Published in final edited form as:
Arch Dermatol Res. 2014 August ; 306(6): 511–519. doi:10.1007/s00403-014-1457-7.

Targeting the PD-1 Pathway: A Promising Future for the Treatment of Melanoma

Andrew Mamalis[1,2], **Manveer Garcha**[1,2], and **Jared Jagdeo**[1,2]

[1]Department of Dermatology, University of California at Davis, 3301 C Street, Sacramento, CA 95816, USA

[2]Dermatology Service, Sacramento VA Medical Center, Mather, CA 95655, USA

Abstract

Advanced melanoma presents a significant therapeutic challenge to clinicians. Many therapies for metastatic melanoma are limited by low response rates, severe toxicities, and/or relatively short response duration. Cancer immunotherapies that act as immune-checkpoint inhibitors to block the localized immune suppression mechanisms utilized by tumors are undergoing development and clinical trials. A clinically relevant immune escape mechanism in melanoma is the activation of the programmed cell death-1 (PD-1) receptor on infiltrating T cells. Activating PD-1 triggers an immune-checkpoint resulting in inhibition of T cells directed against melanoma antigens and prevents the immune system from combating the melanoma. In Phase I clinical trials, two anti-PD1 therapies, Nivolumab and MK-3475, that block the PD-1 receptor to enable T cell killing have demonstrated objective tumor responses in patients with advanced melanoma. The purpose of this review is to present the available clinical evidence on anti-PD-1 and anti-PD-L1 immunotherapy for the treatment of advanced melanoma. We also discuss limitations associated with anti-PD-1 therapy. The blockade of the PD-1-PD-L1 pathway has shown promising results in clinical trials and has revolutionized melanoma immunotherapy.

Introduction

In 2014, it is estimated melanoma will contribute to 76,100 new cancer diagnoses and 9,710 deaths in the United States [29]. Advanced melanoma presents a significant therapeutic challenge to clinicians. Many therapies for metastatic melanoma are limited by low response rates, severe toxicities, and/or relatively short response duration [11]. Historically, treatment for advanced melanoma involved the use of cytotoxic therapies, such as dacarbazine, that have response rates of approximately 10% to 15% and causes dose-limiting toxicities [11,20]. The cytokine interleukin-2 (IL-2) is also used to treat advanced melanoma, however, the response rate is only 6% to 10% and it too is associated with significant toxicities. Newer oncologic treatments for melanoma include targeted therapies, such as

Corresponding author: Jared Jagdeo, MD, MS, jrjagdeo@gmail.com, Telephone: (917) 837-9796, Fax: (916) 451-7245.

kinase inhibitors that are now a mainstay treatment for melanomas that harbor key mutations contributing to melanoma pathogenesis, such as BRAF [20].

BRAF mutations are present in 40–60% of melanoma patients and these mutations lead to activation of kinase activity [11,5,7,8]. Inhibitors of these BRAF mutations, such as vemurafenib and dabrafenib, have shown response rates of 48% to 53% and have revolutionized melanoma treatment, but are limited to treating melanomas that harbor a BRAF mutation [11,5,7,8]. Additionally, the majority of patients treated with BRAF-inhibitors go on to relapse within 6–12 months.

In addition to key mutations such as BRAF, human cancers harbor antigens that allow a patient's immune system to recognize and mount an endogenous immune response against the tumor [23,27,28]. However, endogenous anti-tumor immune responses are often ineffective because tumors can activate key immune-checkpoints that lead to localized immune suppression [9,23,33,14,15]. Cancer immunotherapies that act as immune-checkpoint inhibitors to block the localized immune suppression mechanisms utilized by tumors are undergoing development and being put to test in clinical trials [19].

The first immunotherapy approved for the treatment of advanced melanoma was ipilimumab, a monoclonal antibody (mAb) that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4) and prevents a distinct mechanism of immune suppression that involves CTLA-4 [21]. Ipilimumab has demonstrated improved overall survival in patients with previously treated metastatic melanoma [10,18]. Most recently, immunotherapies targeting another clinically relevant mechanism of immune suppression involving the immune-checkpoint PD-1 receptor and its ligand, PD-L1, are undergoing clinical trials for the treatment of advanced melanoma (Table 1) [24]. Two drugs that bind to PD-1 and block the interaction of the receptor with its ligand to enable T cell killing are nivolumab (MDX-1106 or BMS-936558, Bristol-Myers Squibb) and MK-3475 (Merck). Nivolumab and MK-3475 have demonstrated durable objective clinical response per the RECIST 1.1 criteria in melanoma tumor size in phase I clinical trials and may have the potential to change the treatment paradigm for advanced melanoma [24].

The PD-1 receptor acts as an immune-checkpoint by terminating or inhibiting the immune response through T cell activity downregulation and induction of tolerance to antigens [6,13]. When PD-1 is unbound, T cells are free to react against target cells; when PD-1 is bound to ligand, it suppresses the immune response of T cells (Figure 1A) [38]. The PD-1 immune-checkpoint is believed to normally play a role in ensuring self-tolerance to prevent autoimmunity. However, translational research indicates that interferon-gamma, secreted by tumor-infiltrating cytotoxic T cells, leads to an upregulation of PD-L1 on the surface of melanoma cells that activates the PD-1 receptor to prevent immune recognition and destruction of melanoma cells.

By blocking PD-1 receptors with anti-PD-1 mAbs, T cells are unaffected by the PD-L1 expressed on tumor cells and the patient's T cells are free to respond to melanoma antigens and attack tumor cells (Figure 1B). This new class of immunotherapy, based on anti-PD1, is

now a validated strategy based on efficacy results in Phase I trials, irrespective of mutation type or previous treatments.

Methods

We employed the following search strategy to identify the clinical evidence reported in the biomedical literature: in January 2014, we searched Medline, PubMed, EMBASE, and ClinicalTrials.gov (January 1990-present) using the following search terms: “nivolumab,” “MDX-1106,” “BMS-936558,” “lambrolizumab,” “MK-3475,” “anti-PD-1,” “anti-PD-L1,” “BMS-936559,” “MPDL3280A,” “CD274,” or CD279.” All clinical trials evaluating anti-PD-1 or anti-PD-L1 therapy for the treatment of melanoma were included.

Results

Our search identified 5 clinical trials meeting inclusion criteria for evaluating anti-PD-1 therapy for melanoma. A detailed list of the included clinical trials is presented in Table 2.

Discussion

Anti-PD-1 Monotherapy

Our review of the literature demonstrates that nivolumab is a promising treatment for patients with advanced melanoma. One phase I trial conducted by Brahmer et al investigated the safety, tolerability, and anti-tumor activity of nivolumab in 39 patients with either treatment-refractory advanced melanoma, colorectal cancer (CRC), castrate resistant prostate cancer, non-small-cell lung cancer, or renal cell carcinoma (RCC) [4]. This early study found 1 out of 10 patients with melanoma treated with nivolumab experienced a partial response to therapy, as measured by a reduction in tumor size using the RECIST 1.1 [4]. Investigators also reported another partial response in a patient with RCC and one complete response in CRC [4]. Since only 31% (12/39) of patients received multiple doses of nivolumab, interpretation of the reported response rates is limited because many patients may not have responded due to an ineffective dose [4]. Investigators reported no dose limiting toxicities; however, they report a drug-related episode of grade 3 inflammatory colitis and an episode of grade 2 hypothyroidism in another patient. These immune-related adverse events are of particular interest in anti-PD-1 trials and are similar to those seen in ipilimumab trials [3,22]. Immune-related adverse events are likely a critical dose-limiting toxicity of PD-1 inhibitors.

Another phase I trial investigating the use of nivolumab for the treatment of a variety of solid tumors reported 28% (26/94) of patients with advanced melanoma who had melanoma progression while on previous tumor therapies showed an objective response to treatment after receiving nivolumab at a dose of 0.1 to 10.0 mg per kilogram of body weight (mg/kg) every 2 weeks over an 8 week cycle period. In addition, objective responses were observed in 41% (7/17) of patients receiving nivolumab at a dose of 3 mg/kg. Patients received treatment for up to 12 cycles until disease progression was noted or complete response occurred [31]. This study also reported similar objective response rates in patients with renal-cell cancer and non-small cell lung cancer. In addition, 72% (13/18) of patients who

responded to nivolumab treatment with adequate follow-up had responses lasting one year or longer [31]. The investigators found that drug-related grade 3 or 4 toxic effects occurred in 14% (41/296) of patients with advanced melanoma, renal cell cancer, or non-small cell lung cancer [31]. This study also assessed the role of tumoral PD-L1 expression on treatment response and found that 36% (9/25) of patients with PD-L1–positive tumors had an objective response, while no patients with PD-L1–negative tumors had an objective response [31]. However, due to the limited patient sample size, conclusions regarding the predictive power of PD-L1 expression are difficult to make. Preliminary results from another clinical trial investigating the use nivolumab with or without a multi-peptide vaccine reported nivolumab response rates by RECIST were 28% in 34 patients who were naïve to ipilimumab, and 32% in 46 patients who had failed prior ipilimumab therapy [34].

A phase I trial of the anti-PD-1 antibody MK-3475 included 135 patients with advanced melanoma. The trial demonstrated an overall objective response of 38% (44/117) and an objective response of 52% (27/52) in patients receiving the maximum dose of 10 mg per kg every two weeks [17]. The authors report that 13% (17/135) of patients experienced grade 3 or 4 toxicities. In addition, they report that prior exposure to ipilimumab or IL-2, did not appear to have a major effect on response to MK-3475 treatment [17].

Taken together, the promising response rates from these phase I monotherapy trials demonstrate that anti-PD-1 mAbs have the potential to alter the melanoma treatment paradigm. Anti-PD-1 mAbs are associated with adverse events, including immune-related events. However, the results of nivolumab and MK-3475 indicate that as the immunotherapy drug class continues to expand, PD-1 inhibitors will be an effective therapy to combat advanced. In addition, further research to identify biomarkers beyond PD-L1 tumor-expression, may allow clinicians to identify patients who are most likely to respond to anti-PD-1 therapy while minimizing adverse events. Merck has begun a phase III clinical trial comparing MK-3475 against ipilimumab in patients with advanced melanoma.

Immune Checkpoint Combination Therapies

Combining multiple immune checkpoint blocker therapies has demonstrated beneficial results for the treatment of advanced melanoma. One recent clinical trial showed nivolumab combined with ipilimumab resulted in greater response rates than monotherapy with either drug [37]. 53 patients received concurrent therapy with nivolumab and ipilimumab, and 33 received sequenced treatment (nivolumab administered within 4 to 12 weeks following last ipilimumab dose) [37]. The authors report that 53% of patients who received combination therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg had an objective response versus only 20% of patients who received the sequential treatment. All responders had tumor reductions of 80% or more [37]. The trial observed Grade 3 or 4 adverse events occurred in 53% of patients in the concurrent-regimen group, and in 18% of patients in the sequenced-regimen group. This study illustrated that concurrent therapy with nivolumab and ipilimumab may act synergistically and result in improved response rate versus monotherapy while maintaining a manageable rate of adverse events [37]. In addition, the authors reported that concurrent nivolumab plus ipilimumab therapy resulted in objective response in both patients with PD-L1–positive tumors (6/13) and with PD-L1–negative tumors (9/22). The

effectiveness of nivolumab on PD-1–negative tumors is uncertain, further evaluation of tumor PD-L1 expression in clinical trials may clarify PD-1's utility as a biomarker for response rate to mono– and combination–therapy.

These promising synergistic findings have resulted in a phase III clinical trial to further investigate the utility of nivolumab plus ipilimumab combination therapy for the treatment of melanoma. Future studies investigating the combination of nivolumab with existing or newly developed therapies for melanoma may provide enhanced survival benefit and decreased immunotherapy related adverse effects. In addition, future Phase III trials will likely elucidate further details regarding the safety and effectiveness of PD-1 inhibitors, while also evaluating their effectiveness when combined with existing melanoma chemotherapeutics.

Anti-PD-L1 Therapy

In addition to mAbs targeting the PD-1 receptor, mAbs have also been developed that target PD-L1. A phase I trial of the anti-PD-L1 antibody BMS-936559 reported objective responses to therapy in 17% (9/52) of patients with melanoma [31]. The trial also demonstrated prolonged stabilization of disease in 27% (14/52) of patients assessed 24 weeks after beginning therapy [31]. The investigators found that 39% (81/207) of patients experienced immune-related adverse events of any grade [31]. This study also assessed the median anti-PD-1 receptor occupancy in peripheral-blood T cells and found it was more than 65% in all 29 patients tested with melanoma [31]. Further studies are needed to evaluate if peripheral-blood receptor occupancy correlates with treatment outcomes.

Roche Genentech is developing another anti-PD-L1 mAb known as MPDL3280A. Data on MPDL3280A presented at the annual 2013 American Society of Clinical Oncology conference (ASCO) reported that objective responses were observed in 29% (10/35) of patients with advanced metastatic melanoma receiving the PD-L1 antibody [17]. Further studies on the efficacy of anti-PD-L1 therapies are forthcoming and we anticipate that combination therapies may prove to be a promising option when utilizing anti-PD-L1.

Limitations and future directions

Similar to other cancer therapies, nivolumab treatment is commonly associated with adverse events that include fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, dermatitis, pyrexia, and headache [31]. Additional immune-related adverse events include pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis [31]. These immune-related adverse events may prove to be limitation of PD-1 inhibitors for some patients, however, adverse events are less frequent and severe than with ipilimumab and most patients who discontinue due to toxicity still have durable and ongoing response [30]. Larger studies may reveal how to best manage immune-related adverse events when taking immunotherapy anti-PD-1 mAbs without limiting clinical efficacy.

Due to the cost of immunotherapy, chance of adverse events, and heterogeneity of individual tumors, it is important for clinicians and researchers to be able to predict a patient's likelihood of response and adverse events. One method is to utilize biomarkers to predict likelihood of response in order to stratify patients prior to therapy. Initial data on nivolumab

showed that 36% (9 out of 25) of patients with PD–L1-positive tumors responded to therapy and 0 out of 17 patients with PD-L1-negative tumors responded to therapy [31]. Reports at ASCO 2013 have suggested that PD-L1 detected in biopsy samples by immunohistochemistry may be capable of predicting activity of nivolumab in advanced cancer [35,16]. In addition, a recent study noted that PD-L1 tumor expression and T-cell gene signature correlated with responses to MPDL3280A [26]. However, data presented at the annual 2013 ASCO conference has also reported objective responses to nivolumab in patients with PD-L1-negative tumors [32]. This may be due to heterogenous tumor expression of PD-1, thus making a single negative biopsy insufficient to determine if a tumor is truly PD-L1 negative. Further randomized clinical trials are needed to evaluate the utility of PD-L1 as biomarker for patient selection.

Given the uncertainty of predictions based on PD-L1 expression or any other single biomarker, clinicians may choose to utilize a panel of specific biomarkers that can accurately predict and stratify patients based on their likelihood of response, should a useful biomarker panel become available [1,2]. The use of biomarkers to profile immune cells that have infiltrated a tumor may also prove valuable to clinicians [1]. These profiling tools could be used to understand the dynamic state of the immune system in the individual tumor and tailor immunotherapy selection accordingly.

In addition, translational research on serial tumor biopsies from patients treated with BRAF-inhibitors has demonstrated that BRAF inhibition is associated with an increase in melanoma antigen expression and T cell infiltrate, and a decrease in immunosuppressive cytokines in tumors of treated patients [12,36]. These findings suggest that BRAF-inhibitors may work synergistically with immunotherapy agents such as PD-1 inhibitors. Clinical trials are currently in progresses that are investigating combining BRAF-targeted therapy and immunotherapy for the treatment of advanced melanoma.

Although the results of the phase I clinical trials are impressive, it remains to be seen if PD-1 inhibitors demonstrate improved patient survival in phase III trials. In addition, because immunotherapies require time for induction of an immune response, they take longer to show an effect compared to cytotoxic or targeted therapies. Due to this delay, immunotherapies have been reported to cause transient progression in disease prior to objective reductions in tumor size [25]. Therefore, phase I trials may underestimate the actual response rate to immunotherapy by using objective response measurements that capture transient progression in disease prior to reductions in tumor size [25]. As new immunotherapies are developed, we anticipate additional targets involved in the PD-1–PD-L1 signaling pathway, as well as additional pathways related to tumor immune suppression, will likely emerge.

Conclusion

The treatment of advanced melanoma is evolving as exciting new drugs that inhibit immune-checkpoints are developed. These immune-checkpoint inhibitors allow a patient's endogenous immune response to assist in combating advanced melanoma or other types of cancer. Nivolumab alone and in combination with ipilimumab, has been shown to be

effective in the treatment of advanced melanoma. Moving forward, there is a need to develop biomarkers to predict response to anti-PD-1 mAbs and design strategies to manage and avoid adverse immune-related events. We anticipate that as immunotherapies continue to develop, additional targets involved in the PD-1–PD-L1 signaling pathway, as well as additional related immunotherapy pathways, will likely emerge. The use of antibodies targeting the PD-1–PD-L1 pathway, in combination with existing and new immunotherapies, has the potential to alter the current melanoma treatment paradigm and usher in an exciting new era of advanced melanoma treatment with improved patient outcomes.

Acknowledgments

Funding Source:

The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR000002 and linked award TL1 TR000133.

The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR000002 and linked award KL2 TR000134.

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number R33AI080604.

Abbreviations

ASCO	American Society of Clinical Oncology conference
CRC	colorectal cancer
CTLA-4	cytotoxic T-lymphocyte antigen-4
mAb	monoclonal antibody
PD-1	programmed cell death-1 receptor
PD-L1	programmed cell death-1 receptor ligand
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

References

1. Ascierto PA, Capone M, Urba WJ, Bifulco CB, Botti G, Lugli A, Marincola FM, Ciliberto G, Galon J, Fox BA. The additional facet of immunoscore: immunoprofiling as a possible predictive tool for cancer treatment. J Transl Med. 2013; 11:54. [PubMed: 23452415]
2. Ascierto PA, Kalos M, Schaer DA, Callahan MK, Wolchok JD. Biomarkers for immunostimulatory monoclonal antibodies in combination strategies for melanoma and other tumor types. Clin Cancer Res. 2013; 19 (5):1009–1020. [PubMed: 23460532]
3. Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, Sherry RM, Topalian SL, Kammula US, Royal RE, Restifo NP, Haworth LR, Levy C, Mavroukakis SA, Nichol G, Yellin MJ, Rosenberg SA. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol. 2005; 23 (25):6043–6053. [PubMed: 16087944]
4. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman

AJ, Pardoll DM, Lowy I, Topalian SL. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010; 28 (19):3167–3175. [PubMed: 20516446]

5. Bucheit AD, Syklawer E, Jakob JA, Bassett RL Jr, Curry JL, Gershenwald JE, Kim KB, Hwu P, Lazar AJ, Davies MA. Clinical characteristics and outcomes with specific BRAF and NRAS mutations in patients with metastatic melanoma. Cancer. 2013; 119 (21):3821–3829. [PubMed: 23922205]
6. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 2007; 27 (1):111–122. [PubMed: 17629517]
7. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, Cho KH, Aiba S, Brocker EB, LeBoit PE, Pinkel D, Bastian BC. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005; 353 (20):2135–2147. [PubMed: 16291983]
8. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature. 2002; 417 (6892): 949–954. [PubMed: 12068308]
9. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol. 2006; 90:51–81. [PubMed: 16730261]
10. Fellner C. Ipilimumab (yervoy) prolongs survival in advanced melanoma: serious side effects and a hefty price tag may limit its use. P T. 2012; 37 (9):503–530. [PubMed: 23066344]
11. Finn L, Markovic SN, Joseph RW. Therapy for metastatic melanoma: the past, present, and future. BMC Med. 2012; 10:23. [PubMed: 22385436]
12. Frederick DT, Piris A, Cogdill AP, Cooper ZA, Lezcano C, Ferrone CR, Mitra D, Boni A, Newton LP, Liu C, Peng W, Sullivan RJ, Lawrence DP, Hodi FS, Overwijk WW, Lizee G, Murphy GF, Hwu P, Flaherty KT, Fisher DE, Wargo JA. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res. 2013; 19 (5):1225–1231. [PubMed: 23307859]
13. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med. 2000; 192 (7):1027–1034. [PubMed: 11015443]
14. Fridman WH, Pages F, Sautes-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012; 12 (4):298–306. [PubMed: 22419253]
15. Galon J, Angell HK, Bedognetti D, Marincola FM. The continuum of cancer immunosurveillance: prognostic, predictive, and mechanistic signatures. Immunity. 2013; 39 (1):11–26. [PubMed: 23890060]
16. Grosso J, Horak CE, Inzunza D, Cardona DM, Simon JS, Gupta AK, Sankar V, Park J-S, Kollia G, Taube JM, Anders R, Jure-Kunkel M, Novotny J, Jim, Taylor CR, Zhang X, Phillips T, Simmons P, Cogswell J. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). ASCO Meeting Abstracts. 2013; 31 (15_suppl):3016.
17. Hamid O, Sosman JA, Lawrence DP, Sullivan RJ, Ibrahim N, Kluger HM, Boasberg PD, Flaherty K, Hwu P, Ballinger M, Mokatrin A, Kowanetz M, Chen DS, Hodi FS. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM). ASCO Meeting Abstracts. 2013; 31 (15_suppl):9010.
18. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber

JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363 (8):711–723. [PubMed: 20525992]

19. Kline J, Gajewski TF. Clinical development of mAbs to block the PD1 pathway as an immunotherapy for cancer. Curr Opin Investig Drugs. 2010; 11 (12):1354–1359.
20. Mackiewicz J. What is new in the treatment of advanced melanoma? State of the art. Contemp Oncol (Pozn). 2012; 16 (5):363–370. [PubMed: 23788912]
21. Mackiewicz J, Mackiewicz A. Recent advances in melanoma treatment - American Society of Clinical Oncology (ASCO) 2012 perspective. Contemp Oncol (Pozn). 2012; 16 (3):197–200. [PubMed: 23788878]
22. Maker AV, Attia P, Rosenberg SA. Analysis of the cellular mechanism of antitumor responses and autoimmunity in patients treated with CTLA-4 blockade. J Immunol. 2005; 175 (11):7746–7754. [PubMed: 16301685]
23. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011; 480 (7378): 480–489. [PubMed: 22193102]
24. Mullard A. New checkpoint inhibitors ride the immunotherapy tsunami. Nat Rev Drug Discov. 2013; 12 (7):489–492. [PubMed: 23812256]
25. Oxnard GR, Morris MJ, Hodi FS, Baker LH, Kris MG, Venook AP, Schwartz LH. When progressive disease does not mean treatment failure: reconsidering the criteria for progression. J Natl Cancer Inst. 2012; 104 (20):1534–1541. [PubMed: 22927506]
26. Powderly JD, Koeppen H, Hodi FS, Sosman JA, Gettinger SN, Desai R, Tabernero J, Soria J-C, Hamid O, Fine GD, Xiao Y, Mokatrin A, Wu J, Anderson M, Irving BA, Chen DS, Kowanetz M. Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. ASCO Meeting Abstracts. 2013; 31 (15_suppl):3001.
27. Rosenberg SA. Development of effective immunotherapy for the treatment of patients with cancer. J Am Coll Surg. 2004; 198 (5):685–696. [PubMed: 15110801]
28. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med. 2004; 10 (9):909–915. [PubMed: 15340416]
29. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64 (1):9–29. [PubMed: 24399786]
30. Sznol M, Kluger HM, Hodi FS, McDermott DF, Carvajal RD, Lawrence DP, Topalian SL, Atkins MB, Powderly JD, Sharfman WH, Puzanov I, Smith DC, Wigginton JM, Kollia G, Gupta AK, Sosman JA. Survival and long-term follow-up of safety and response in patients (pts) with advanced melanoma (MEL) in a phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538). ASCO Meeting Abstracts. 2013; 31(15_suppl):CRA9006.
31. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012; 366 (26): 2443–2454. [PubMed: 22658127]
32. Topalian SL, Sznol M, Brahmer JR, McDermott DF, Smith DC, Gettinger SN, Taube JM, Drake CG, Pardoll DM, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Antonia SJ, Spigel DR, Lawrence DP, Kollia G, Gupta AK, Wigginton JM, Hodi FS. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solid tumors: Survival and long-term safety in a phase I trial. J Clin Oncol. 2013; 31:S3002.
33. Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. J Clin Oncol. 2011; 29 (36):4828–4836. [PubMed: 22042955]
34. Weber JS, Kudchadkar RR, Gibney GT, De Conti RC, Yu B, Wang W, Sarnaik A, Martinez AJ, Kroeger J, Eysmans C, Gallenstein D, Zhao X, Chen A. Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab. ASCO Meeting Abstracts. 2013; 31 (15_suppl):9011.
35. Weber JS, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, Zhao X, Martinez AJ, Wang W, Gibney G, Kroeger J, Eysmans C, Sarnaik AA, Chen YA. Safety, efficacy, and

biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol. 2013; 31 (34):4311–4318. [PubMed: 24145345]

36. Wilmott JS, Long GV, Howle JR, Haydu LE, Sharma RN, Thompson JF, Kefford RF, Hersey P, Scolyer RA. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012; 18 (5):1386–1394. [PubMed: 22156613]
37. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, Burke MM, Caldwell A, Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013; 369 (2):122–133. [PubMed: 23724867]
38. Zielinski C, Knapp S, Mascaux C, Hirsch F. Rationale for targeting the immune system through checkpoint molecule blockade in the treatment of non-small-cell lung cancer. Ann Oncol. 2013; 24 (5):1170–1179. [PubMed: 23393121]
39. Crisan M, Crisan D, Sannino G, Lupsor M, Badea R, Amzica F. Ultrasonographic staging of cutaneous malignant tumors: an ultrasonographic depth index. Arch Dermatol Res. 2013; 305:305–313. [PubMed: 23400334]
40. Eiro N, Ovies C, Fernandez-Garcia B, Alvarez-Cuesta CC, Gonzalez L, Gonzalez LO, Vizoso FJ. Expression of TLR3, 4, 7 and 9 in cutaneous malignant melanoma: relationship with clinicopathological characteristics and prognosis. Arch Dermatol Res. 2013; 305:59–67. [PubMed: 23179584]
41. Sinnya S, De'ambrosis B. Stress and melanoma: increasing the evidence towards a causal basis. Arch Dermatol Res. 2013
42. Spagnolo F, Queirolo P. Upcoming strategies for the treatment of metastatic melanoma. Arch Dermatol Res. 2012; 304:177–184. [PubMed: 22350184]

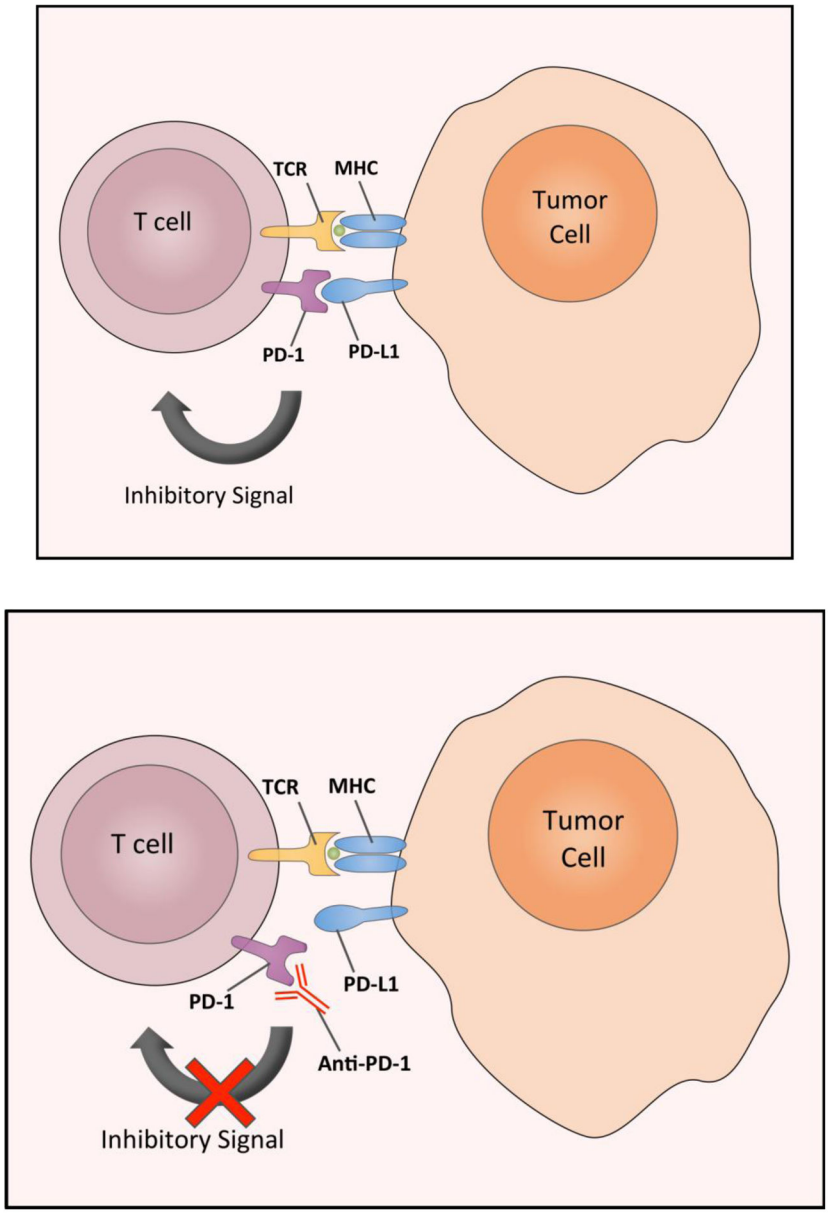

Figure 1.

PD-1's role in inhibiting the immune response through T cell activity downregulation. T cells recognize antigens presented by the major histocompatibility complex (MHC) on tumor cells through interactions with the T cell receptor (TCR). Programmed death 1 (PD-1) is an inhibitory receptor that can terminate or inhibit T cell immune response when interacting with programmed death ligand 1 (PD- L1). (A) Tumor cells that express PD-L1 can evade immune response by regulating the activity of T cells through PD-1. (B) By blocking the PD-1 receptor with an anti-PD-1 mAb, such as nivolumab or MK-3475, T cells are not inhibited by tumor-expressed PD-L1 and are free to mount an immune response against melanoma tumor cells.

Table 1

Summary of PD-1–PD-L1 Immunotherapies Under Development.

Drug Name	Company	Antibody Description	Target	Phase
Nivolumab	Bristol-Myers Squib	Fully human IgG4 monoclonal antibody	PD-1 Receptor	III
MK-3475	Merck & Co.	Humanized IgG4 monoclonal antibody	PD-1 Receptor	III
BMS-936559	Bristol-Myers Squibb	Fully human IgG4 monoclonal antibody	PD-Ligand 1	I
MPDL3280A	Roche	Monoclonal antibody	PD-Ligand 1	I

Table 2

Summary of Phase I Studies Investigating Anti-PD-1 or Anti-PD-L1 Immunotherapies.

Study (ClinicalTrials.gov)	Treatment Regimen	Patient Sample	Efficacy/Conclusion	Adverse Event Rate	Immune-related Adverse Events
Anti–PD-1 Phase I Trials					
Brahmer et al., 2010 (NCT00441337)	Nivolumab: Dosed at 0.3, 1.0, 3.0, or 10 mg/kg.	39 patients with advanced metastatic melanoma, colorectal cancer (CRC), castrate-resistant prostate cancer (CRPC), non-small-cell lung cancer (NSCLC), or renal cell carcinoma (RCC).	1 complete response (1 CRC); 2 partial responses (1 melanoma, 1 RCC).	Most commonly decreased CD4+ lymphocyte counts in 35.9% (14/39), lymphopenia in 25.6% (10/39), and fatigue or musculoskeletal events in 15.4% (6/39) of patients.	Grade 3 inflammatory colitis (n=1), grade 2 hypothyroidism (n=1).
Topalian et al., 2012 (NCT00730639)	Nivolumab: Dosed at 0.1 to 10 mg/kg every 2 weeks in 8-week cycles for up to 12 cycles or until the patient had a complete response or confirmed disease progression.	296 patients with advanced metastatic melanoma, colorectal cancer (CRC), castrate-resistant prostate cancer (CRPC), non-small-cell lung cancer (NSCLC), or renal cell carcinoma (RCC).	28% (26/94) of patients with melanoma responded to therapy. In patients with 1 year or more of follow up, 64.5% (20/31) of responses lasted at least 1 year.	Drug-related pneumonitis occurred in 3% (9/296) of patients. 3 patients died from pulmonary toxicity.	Grade 3 or 4 drug-related adverse events occurred in 14% of patients.
Wolchok et al., 2013 (NCT01024231)	Nivolumab plus ipilimumab: Nivolumab 0.3 to 10 mg/kg; Ipilimumab 3 to 10 mg/kg.	86 patients total. 53 patients received concurrent therapy with nivolumab and ipilimumab. 33 patients received sequenced treatment (had previously taken at least 3 treatments of ipilimumab followed by nivolimumab alone).	Concurrent-regimen Nivolumab 1 mg/kg and ipilimumab 3 mg/kg results in an objective response of 53%, all with tumor reduction of 80% or more. Sequenced-regimen resulted an objective-response rate was 20%.	In concurrent-regimen, treatment-related adverse events were observed in 93% of patients. Most common events were rash (55% of patients), pruritus (47%), fatigue (38%), and diarrhea (34%).	Grade 3 or 4 adverse events occurred in 53% of patients in the concurrent-regimen group, and in 18% of patients in the sequenced-regimen group.
Hamid et al., 2013 (NCT01295827)	MK-3475: Dosed at 10 mg/kg every 2 to 3 weeks or 2.0 mg every 3 weeks.	135 patients with advanced melanoma. Patients with and without prior treatment with ipilimumab were included.	The response rate across all dose cohorts was 38%. The response rate across patients in the 10 mg/kg, 2 weeks interval cohort was 52%. After average 11 months follow-up, 81% (42 of 52) of patients continued to respond.	79% reported drug-related adverse events of any grade, of these 13% (n=17) experienced severe adverse effects. Highest incidence of adverse events in 10 mg/kg group taking every 2 weeks (23%) versus every 3 weeks (4%).	Grade 3 or 4 events included: asymptomatic pneumonitis (n=1), elevated aminotransferase (n=2), renal failure (n=2), hypothyroidism (n=1).
Anti–PD-Ligand 1 Phase I Trials					
Brahmer et al., 2012 (NCT00729664)	Anti–PD-L1: Dosed at 0.3 to 10 mg/kg every 2 weeks in 6-week cycles for up to 16 cycles or until the patient had a complete response or	55 patients with melanoma, 75 with non–small-cell lung cancer, 18 with colorectal cancer, 17 with renal-	17.3% (9/52) of patients with melanoma had an objective response (complete or partial). 7.4% (2/17) with renal-cell cancer, 10.2% (5/49) with non–	Adverse events of any grade were reported in 188 of 207 patients (91%) 9% of patients experienced grade 3 or 4	39% (81/207) of patients experienced immune-related adverse events of any grade including rash, hypothyroidism, hepatitis, and one case each of

Study (ClinicalTrials.gov)	Treatment Regimen	Patient Sample	Efficacy/Conclusion	Adverse Event Rate	Immune-related Adverse Events
	confirmed disease progression. confirmed disease progression.	cell cancer, 17 with ovarian cancer, 14 with pancreatic cancer, 7 with gastric cancer, and 4 with breast cancer.	small-cell lung cancer, and 3.7% (1/17) with ovarian cancer. 50% (8/16) of patients had responses last 1 year or longer.	adverse events related to treatment.	sarcoidosis, endophthalmiitis, diabetes mellitus, and myasthenia gravis.

Table 3

Summary of Current Clinical Studies Investigating Anti-PD-1 or Anti-PD-L1 Immunotherapies.

NCT Number	Trial Title	Phase	Interventions	Sponsor/Collaborators	Recruitment Status as of January 2014
Anti–PD-1 Phase I Trials					
NCT00441337	A Study of MDX-1106 in Patients With Selected Refractory or Relapsed Malignancies	Phase 1	Nivolumab	Bristol-Myers Squibb	Completed
NCT00730639	A Phase 1b Study of MDX-1106 in Subjects with Advanced or Recurrent Malignancies (MDX1106-03)	Phase 1	Nivolumab	Bristol-Myers Squibb	Active, not recruiting
NCT01024231	Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma	Phase 1	Nivolumab	Bristol-Myers Squibb	Recruiting
NCT01176461	Multiple Class I Peptides & Montanide ISA 51 VG w Escalating Doses of Anti-PD-1 ab BMS936558	Phase 1	Nivolumab	Bristol-Myers Squibb	Recruiting
NCT01176474	Multiple Class I Peptides & Montanide ISA 51 VG w Escalating Doses of Anti-PD-1 Antibody BMS936558	Phase 1	Nivolumab	Bristol-Myers Squibb	Recruiting
NCT01621490	Phase 1 Biomarker Study of Anti-PD-1 in Advanced Melanoma	Phase 1	Nivolumab	Bristol-Myers Squibb	Recruiting
NCT01783938	Study of Nivolumab Given Sequentially With Ipilimumab in Subjects With Advanced or Metastatic Melanoma (CheckMate 064)	Phase 2	Nivolumab, Ipilimumab	Bristol-Myers Squibb	Recruiting
NCT01927419	Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination With Ipilimumab vs Ipilimumab Alone in Subjects With Previously Untreated, Unresectable or Metastatic Melanoma (CheckMate 069)	Phase 2	Nivolumab, Ipilimumab	Bristol-Myers Squibb	Recruiting
NCT01721746	A Study to Compare BMS-936558 to the Physician's Choice of Either Dacarbazine or Carboplatin and Paclitaxel in Advanced Melanoma Patients That Have Progressed Following Anti-CTLA-4 Therapy (CheckMate 037)	Phase 3	Nivolumab, Dacarbazine, Carboplatin, Paclitaxel	Bristol-Myers Squibb	Active, not recruiting
NCT01721772	Study of BMS-936558 vs. Dacarbazine in Untreated, Unresectable or Metastatic Melanoma (CheckMate 066)	Phase 3	Nivolumab, Dacarbazine	Bristol-Myers Squibb	Recruiting
NCT01844505	Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate 067)	Phase 3	Nivolumab, Ipilimumab	Bristol-Myers Squibb	Recruiting
NCT01295827	Study of MK-3475 in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/MK-3475-001)	Phase 1	MK-3475	Merck Sharp & Dohme Corp.	Recruiting
NCT01704287	Study of MK-3475 Versus Chemotherapy in Participants With Advanced Melanoma	Phase 2	MK-3475, Carboplatin, Paclitaxel, Dacarbazine, Temozolomide	Merck Sharp & Dohme Corp.	Active, not recruiting

NCT Number	Trial Title	Phase	Interventions	Sponsor/Collaborators	Recruitment Status as of January 2014
NCT01866319	Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of MK-3475 Compared to Ipilimumab in Participants With Advanced Melanoma (MK-3475-006 AM1)	Phase 3	MK-3475, Ipilimumab	Merck Sharp & Dohme Corp.	Recruiting
Anti–PD-Ligand 1 Phase I Trials					
NCT01656642	A Study of The Safety and Pharmacology of MPDL3280A Administered in Combination With Vemurafenib in Patients With Previously Untreated BRAFV600-Mutation Positive Metastatic Melanoma	Phase 1	MPDL3280A, Vemurafenib	Genentech	Recruiting
NCT01375842	Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously As a Single Agent to Patients With Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies	Phase 1	MPDL3280A	Genentech	Recruiting
NCT00729664	Multiple Ascending Dose (MDX1105-01)	Phase 1	BMS-936559	Bristol-Myers Squibb	Active, not recruiting