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Harnessing the power of the immune system via blockade of PD-1 and PD-L1: a promising new anticancer strategy

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Abstract

Cancer cells employ several mechanisms to evade the immune system of their host, thus escaping immune recognition and elimination. Of particular interest is a cancer cell's ability to co-opt the immune system's innate ligands and inhibitory receptors (also known as checkpoints), thus creating an immunosuppressive microenvironment that downregulates T-cell activation and cell signaling. The recent development of the checkpoint inhibitors anti-programmed death-1 and anti-programmed death ligand-1 has generated an enormous amount of interest as a potential new anticancer strategy in solid tumors, particularly in non-small-cell lung cancer, renal cell carcinoma and melanoma. Data suggest significant disease response rates using anti-programmed death-1 and anti-programmed death ligand-1 antibodies, even in heavily pretreated patients. Future directions include optimization of drug delivery sequence and combination of immunotherapy with other therapies including cytotoxic chemotherapy, radiation, antiangiogenic agents and small-molecule tyrosine kinase inhibitors.

Keywords

antibody; cancer; checkpoint inhibitor; immunotherapy; melanoma; non-small-cell lung cancer; PD-1; PD-L1/2; renal cell carcinoma

Cancer & the immune system

Cancer cells have genetic and epigenetic abnormalities that drive the production of antigens used by the immune system to distinguish tumor cell from self. The expression of these non-self-antigens by the tumor and their identification by the host results in the ability of the host

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system to determine both tumor quantity and quality [1]. This process, known as immunoediting, occurs in three phases: elimination, equilibrium and escape [1]. The elimination phase (also referred to as immunosurveillance) refers to the process in which the host's innate immune system eradicates tumor cells existing at a microscopic level. Tumor cells that are not destroyed during this initial phase go into the equilibrium phase or latent period, during which the adaptive immune system regulates the immunogenicity of tumor cells and prevents tumor growth. However, because tumor cells are inherently genetically unstable, variants that can evade the host's adaptive immune system eventually emerge. These variant cells enter the escape phase either by being unidentifiable to the host or resistant to the host's immune response, or by actively evading identification by inducing an immunosuppressive microenvironment [2].

In order to avoid identification by the adaptive immune system, these tumor cells appear to co-opt the immune system's natural inhibitory ligands and receptors (also known as checkpoints) in order to turn off T-cell activation and signaling [3]. In addition, cancer cells downregulate the MHC class I molecules, further inhibiting the immune cascade, including the ability to recognize and destroy nascent tumor [1]. The ability of cancer cells to escape antitumor T-cell activity in this way is now recognized as a trademark of cancer development and progression [4]. In that setting, a tremendous interest in using immune-mediated therapies as an anticancer strategy has developed, resulting in the emergence of several new treatment modalities, including vaccine-based approaches and agents that target coinhibitory or costimulatory immune checkpoints. Immune checkpoints are molecules expressed on immune cells that modulate the T-cell response to antigens by either upregulating (costimulatory pathways) or downregulating (coinhibitory pathways) immune signaling. Ipilimumab is approved for use in melanoma as an antibody that blocks the cytotoxic T-lymphoctye-associated antigen 4. Several immunomodulatory antibodies or small molecules targeting the programmed death-1 (PD-1) coinhibitory pathway are currently in advanced clinical development for the treatment of solid tumors. Their development and potential future uses will be discussed in this review.

PD-1 is a coinhibitory receptor that downregulates T-cell activity in peripheral tissues during inflammatory states caused by infection, thereby limiting collateral tissue damage and preventing autoimmunity [3]. PD-1 is activated by interacting with its ligands, programmed death ligand-1 (PD-L1; also known as B7-H1) and programmed death ligand-2 (PD-L2; also known as B7-DC) [5], which are upregulated during inflammation. PD-L1 is upregulated on diverse cell types in response to certain proinflammatory cytokines (primarily IFN-γ), while PD-L2 is upregulated on dendritic cells and macrophages in response to different inflammatory cytokines, most notably IL-4 [6,7]. The physiologic coexpression of receptor and ligand during inflammatory states prevents excessive T-cell tissue destruction at those sites. As a demonstration of this biology, PD-1 and PD-L1 knock-out mice demonstrate amplified tissue response to infection or mild strain-specific and organ-specific autoimmune disease later on in life [3].

Tumor cells may upregulate PD-L1 as a way to locally dampen the host immune response and therefore escape damage and destruction. PD-L1 has been found to be upregulated on several types of solid tumor cells, including non-small-cell lung cancer (NSCLC), pancreatic

cancer, ovarian cancer, breast cancer, glioblastoma multiforme, colon cancer and gastric cancer [8–14], as well as in some hematologic malignancies [12,15–18], thus limiting local T-cell responses to tumor [19,20]. In addition, the majority of tumor-infiltrating lymphocytes express PD-1 [21,22]. Although data are mixed, some studies suggest that in several tumor types, increased expression of PD-L1 on the surface of tumor cells correlates with poor clinical outcomes [14,19,23–24]. These findings have led to the hypothesis that blocking the PD-1:PD-L1/PD-L2 interaction might increase local T-cell activity at the tumor site and induce an immune-mediated response [25,26]. As a consequence, several anti-PD-1 and anti-PD-L1 antibodies have been developed (Table 1) and are currently undergoing late-stage clinical trial investigation for the treatment of advanced renal cell carcinoma (RCC), melanoma and NSCLC.

Anti-PD-1 & anti-PD-L1 clinical trials in general solid tumor malignancies

In 2010, a multi-institutional, open-label Phase I clinical trial demonstrated a tolerable safety profile and preliminary antitumor activity of the anti-PD-1 antibody nivolumab (BMS-936558/MDX-1106/ONO-4538) in patients with advanced solid tumors [27]. Nivolumab is a genetically engineered, fully human IgG_4 monoclonal antibody specific for human PD-1. The antibody contains an engineered hinge region mutation (S228P) that prevents IgG_4 molecule exchange [27]. It binds to PD-1 with high affinity, thereby blocking its interactions with PD-L1 and PD-L2. Finally, it increases cytokine release and tumor antigen-specific T-cell division [27]. In total, 39 patients with metastatic melanoma, colorectal cancer (CRC), castration-resistant prostate cancer, NSCLC and RCC received nivolumab in dose-escalating cohorts, using doses of 0.3, 1, 3 and 10 mg/kg. The maximum tolerated dose was not reached. Notable grade 3 and 4 toxicities included decreased CD4 count (17.9%), lymphopenia (2.6%), hypocalcemia (2.6%), ascites (2.6%), colitis (2.6%), fatigue (2.6%) and anemia (2.6%). The only serious adverse event reported was inflammatory colitis that developed in a patient with melanoma following five doses of drug at 1 mg/kg. Objective responses (ORs) were observed starting at the 3 mg/kg dose level, where a patient with multiorgan metastatic RCC experienced a complete response (CR) that lasted 21 months. At the 10 mg/kg dose level, two partial responses were seen (RCC and melanoma), one CR was seen (CRC) and two mixed responses were seen. Tumor biopsies were obtained from nine patients and were analyzed by immunohistochemistry for expression levels of PD-L1. Lack of PD-L1 expression correlated significantly with lack of response to anti-PD-1 therapy ($p = 0.0476$) [27].

Subsequently, a large Phase IB trial enrolled 304 patients with heavily pretreated advanced solid tumor malignancies. Patients with melanoma (107), NSCLC (129), castration-resistant prostate cancer (17), RCC (34) or CRC (19) received nivolumab at doses of 1, 3 or 10 mg/kg every 2 weeks; a maximum tolerated dose was not reached. Treatment-related toxicities of all grades were seen in 72% (220 out of 304) of patients. Grade 3 and 4 toxicities were observed in 15% (45 out of 304) of patients. Of note, there were three treatment-related deaths secondary to pneumonitis, thought to be due to immune activation. Antitumor activity was observed in patients with NSCLC, RCC and melanoma. Among the 129 patients with NSCLC, 22 (17%) ORs were observed across all tested doses. Durable disease stability (≥24 weeks) was observed in 13 (10%) patients. Among the 107 patients with

melanoma, 33 (31%) ORs were observed across all tested doses. Half of the responders had a duration of response beyond 1 year. Durable disease stability was seen in an additional seven (7%) patients. Among the 34 patients with RCC, ORs were observed in ten (29%) patients and durable disease stability was seen in an additional nine (27%) patients. Pretreatment tumor tissue from 42 patients (melanoma, NSCLC, CRC, RCC and castration-resistant prostate cancer) was analyzed for PD-L1 expression by immunohistochemistry, with positivity defined as ≥5% PD-L1 expression. PD-L1 positivity was seen in 17 out of 38 tumors analyzed. Importantly, none of the patients with PD-L1-negative tumors had a response to treatment [28].

The authors presented long-term follow-up data on this study in May at the 2013 American Society of Clinical Oncology (ASCO) meeting. They reported that, of the 54 total responders in melanoma, RCC and NSCLC who had at least 1 year of follow-up, 28 of the responses had lasted 1 year or more. Of particular interest was the prolonged duration of responses in NSCLC lasting a median of 17 months. Median overall survival (OS) of the cohort was as follows: 16.8 months in patients with melanoma, 9.6 months in patients with NSCLC and >22 months in patients with RCC [29,30].

Data have also been reported on the safety and efficacy of BMS-936559, an anti-PD-L1 antibody. In a Phase I study, 207 patients with NSCLC (75), melanoma (55), CRC (18), RCC (17), ovarian cancer (17), pancreatic cancer (14), gastric cancer (7) and breast cancer (4) were enrolled and received the antibody in escalating doses every 2 weeks for up to 16 weeks. Treatment-related grade 3 and 4 toxicities occurred in 9% of patients. Overall, 81 (39%) patients experienced a toxicity that was potentially immune mediated. These included hypothyroidism, rash, hepatitis, sarcoidosis, myasthenia gravis, diabetes mellitus and endophthalmitis. Nine of these patients required treatment with glucocorticoids with resolution or improvement of symptoms. ORs (CR or PR) were observed in patients with melanoma, NSCLC, RCC and ovarian cancer and were seen at all dose levels at or above 1 mg/kg. Among the 52 melanoma patients, nine achieved an OR, including three who had a CR. An additional 14 patients had durable disease stabilization (≥24 weeks). Among the NSCLC patients, five patients had an OR and six additional patients had durable disease stabilization. Among the 17 RCC patients, two had an OR and seven additional patients had durable disease stabilization [31].

In addition, a study by Herbst *et al*. using the anti-PD-L1 antibody MPDL3280A in doses of 1–20 mg/kg in patients with advanced solid tumor malignancies demonstrated an overall response rate (ORR) of 21%. When the analysis was subdivided into patients with PD-L1-positive and PD-L1-negative tumors, it became evident that those with PD-L1-positive tumors had an ORR of 39% while those with PD-L1-negative tumors had an ORR of 13% [32].

A Phase I study using MK-3475, an anti-PD-1 monoclonal antibody, in patients with solid tumor malignancies was presented at the ASCO annual meeting in 2012. Nine patients with advanced solid tumor malignancies were treated with MK-3475 at doses of 1–10 mg/kg. One patient with melanoma achieved a partial response. Three additional patients had stabilization of disease [33].

There are several currently ongoing studies that are summarized in Table 2.

Anti-PD-1 & anti-PD-L1 clinical trials in melanoma

Combining PD1/PD-L1 modulating agents with cytotoxic chemotherapy, targeted therapy or alternate immune checkpoint antibodies is an attractive strategy with the potential for enhanced antitumor activity. Particularly promising data have recently been reported from a Phase I trial combining nivolumab with the anti-cytotoxic T-lymphoctye-associated antigen 4 antibody, ipilimumab [32]. In this study, 86 patients with advanced-stage melanoma were randomized to receive nivolumab at 1 mg/kg concurrently or sequentially with ipilimumab at 3 mg/kg; 53 patients received concurrent therapy while the remaining 33 received sequential treatment. Toxicities were more common in the concurrent group, with grade 3–4 toxicities occurring in 42% of patients receiving concurrent therapy and in 18% of patients receiving sequential therapy. The most common toxicities in both groups included lipase elevation, hepatic disorders (e.g., alanine aminotransferase or aspartate aminotransferase elevation), nonfatal pneumonitis, gastrointestinal disorders (e.g., diarrhea), renal disorders and rash. Hypophysitis was also a notable toxicity. This study reported an unprecedented ORR of 40% in the concurrently treated group of patients, with 16 patients (53% of the responders) having at least an 80% reduction in tumor burden. In the sequentially treated group, the response rate was 20%, with four patients having at least an 80% reduction in tumor burden [37].

Another recent Phase I study enrolled 135 patients with advanced melanoma who were treated with the anti-PD-1 antibody MK-3475 at doses of 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks or 2 mg/kg every 3 weeks (only patients without prior ipilimumab exposure). Patients had either been treated previously with ipilimumab (n = 48) or with at least two prior lines of non-ipilimumab therapy (n = 87). Across all groups, grade 3–4 toxicities were seen in 13% of patients and included hypo-/hyperthyroidism, diarrhea, abdominal pain, decreased appetite, fatigue, aspartate aminotransferase elevation, renal failure, rash and pruritus. Treatment-related pneumonitis was seen in 4% of patients, but none of the cases were above grade 2 in severity. Response rates were assessed by two criteria: standard Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and by immune-related response criteria [38]. Immune-related response criteria attempt to account for the unusual patterns of response that may be seen with immune-based therapeutics; these include initial increase in tumor size followed by regression and even initial appearance of new tumors before response. These response patterns are thought to be due to the infiltration of activated immune cells around sites of tumor, both clinical and subclinical. Using the RECIST 1.1 criteria in the MK-3475 Phase I study, ORR across all groups was 38%, with the highest response rate in the group receiving MK-3475 10 mg/kg every 2 weeks (52% ORR). Using the immune-related response criteria, ORR across all groups was 37%, with the highest response rate in the group receiving MK-3475 10 mg/kg every 2 weeks (56% ORR). Progression-free survival (PFS) across all groups was found to be over 7 months and, at the time of publication, the median OS had not yet been reached [14].

Finally, in a Phase I study of the anti-PD-L1 antibody MPDL3280A, 45 patients with advanced melanoma were treated at doses of 1–20 mg/kg every 3 weeks with an ORR of 26% and PFS of 35% at 24 weeks [27].

Several ongoing studies were presented at the 2013 ASCO annual meeting. Five of these clinical trials are currently using nivolumab in patients with advanced melanoma, both ipilimumab-treated and ipilimumab-naive [39–43]. The fourth trial uses MK-3475 [44]. At this time, toxicity and response details have not yet been completely reported. These studies are summarized in Table 3.

Anti-PD-1 & anti-PD-L1 clinical trials in renal cell carcinoma

Prior to the recent ASCO meeting, no dedicated trials treating RCC with anti-PD-1 or anti-PD-L1 agents had been reported. However, as previously discussed, Phase I trials in which patients with RCC had been enrolled reported promising response rates in RCC to both anti-PD-1 and anti-PD-L1 antibodies. At the annual ASCO meeting this year, several studies dedicated to patients with RCC were reported. Most are ongoing and details have not yet become fully available regarding outcomes and toxicities. Highlights included a Phase I trial in which 34 patients with RCC (44% of whom had received at least three prior therapies) received nivolumab at 1 or 10 mg/kg. Grade 3–4 toxicities were seen in 21% of patients. ORR was 29% and PFS was 58% at 24 weeks. In addition, 70% of patients were alive at 1 year and 52% at 2 and 3 years [23]. In another RCC-specific report, 53 patients with RCC received MPDL3280A at doses ranging from 3 to 20 mg/kg. At the time of report, 39 patients were evaluable for efficacy. Grade 3–4 toxicities were seen in 43% of patients and included hypophosphatemia, fatigue and dyspnea. Although ORR was not yet reported, 50% of the cohort were free from tumor progression at 24 weeks [14]. A comprehensive table of the relevant clinical trials is presented in Table 4.

Anti-PD-1 & anti-PD-L1 clinical trials in NSCLC

Much like in RCC, dedicated trials of anti-PD-1 and anti-PD-L1 therapy in patients with NSCLC have not yet been published; however, promising signals of activity for both anti-PD-1 and anti-PD-L1 therapies in NSCLC have been observed in Phase I studies in diverse solid tumors. Spigel *et al.* presented the data on NSCLC patients who received the anti-PD-L1 antibody MPDL3280A. The antibody was administered to 53 patients with advanced NSCLC at doses ranging from 1 to 20 mg/kg every 3 weeks. Grade 3–4 toxicities were seen in 34% of patients and included pericardial effusion, dehydration, fatigue and dyspnea. Of the 34 evaluable patients, an ORR was seen in 24%, and 48% had PFS at 24 weeks [49]. In follow-up data on the NSCLC subset from the nivolumab Phase I study, patients were stratified by histology (squamous or nonsquamous). OR rate was 17%, with a prolonged median duration of response lasting 17 months. OS in the squamous versus nonsquamous patients at 1 year did not differ significantly (44 and 41%, respectively). However, OS at 2 years was significantly better in the squamous cell lung group (44%) compared with the non-squamous cell lung group (17%) [50].

More recently, Garon *et al.* presented data from a Phase I trial of MK-3475, a highly selective anti PD-1 antibody. The preliminary data revealed that, of 38 patients with

advanced NSCLC, an ORR of 24% was seen by immune-related response criteria (irRC) and 21% by RECIST v.1.1. However, when patients were stratified by PD-L1 expression, the ORR in the PD-L1-high group was 67% (irRC) or 57% (RECIST), in contrast to an ORR of 4% (irRC) or 9% (RECIST) in the PD-L1-negative group [51]. One case of grade 3 pulmonary edema was seen. Based on these data, a Phase II/III trial of MK-3475 versus single-agent docetaxel is currently underway. In addition, Soria *et al.* presented further data from a Phase I trial using the anti-PD-L1 antibody MPDL3280A in solid tumor malignancies. As in the Garon study, PD-L1 expression by immunohistochemistry was predictive of response, as was smoking status. ORR was 46% in those with intermediate PD-L1 expression and 83% in the small number of patients with the highest level of PD-L1 expression. Smoking history was also predictive of response, with a 26% ORR in smokers versus a 10% ORR in nonsmokers. The 24-week PFS was 44% in patients with squamous histology and 46% in patients with nonsquamous histology. MPDL3280A was well tolerated overall, with grade 3 or 4 adverse events reported in nine (11%) patients. There were no reports of grade 3–5 diarrhea or pneumonitis [52].

Of additional interest is an ongoing Phase III registration trial comparing nivolumab at 3 mg/kg every 2 weeks versus single-agent docetaxel in patients with NSCLC (squamous and nonsquamous subtypes) who have failed platinum-doublet or tyrosine kinase inhibitor therapy (if EGF receptor or anaplastic lymphoma kinase positive) [53,54]. A comprehensive table of the relevant clinical trials is presented in Table 5.

Future perspective

While significant progress has been made in the development of immune checkpoint modulation as a therapeutic strategy, much work remains to be done. Despite efforts to develop PD-L1 expression as a reliable bio-marker of response to the anti-PD-1 and anti-PD-L1 antibodies, results to date have been mixed [56,57]. Currently, we are developing a neoadjuvant study of nivolumab in NSCLC that will aim to collect both pre- and post-treatment tumor tissues. We hope that this will allow comprehensive immune profiling of the tumor microenvironment to further tailor immunotherapies. Similar studies are underway in other tumor types. Priming strategies are also being explored with the aim of exploiting either antigen exposure after initial highly effective therapy (e.g., erlotinib in EGF receptor-mutant NSCLC) or altered tumor gene expression following hypomethylating therapy. Combinational strategies with other immune checkpoint modulators are also underway, for example: dual inhibition of the coinhibitory immune checkpoints killer immunoglobulin-like receptor (KIR), lymphocyte activation gene 3 protein (LAG3) or T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3) with an anti-PD-1 antibody. Finally, preclinical data combining anti-PD-1 antibodies with vaccines [58], adoptive T-cell immunotherapy [59] and radiation [60] have also emerged and show promise for the future. A summary of the currently ongoing trials is presented in Table 6.

Conclusion

The dance between PD-1 and its two ligands, PD-L1 and PD-L2, is an innate way in which the body prevents excess tissue damage by T cells and the development of autoimmunity during infection-mediated inflammation. Tumor cells manipulate this mechanism to escape

from the host's adaptive immune system. The recent development of several anti-PD-1 and anti-PD-L1 antibodies marks the beginning of an exciting revolution in the management of certain malignancies, most notably NSCLC, RCC and melanoma. In the case of NSCLC, this is the first time that immunotherapy has shown activity in a historically 'nonimmunogenic' tumor, and results show improved durable response rates in comparison with second-line docetaxel chemotherapy, particularly when one considers that patients receiving immunotherapy have a higher median number of prior therapies [66,67]. Several Phase I trials have shown significant promise in this arena and many additional studies are currently underway, as was highlighted by the presentations at the 2013 ASCO conference. Significant challenges remain, in particular elucidating the optimal sequence and combination of immunotherapy with other therapies such as cytotoxic chemotherapy, radiation, antiangiogenic agents and small-molecule tyrosine kinase inhibitors. It is hoped and anticipated that the next wave of clinical studies will help answer these important questions.

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Executive summary

Immunoediting rids the body of potential cancers

- Tumors express unique antigens that lead to recognition by the innate immune system via a process known as immunoediting.
- Immmunoediting has three phases: elimination, equilibrium and escape.
- Elimination: the innate immune system eradicates microscopic tumor cells.
- Equilibrium: tumor cells not eliminated during the first phase enter the latent phase, during which the adaptive immune system regulates them and prevents growth.
- Escape: due to genetic instability, variants emerge that evade the host immune system by being unidentifiable, resistant to the immune response or by actively inducing an immunosuppressive microenvironment.

The immune system self-regulates via a system of inhibitory receptors and ligands; cancer cells co-opt this system to create an immunosuppressive state

- To prevent excessive tissue damage and autoimmunity during inflammation, programmed death-1 (PD-1) is activated by its ligands programmed death ligand (PD-L)1/B7-H1 and PD-L2/B7-DC. Activation leads to dampening of the T-cell response.
- PD-L1 is upregulated in certain solid and hematologic tumor types.
- Elevated expression of PD-L1 in tumors is correlated with poor clinical outcomes.
- Downregulation of MHC class I molecules also inhibits the immune cascade and prevents recognition and destruction of nascent tumor cells.

Checkpoint inhibitors increase the local immune response to tumors

- It has been hypothesized that blocking the PD-1/PD-L1/2 interaction may increase T-cell response to tumors and result in their destruction.
- Several PD-1 and PD-L1 antibodies have been generated and are being tested in clinical trials.

Trial results are encouraging

- Clinical responses to some solid tumors, particularly non-small-cell lung cancer, renal cell carcinoma and melanoma, are very encouraging.
- Responses appear to be durable and the toxicity profile of the antibodies is acceptable.
- Patients with active autoimmune illness have been excluded from all trials to this point and, as expected, the most notable toxicities are of autoimmune origin (including but not limited to pneumonitis, thyroiditis and hepatitis).

Future directions

- Many trials presented at the American Society of Clinical Oncology 2013 annual meeting are currently underway.
- Combinations of PD-1 and PD-L1 antibodies with other agents such as cytotoxic drugs, tyrosine kinase inhibitors and antiangiogenic medications need to be studied further.

Table 1

Currently used anti-programmed death-1 and anti-programmed death ligand-1 antibodies.

Target	Drug	Molecule	Common dose (mg/kg)
Anti-PD-1	Nivolumab (BMS-936558/MDX-1106/ONO-4538) MK-3475	Fully human IgG_4 Humanized IgG_4	0.1–10 1–10
Anti-PD-L1	MPDL3280A BMS-936559/MDX-1105 MEDI-4736	Engineered human IgG_1 Fully human IgG_4 Engineered human IgG_1	1–20 0.3–10 In Phase I trials

PD-1: Programmed death-1; PD-L1: Programmed death ligand-1.

Table 2

Phase I/II trials of anti-programmed death-1 and anti-programmed death ligand-1 in general populations of solid tumor malignancies.

Trial (authors, year)	Drug/dose	Patients	Grade 3–4 toxicities (n, %)	Overall response rate (%)	PFS (%)	Overall survival (months)	Ref.
PD-1							
Phase II experience with MDX-1106 (ONO-4538), an anti-PD-1 monoclonal antibody, in patients with selected refractory or relapsed malignancies (Brahmer *et al.*, 2009)†	Nivolumab/10 mg/kg	21 patients with refractory solid tumor malignancies	None	One patient with RCC had PR lasting 5 months; MXR seen in two melanoma patients	Not yet reported	Not yet reported	[34]
A Phase I study of single-agent anti-PD-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics and immunologic correlates (Brahmer *et al.*, 2010)	Nivolumab/0.3, 0.1, 3 and 10 mg/kg	39 patients with advanced solid tumor malignancies	Anemia (1, 2.6) Decreased CD4 (7, 17.9) Lymphopenia (1, 2.6) Hypocalcemia (1, 2.6) Ascites (1, 2.6) Colitis (1. 2.6) Fatigue (1, 2.6) Musculoskeletal (2, 5)	CR (2.6) PR (5) MXR (5)	Not reported	Not reported	[27]
Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS 936558/ONO-4538) in patients with advanced refractory malignancies (Sznol *et al.*, 2010)‡	Nivolumab/1, 3 and 10 mg/kg	16 patients with advanced solid tumor malignancies (recruitment for expansion cohort is ongoing)	None. One possible drug-related MDS in a melanoma patient	Six responses: RCC (one PR, one CR), NSCLC (one PR), melanoma (three PRs)	Not reported	Not reported	[35]
Safety, activity and immune correlates of anti-PD-1 antibody in cancer (Topalian *et al.*, 2012)	Nivolumab/0.1, 3 and 10 mg/kg	296 patients with advanced solid tumor malignancies	Pneumonitis, fatal (3, 1) Diarrhea (3) Pruritus (1) ALT increase (2) TSH increase (1) AST increase (2) Hypothyroidism (1) Hyperthyroidism (1) Infusion reaction (1)	Melanoma (28) NSCLC (18) RCC (27)	Melanoma at 24 weeks (41) NSCLC at 24 weeks (26) RCC at 24 weeks (27)	Not reported	[28]
Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors (Patnaik *et al.*, 2012)§	MK-3475/1, 3 and 10 mg/kg	Nine patients with advanced solid tumor malignancies	None	One patient with melanoma had PR; stable disease in three other patients	Not reported	Not reported	[33]
Nivolumab in patients with advanced solid tumors: survival and long-term safety in a Phase I trial (Topalian *et al.*, 2013)¶	Nivolumab/0.1–10 mg/kg	304 patients with advanced solid tumor malignancies	Any grade 3–4 toxicity (45, 15) Pneumonitis, fatal (3, 1)	Melanoma (31) NSCLC (16) RCC (29)	Not reported	Melanoma (16.8) NSCLC (9.6) RCC (>22)	[29]
PD-L1							

Trial (authors, year)	Drug/dose	Patients	Grade 3–4 toxicities (n, %)	Overall response rate (%)	PFS (%)	Overall survival (months)	Ref.
Safety and activity of anti-PD-L1 antibody in patients with advanced cancer (Brahmer *et al.*, 2012)	BMS-936559/ MDX-1109/0.3, 1, 3 and 10 mg/kg	207 patients with advanced solid tumor malignancies	Any grade 3–4 toxicity (9%) Infusion reaction (1, <1) Adrenal insufficiency (1, <1)	Melanoma (17) NSCLC (10) RCC (12)	Melanoma at 24 weeks (42) NSCLC at 24 weeks (31) RCC at 24 weeks (53)	Not reported	[31]
PD-1/PD-L1 pathway as a target for cancer immunotherapy: safety and clinical activity of BMS-936559, an anti-PD-L1 antibody, in patients with solid tumors (Tykodi *et al.*, 2013)¶	BMS-936559/MDX-1109/1, 3 and 10 mg/kg	162 patients with advanced solid tumor malignancies	Any grade 3–4 toxicity (14, 8.6)	Melanoma at 10 mg/kg (18) NSCLC at 10 mg/kg (28) RCC (18)	Not reported	Not reported	[36]
A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors (Herbst *et al.*, 2013)¶	MPDL3280A/≤1 to 20 mg/kg	171 patients with locally advanced or metastatic solid tumors	Any grade 3–4 toxicity (39%) No pneumonitis over grade 2	21 PD-L1 positive (39) PD-L1 negative (13)	At 24 weeks (44)	Not reported	[32]

†American Society of Clinical Oncology 2009 annual meeting abstract.

‡American Society of Clinical Oncology 2010 annual meeting abstract.

§American Society of Clinical Oncology 2012 annual meeting abstract.

¶American Society of Clinical Oncology 2013 annual meeting abstract.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CR: Complete response; MDS: Myelodysplastic syndrome; MXR: Mixed response; NSCLC: Non-small-cell lung cancer; death-1; PD-L1: Programmed death ligand-1; PFS: Progression-free survival; PR: Partial response; RCC: Renal cell carcinoma; TSH: Thyroid-stimulating hormone.

Table 3

Clinical trials of anti-programmed death-1 and anti-programmed death ligand-1 in melanoma.

Phase/trial (author, year)	Drug/dose	Patients	Grade 3–4 toxicities (n, %)	Overall response rate (%)	PFS (%)	OS (months)	Ref.
Phase I							
Nivolumab plus ipilimumab in advanced melanoma (Wolchok *et al.*, 2013)	Nivolumab/1 mg/kg; ipilimumab 3 mg/kg; given either concurrently or sequentially	86 patients with advanced melanoma (stage III or IV)	Concurrent group: Any grade 3–4 toxicity (22, 42) Lipase elevation (3, 6) Hepatic disorder (8, 15) Pneumonitis, nonfatal (1, 2) Gastrointestinal disorder (5, 9) Renal disorder (3, 6) Rash (2, 4) Hypophysitis (1, 2) Sequential group: Any grade 3–4 toxicity (6, 18) Elevated lipase (2, 6) Amylase elevation (1, 3) Adrenal insufficiency (1, 3) Hypophysitis (1, 3)	Concurrent group: Overall response rate (40) (16 patients with ≥80% tumor reduction) Sequential group: Overall response rate (20) Four patients with ≥80% tumor reduction	Not reported	Not reported	[37]
Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma (Hamid *et al.*, 2013)	MK-3475/10 mg/kg every 2–3 weeks, 2 mg/kg every 3 weeks	135 patients with advanced melanoma (ocular excluded) who had either been treated with ipilimumab (n = 48) or two other prior lines of therapy (n = 87)	Any grade 3–4 toxicity (17, 13) Hypothyroidism (1) Diarrhea (1) Abdominal pain (1) Fatigue (2) Decreased appetite (1) AST elevation (2) Renal failure (2) Rash (3) Pruritus (1)	Overall response rate (38) 10 mg/kg every 2 weeks (52) 10 mg/kg every 3 weeks (27) 2 mg/kg every 3 weeks (25)	>7 months	Median OS not yet reached	[45]
Survival and long-term follow-up of safety and response in patients with advanced melanoma in a Phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538) (Sznol *et al.*, 2013)[†]	Nivolumab/0.1–10 mg/kg (expansion cohort)	107 patients with advanced melanoma	Any grade 3–4 toxicity (21%) Lymphopenia (3%) Lipase elevation (2%) Diarrhea (2%) Endocrine disorder (2%) Hepatitis (1%)	31	Not reported	Median OS (16.8) At 1 year: 50 patients at risk At 2 years: 24 patients at risk At 3 years: one patient at risk	[30]
Phase II							
Clinical activity, safety and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (Hamid *et al.*, 2013)[†]	MPDL3280A/1–20 mg/kg every 3 weeks	45 patients with advanced melanoma	Any grade 3–4 toxicity (33%) Hyperglycemia (7%) ALT elevation (7%) AST elevation (4%)	Overall response rate (26)	At 24 weeks (35)	Not yet reported	[46]

[†]American Society of Clinical Oncology 2013 annual meeting abstract.

ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase; OS: Overall survival; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; PFS: Progression-free survival.

Table 4

Clinical trials of anti-programmed death-1 and anti-programmed death ligand-1 in renal cell carcinoma.

Phase/trial (authors, year)	Drug/dose	Patients	Grade 3–4 toxicities	Overall response rate (n, %)	PFS (%)	OS (%)	Ref.
Survival, safety and response duration of nivolumab anti-PD-1 (BMS 936558; ONO-4538) in a Phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): long term patient follow-up (Drake *et al.*, 2013)[†]	Nivolumab/1 or 10 mg/kg	34 patients with mRCC, 44% with ≥3 prior therapies	Any grade 3–4 toxicity (21%) Hypophosphatemia (6%) Respiratory disorder, nonfatal (6%)	10, 29	At 24 weeks (58)	At 1 year (70) At 2 years (52) At 3 years (52)	[47]
Clinical activity, safety and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with mRCC (Cho *et al.*, 2013)[†‡]	MPDL3280A/3–20 mg/kg	53 patients with mRCC, 83% with prior systemic therapy (39 evaluable for efficacy by July 2013)	Any grade 3–4 toxicity (43%) Hypophosphatemia (4%) Fatigue (4%) Dyspnea (4%) Hyperglycemia (4%) (Of 39 patients reported)	Not yet reported	At 24 weeks (50)	Not yet reported	[48]

[†]American Society of Clinical Oncology 2013 annual meeting abstract.

[‡]This trial is ongoing.

mRCC: Metastatic renal cell carcinoma; OS: Overall survival; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; PFS: Progression-free survival.

Table 5

Clinical trials of anti-programmed death-1 and anti-programmed death-ligand 1 in non-small-cell lung cancer.

Trial	Drug/dose	Patients	Grade 3–4 toxicities (n, %)	Overall response rate (%)	PFS (%)	OS (%)	Ref.
A Phase I study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) plus platinum-based doublet chemotherapy (PT doublet) in chemotherapy-naive NSCLC patients (Rizvi *et al.*, 2013)†	Nivolumab/10 mg/kg every 3 weeks	43 patients with NSCLC who had failed ≥1 chemotherapy regimen (arm A: squamous; arm B: nonsquamous; arm C: combination)	Any grade 3–4 toxicity (21, 49) Pneumonitis (3, 7) Rash (2, 5) Nephritis (1, 2) Colitis (1, 2)	Arm A: 33 Arm B: 33 Arm C: 31	Not reported	Not reported	[55]
Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic NSCLC (Spigel *et al.*, 2013)†	MPDL3280A/1–20 mg/kg every 3 weeks	53 patients with advanced NSCLC evaluable at time of presentation	Any grade 3–4 toxicity (34%) Pericardial effusion (6%) Dehydration (4%) Dyspnea (4%) Fatigue (4%)	Of 37 patients reported (24) PD-L1^{+} (100) PD-L1^{-} (15)	At 24 weeks: 48	Not reported	[56]
Survival and long-term follow-up of the Phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with previously treated advanced NSCLC (Brahmer *et al.*, 2013)†	Nivolumab/1, 3 or 10 mg/kg every 2 weeks	127 patients with advanced NSCLC evaluable at time of presentation	Fatigue Pneumonitis (2%) AST elevation (2%)	Of 122 patients reported (16) Nonsquamous (15) Squamous (19)	Not reported	Squamous at 1 year (44) Squamous at 2 years (44) Nonsquamous at 1 year (41) Nonsquamous at 2 years (17)	[50]
Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with NSCLC (Garon *et al.*, 2013)	MK-3475 10 mg/kg every 3 weeks	38 patients with advanced NSCLC	Pulmonary edema (1, 3)	Overall: 24 (by irIC) 21 (by RECIST v1.1) PD-L1 high: 67 (by irIC) 57 (by RECIST v1.1) PD-L1 low: 4 (by irIC) 9 (by RECIST v1.1)	Not yet reported	Not yet reported	[51]
Clinical activity, safety and biomarkers of PD-L1 blockade in non-small-cell lung cancer (NSCLC) (Soria *et al.*, 2013)	MPDL3280A intravenously every 3 weeks	85 patients with advanced NSCLC	Pericardial effusion (6%) Dehydration (4%) Dyspnea (4%) Fatigue (4%)	Overall (23) PD-L1 intermediate (46) PD-L1 high (83) Smokers (26) Nonsmokers (10)	At 24 weeks: Squamous: 44 Nonsquamous: 46	Not yet reported	[52]

† American Society of Clinical Oncology 2013 abstract.

AST: Aspartate aminotransferase; irlC: Immune-related response criteria; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PD-1: programmed death-1; PD-L1: Programmed PFS: Progression-free survival; PT: Platinum; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 6

Currently ongoing clinical trials.

Trial	Phase	Drug/dose	Patients	Any reported results	Ref.
Phase I dose escalation of recombinant interleukin-2 in combination with nivolumab in patients with advanced or metastatic solid tumors (Chow *et al.*, 2013)†	I	Nivolumab/3 mg/kg/IL-2 in escalating doses	Patients with advanced solid tumors. Recruiting	None	[61]
Clinical activity, safety and biomarkers of MPDL3280A, an engineered anti-PD-L1 antibody in patients with locally advanced or metastatic CRC, gastric cancer, SCCHN, or other tumors (Taberero *et al.*, 2013)†	I	MPDL3280A/0.01–20 mg/kg	20 patients with locally advanced or metastatic tumors other than NSCLC, melanoma and RCC	Any grade 3–4 toxicity (50%); no pneumonitis or diarrhea >grade 2. Authors report RECIST responses observed	[62]
MEDI4736, an anti-PD-L1 antibody with modified Fc domain: preclinical evaluation and early clinical results from a Phase 1 study in patients with advanced solid tumors (Khleif *et al.*, 2013)	I	MEDI-4736	Eight patients with advanced solid tumor malignancies		[63]
Safety and clinical activity of nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with ipilimumab in patients with advanced melanoma (Wolchok *et al.*, 2013) †	I	Nivolumab/0.3, 1 or 3 mg/kg; ipilimumab 1 or 3 mg/kg; given concurrently (unless prior ipilimumab exposure)	69 patients with advanced melanoma	Any grade 3–4 toxicity at MTD (59%) DLT: lipase elevation Most common: uveitis, colitis, laboratory abnormalities Of 37 patients reported, ORR 38%	[39]
Clinical efficacy and safety of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced melanoma (Ribas *et al.*, 2013)†‡	I	MK-3475/2 or 10 mg/kg every 2–3 weeks	294 patients with advanced melanoma (171 ipilimumab naive; 115 ipilimumab treated)	Any grade 3–4 toxicity (10%) Hypothyroidism (one patient) Hyperthyroidism (one patient) (of 133 patients reported) Of 85 patients reported, ORR 35%	[44]
A Phase I study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib, pazopanib or ipilimumab in patients with mRCC (Amin *et al.*, 2013)†‡	I	Nivolumab/2 or 5 mg/kg plus sunitinib or pazopanib; 3 mg/kg plus ipilimumab (1 mg/kg induction); 1 mg/kg plus ipilimumab (3 mg/kg induction)	Not yet reported		[64]
An exploratory study of the biological effects of nivolumab (anti-PD-1; BMS-936558; ONO-4538) treatment in patients with advanced (unresectable or metastatic) melanoma (Sosman *et al.*, 2013)†‡	II	Nivolumab/3 mg/kg every 2 weeks	80 patients with advanced melanoma (50% ipilimumab naive; 50% ipilimumab refractory). Currently recruiting		[40]
An open-label, randomized, Phase II study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) given sequentially with ipilimumab in patients with advanced or metastatic melanoma (Hodi *et al.*, 2013)†‡	II	Nivolumab/3 mg/kg every 2 weeks followed by ipilimumab/3 mg/kg every 3 weeks	80 patients with advanced melanoma. Currently recruiting		[41]
A Phase III open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice in	III	Nivolumab/3 mg/kg every 2 weeks versus carboplatin, dacarbazine or paclitaxel	390 patients with advanced melanoma with prior anti-CTLA4		[42]

Trial	Phase	Drug/dose	Patients	Any reported results	Ref.
advanced melanoma patients progressing post anti-CTLA4 therapy (Chmielowski *et al.*, 2013)[†‡]			or BRAF inhibitor exposure. Currently recruiting		
A Phase III, randomized, double-blind study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus dacarbazine in patients with previously untreated, unresectable, or metastatic melanoma (Robert *et al.*, 2013)[†‡]	III	Nivolumab/3 mg/kg every 2 weeks versus dacarbazine	410 patients with untreated, unresectable stage III or IV melanoma (*BRAF* mutation excluded). Currently recruiting		[43]
A Phase III comparative study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus everolimus in patients with advanced or mRCC previously treated with antiangiogenic therapy (Motzer *et al.*, 2013)[†‡]	III	Nivolumab/3 mg/kg versus everolimus/10 mg p.o. daily	822 patients with metastatic RCC who received ≤2 prior antiangiogenic therapies		[65]
A Phase III comparative study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus docetaxel in patients with previously treated advanced/metastatic non-squamous NSCLC (Gettinger *et al.*, 2013)[†‡]	III	Nivolumab/3 mg/kg every 2 weeks versus docetaxel 75 mg/m^2 every 3 weeks	574 patients with advanced NSCLC who have failed prior treatment with platinum-doublet therapy or TKI (if EGF receptor or ALK positive). Currently recruiting		[53]
A Phase III comparative study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus docetaxel in patients with previously treated advanced or metastatic squamous cell non-small-cell lung cancer (Borghaei *et al.*, 2013)[†‡]	III	Nivolumab/3 mg/kg every 2 weeks versus docetaxel 75 mg/m^2 every 3 weeks	264 patients with advanced squamous cell NSCLC, following failure of treatment with platinum-doublet therapy		[54]

[†]American Society of Clinical Oncology 2013 annual meeting abstract.

[‡]Study is ongoing.

ALK: Anaplastic lymphoma kinase; CRC: Colorectal cancer; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4; DLT: Dose-limiting toxicity; mRCC: Metastatic renal cell carcinoma; dose; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; p.o.; Per os; RCC: Renal cell carcinoma; Criteria in Solid Tumors; SCCHN: Squamous cell carcinoma of the head and neck; TKI: Tyrosine kinase inhibitor.