizumab (MK-3475) + ACP-196	Acerta/Merck	NCT02454179
I	PD-L1	Atezolizumab (MPDL3280A) + CPI-444 (adenosine-A2A receptor target)	Corvus/Genentech	NCT02655822
I	PD-L1	Durvalumab (MEDI4736) ± Tremelimumab	Astrazeneca	NCT02262741
I	PD-L1	Durvalumab (MEDI4736) + Tremelimumab + chemotherapy	Astrazeneca	NCT02658214

Phase	Target	Monoclonal antibody	Company	www.clinicaltrials.gov
I	PD-L1	Durvalumab (MEDI4736) + mogamulizumab	Kyowa Hakko Kirin Pharma/Astrazeneca	NCT02301130
I	PD-L1	Durvalumab (MEDI4736) + selumetinib	Astrazeneca	NCT02586987
Ib/II	PD-L1	Avelumab (MSB0010718C) + PF 05082566 (4-1BB)	Pfizer	NCT02554812
I/II	PD-L1	Durvalumab (MEDI4736) ± AXD9150 or AZD5069	Astrazeneca	NCT02499328
I/II	PD-L1	Durvalumab (MEDI4736) + epacadostat	Incyte/MedImmune	NCT02318277
I/II	PD-L1	Durvalumab (MEDI4736) + Tremelimumab + polyICLC	Ludwig Institute for Cancer Research/MedImmune	NCT02643303
I/II	PD-L1	Atezolizumab (MPDL3280A) + Varlilumab (CDX-1127, anti-CD27)	Celldex/Genentech	NCT02543645
III	PD-L1	Durvalumab (MEDI4736) ± Tremelimumab	Astrazeneca	NCT02551159
III	PD-L1	Durvalumab (MEDI4736) ± Tremelimumab	Astrazeneca	NCT02369874

^aAs of April 15, 2016.

Table 2

Monoclonal antibodies targeting the PD-1:PD-L1 pathway.

Monoclonal antibody	Company	Target	Isotype	ADCC ^a
Nivolumab (BMS-936558)	Bristol-Myers Squibb	PD-1	IgG4	No
Pembrolizumab (MK-3475)	Merck	PD-1	IgG4	No
MEDI0680 (AMP-514)	MedImmune	PD-1	IgG4	No
PDR001	Novartis	PD-1	IgG4	No
Durvalumab (MEDI4736)	Astrazeneca/MedImmune	PD-L1	IgG1	No
Atezolizumab (MPDL3280A)	Genentech/Roche	PD-L1	IgG1	No
Avelumab (MSB0010718C)	Pfizer/Merck KGaA	PD-L1	IgG1	Yes

^aAntibody-dependent cell-mediated cytotoxicity.