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PD-1 and PD-L1 antibodies for melanoma

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Abbreviations: AE, adverse event; APC, antigen presenting cell; ASCO, American Society of Clinical Oncology; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FDA, Food and Drug Administration; gp100, glycoprotein 100 vaccine; Ig, immunoglobulin; ITIM , immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; NK, natural killer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression free survival; TCR, T cell receptor; TIL, tumor infiltrating lymphocyte.

Melanoma is the most serious form of skin cancer. Metastatic melanoma historically carries a poor prognosis and until recently there have been few effective agents available to treat widely disseminated disease. Recognition of the immunogenic nature of melanoma has resulted in the development of various immunotherapeutic approaches, especially with regards to the programmed cell death 1 (PD-1) receptor and its ligand (PD-L1). Antibodies targeting the PD-1 axis have shown enormous potential in the treatment of metastatic melanoma. Here, we will review the immune basis for the disease and discuss approved immunotherapeutic options for advanced melanoma, as well as the current state of development of PD-1 and PD-L1 antibodies and their importance in shaping the future of melanoma treatment.

Introduction

The immune system is a complex and dynamic assemblage that functions to detect and destroy pathogens and neoplasms while preserving host health. In order to maintain this balance, the immune system has complex feedback and feedforward loops to ensure that is it primed to attack at the right place and the right time. A rapidly evolving understanding of these mechanisms of immunity and of cancer biology have formed the basis for a revolution in systemic therapies for melanoma. Melanoma is the most fatal form of skin cancer, and historically there were few effective treatments for advanced disease. The identification of driver oncogenes and immune checkpoints has ushered us away from traditional cytotoxic chemotherapy-based regimens and into a new era of targeted therapies and immunotherapies. In routine clinical practice now are drugs inhibiting the mitogen-activated protein kinase (MAPK) pathway and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and most recently the programmed death 1 (PD-1) receptor. Targeting the PD-1 receptor ligands (PD-L1, PD-L2) has also shown promise in ongoing clinical trials. The success of the anti-CTLA-4 and anti-PD-1 drugs highlights the promise of immune checkpoint inhibitors in treating melanoma, and trials are underway to investigate new classes of drugs as well as combinations of these drugs. Here, we review the basis for the mechanism of action of immunotherapy, and focus on the state of development of drugs targeting the PD-1 axis that may further improve patient outcomes in melanoma.

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The tumor microenvironment and T cell activation

The initial study of cancer immunobiology focused on the role of the immune system in the recognition and inhibition of cancer growth.[1] The immune system recognizes foreign antigens but also maintains an inventory of self antigens, editing out self-reactive T cell clones and thus preserving immune homeostasis. Cancer growth generates novel antigens which, in the adaptive cellular immune response, are taken up by antigen presenting cells (APCs). These antigens are degraded into peptides which are loaded onto major histocompatibility (MHC) molecules to form peptide-MHC complexes. The APCs then travel from the site of cancer formation into regional draining lymph nodes, where they are scanned by naïve T cells for peptide-MHC complexes that may have complementary interactions with its T cell receptor and associated CD3 complexes (TCR-CD3). If an appropriate complementary complex is engaged, the T cell may be activated and traffic back to the cancer site to destroy the cancer cells expressing those antigens. If the cancer is to avoid eradication by the immune system, it must find some way to escape this cycle of immune surveillance and destruction.[2] Cancer cells under pressure to develop immune resistance have commandeered a set of immune checkpoints to disarm attacking T cells, checkpoints which under normal circumstances function to prevent autoimmunity. To better understand this process, we must first understand in more detail the process by which T cells become activated.

The paradigm for T cell activation is a 2-signal model that was proposed more than 30 y ago.[3] Signal 1 occurs upon the interaction of TCR-CD3 with the peptide-MHC complex. Signal 2 derives from costimulatory signals. If signal 1 occurs in isolation, a state of anergy results, which may be an important mechanism by which the immune system maintains T cell tolerance and avoids autoimmunity.[4] With regards to signal 2, the precise

manner in which costimulation converts anergy to activation is unknown. However, a potent costimulatory interaction between CD28 on T cells and CD80 (B7) on APCs is thought to trigger IL-2 production and hence T cell proliferation.

The signals described above are positive regulatory signals directed toward the induction of a specific effector T cell response to ensure the elimination of foreign and aberrant pathogens. However, in parallel to this positive signaling loop is an important negative regulatory signaling system that serves to turn off T cell activation.[5] It can be imagined that once a pathogen is eliminated, there is a compelling functional reason to turn off a prolonged tissue-damaging immune response. One of the best described families of negative immune checkpoints is the B7:CD28 family.

The B7:CD28 family includes CTLA-4 (also known as CD152), PD-1 (CD279), and its ligands PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273). Cancer cells have been shown to appropriate these inhibitory immune checkpoints to escape immune surveillance and destruction.[6] Fortunately, drugs have been developed to combat these mechanisms and have been shown to be effective against melanoma. Although the bulk of current drug development is centered around the PD-1 axis, the CTLA-4 axis is notable for being the first target of immunotherapy in melanoma and thus warrants discussion here, especially given its continued relevance in combination with anti-PD-1 therapy.

CTLA-4 and ipilimumab

The costimulatory signal 2 required for T cell activation is typically generated when CD28 on the surface of the T cell binds to the B7–1/B7–2 ligand on the APC. After activation, T cells upregulate and translocate CTLA-4 molcules to the cell surface, which bind B7 with a higher avidity than CD28.[7] CTLA-4 is thus a CD28 homolog induced on activated T cells[8] which successfully outcompetes CD28 and generates an inhibitory signal via its immunoreceptor tyrosine-based inhibitory motif (ITIM) with the TCR to inhibit IL-2 secretion and T cell proliferation. The biological function of this axis is most clearly demonstrated in knockout mice.[9] These CTLA4 $^{-/-}$ mice developed a severe, fatal multiorgan autoimmune process due to an uncontrolled immune response. This pre-clinical work led to the development of ipilimumab, a fully human monoclonal antibody targeting CTLA-4. Ipilimumab received regulatory approval in the United States and in Europe in 2011 and in Canada in 2012 based on the results of a pivotal phase III trial showing significantly increased overall survival (OS) in melanoma patients who received ipilimumab (3 mg/kg) compared to those who received glycoprotein 100 (gp100) vaccine alone. Median OS was 10.0 versus 6.4 months (HR 0.68) in patients who received ipilimumab plus gp100 vs. gp100 alone, and 10.1 versus 6.4 months in patients who received ipilimumab alone vs. gp100 alone (HR 0.66).[10] Objective response rate (ORR) was also significantly improved in both groups treated with ipilimumab compared to gp100 alone (5.7 and 10.9% versus 1.5%, respectively). A second phase III trial randomized melanoma patients to ipilimumab (10 mg/kg) plus dacarbazine or placebo plus dacarbazine.[11] Median OS was found to be significantly increased in patients assigned to the ipilimumab plus dacarbazine arm (11.2 vs. 9.1 months), at the cost of a higher incidence of grade 3 and 4 toxicities, especially with immune-related adverse effects (38 versus 4%), most commonly diarrhea and colitis, hepatotoxicity, and dermatitis.

Ipilimumab is currently approved for the treatment of unresectable or metastatic melanoma at 3 mg/kg every 3 weeks for 4 doses. Although this drug can induce durable and prolonged response in patients with advanced melanoma, it is notable that a minority of patients achieve complete response. Response rates to ipilimumab remain comparable to chemotherapy at around 10%. The PD-1 agents, however, have much improved rates of response as well as durability of response in patients with advanced melanoma.

PD-1 and its ligands

PD-1 is an immune inhibitory receptor that was first described by Japanese researchers in 1992.[12] Its name of programmed death 1 derives from its isolation by subtractive hybridization of a T cell hybridoma undergoing programmed cell death. The PD-1 receptor protein is encoded by the *Pdcd1* gene, which is located on chromosome 1 in mice and chromosome 2 in humans. The protein is composed of 288 amino acids and has a globular extracellular domain (Ig), a 20 amino acid transmembrane domain and an intracellular domain of about 95 amino acids containing a immunoreceptor tyrosine-based inhibitory motif (ITIM) and also an immunoreceptor tyrosine-based switch motif (ITSM) that allows binding of adapter molecules with SH2 domains such as the SH2 domain protein IA (SH2DIA).

PD-1 belongs to the CD28 family and is widely expressed by activated CD4+ and CD8+ T cells, B cells and myeloid cells,[13,14] in contrast to the more restricted expression of CD28 and CTLA-4 (predominantly on T cells).

To date, 2 ligands for the PD-1 receptor have been identified; PD-L1 and PD-L2. PD-L-1 was described in 2000.[15] It is a 290 amino acid transmembrane protein encoded by the CD274 gene, which is located on mouse chromosome 19 and human chromosome 9. Inflammatory stimulation induces PD-L1 expression on many types of haematopoietic cells (professional and non-professional APCs) and nonhematopoietic cells (parenchymal cells of heart, placenta, lung). The second ligand for PD-1, PD-L2, was described in 2001.[16] This transmembrane protein is encoded by the Pdcd1lg2 gene, located near the CD274 gene. While PD-L1 is widely expressed in many types of tissues, PD-L2 expression is restricted to professional APCs.[17]

Like the CTLA-4 pathway, the PD-1 pathway attenuates T cell response by regulating overlapping signaling proteins that are part of the immune checkpoint pathway. However, while the CTLA-4 axis regulates T cell activation, PD-1 regulates effector T cell activity in response to infection or tumor progression. Interaction between PD-1 and its ligands triggers a number of inhibitory signals through the recruitment of SHP phosphatases to the ITSM of the cytoplasmic tail of PD-1. SHP-2 binding to the ITSM motif, in particular, is critical for PD-1 induced inhibition of the TCR. In this manner, the major role of PD-1 is to

Table 1. Selected completed and ongoing clinical trials of anti-PD-1 for melanoma or including melanoma

Clinical Trials No.	Phase	Treatment Regimen	Population	Status
NCT00441337	1	Nivolumab	Advanced solid tumors	Completed[21]
NCT00730639	1b	Nivolumab	Advanced solid tumors	Active, not recruiting[22,23]
NCT 01714739	1	Nivolumab + lirilumab (anti-KIR)	Advanced solid tumors	Recruiting
NCT01024231	1	Nivolumab + ipilimumab	Melanoma	Ongoing, not recruiting[29]
NCT01176461	1	Nivolumab + multiple class 1 peptides and montanide ISA 51 VG	Melanoma	Ongoing, not recruiting
NCT01176474	1	Nivolumab + multiple class 1 peptides and montanide ISA 51 VG	Melanoma	Recruiting
NCT01621490	1	Nivolumab vs. nivolumab + ipilimumab vs. ipilimumab	Melanoma	Recruiting
NCT01968109	1	Anti-LAG-3 (BMS-986016) +/- nivolumab	Advanced solid tumors	Recruiting
NCT00836888	1	Nivolumab	Advanced solid tumors	Ongoing, not recruiting
NCT01629758	1	Nivolumab + interleukin-21	Advanced solid tumors	Ongoing, not recruiting
NCT01927419	2	Nivolumab + ipilimumab vs. ipilimumab	Melanoma	Ongoing, not recruiting
NCT01783938	2	Sequential nivolumab and ipilimumab	Melanoma	Ongoing, not recruiting
NCT01721772	3	Nivolumab vs. dacarbazine	Melanoma	Ongoing, not recruiting
NCT1844505	3	Nivolumab +/- ipilimumab vs. ipilimumab	Melanoma	Ongoing, not recruiting
NCT01721746	3	Nivolumab vs. dacarbazine or carboplatin/paclitaxel after ipilimumab	Melanoma	Ongoing, not recruiting
NCT01721772	3	Nivolumab vs. dacarbazine	Melanoma	Ongoing, not recruiting
NCT01840579	1	Pembrolizumab	Advanced solid tumors	Recruiting
NCT01295827	1	Pembrolizumab	Melanoma, NSCLC	Ongoing, not recruiting[24,30]
NCT01704287	2	Pembrolizumab vs. chemotherapy	Melanoma	Ongoing, not recruiting
NCT01866319	3	Pembrolizumab vs. ipilimumab	Melanoma	Ongoing, not recruiting
NCT01435369	2	Pidizilumab (CT-011)	Melanoma	Completed[25]
NCT02013804	1	MEDI0680 (AMP-514)	Advanced solid tumors	Recruiting

regulate effector T cell activity and maintain self-tolerance; given the pattern of expression of the PD-1 ligands, PD-L1 dampens T cell function in peripheral tissues while PD-L2 appears to regulate immune T cell activation in lymphoid organs.

Tumor immunity and the PD-1 pathway

While tumors frequently express novel or aberrant patterns of antigen expression, effective clearance of tumors by T cells is uncommon and interaction between PD-1 and its ligands has been shown to be an escape mechanism to create tumor tolerance. The level of PD-L1 expression may provide the basis to predict which tumor types may be most likely to respond to drugs targeting the PD-1 axis. Tumors of several histologic types have been shown to express PD-L1; melanoma, however, is highly immunogenic as shown by its historical response to interferon alfa[18] and interleukin 2.[19] High levels of PD-L1 expression in melanoma have been correlated with poorer prognosis.[20] Drugs targeting the PD-1 axis have shown significant clinical activity in melanoma, leading to ongoing development of drugs in this area. Here, we will review completed and ongoing studies of anti-PD-1 agents for melanoma.

PD-1 antibodies

Two monoclonal antibodies targeting PD-1, nivolumab and pembrolizumab, have shown significant clinical activity in advanced melanoma. Further investigations of these drugs in combinations as well as several other PD-1 antibodies are in development (**Table 1**).

Nivolumab (BMS-936558, MDX-1106, ONO-4538) is a fully human IgG4 monoclonal antibody against PD-1. The results of the first-in-human trial with an anti-PD-1 agent, evaluating its safety and tolerability in a cohort of 39 patients with advanced refractory solid tumors, were published in 2010.[21] Results of a larger phase 1 trial enrolling 296 patients,[22] including 107 with melanoma,[23] have since been published. A multidose regimen was tested, with doses ranging from 0.1 to 10 mg/kg given once every 2 weeks on a 8-week treatment cycle. An overall response rate of 31% was seen in patients with melanoma, though notably as high as 41% in the 3 mg/kg group ($n = 17$). Median progression free survival (PFS) was 3.7 months (9.7 months in the 3 mg/kg group), median duration of response in 33 responding patients was 24 months (17.3 months in 3 mg/kg), and median overall survival (OS) was 16.8 months (20.3 months in 3 mg/kg). With regards to safety, common adverse events (AEs) of any grade were fatigue (32%), rash (23%) and diarrhea (18%), with 22% of patients experiencing grade 3 to 4 AEs. There were no drug-related deaths in the melanoma patients, although there were 3 deaths in the overall patient population associated with pneumonitis (occurring in 2 patients with non-small cell lung cancer and one with colorectal cancer). Based on the improved efficacy of the 3 mg/kg dose and the lack of a definitive relationship between nivolumab dose and toxicity, the 3 mg/kg dose has been selected for further investigation in late stage trials.

Pembrolizumab (MK-3475, lambrolizumab) is a humanized monoclonal IgG4 antibody against PD-1. The initial phase 1 study evaluating pembrolizumab enrolled 135 patients with

metastatic melanoma and treated them with doses ranging from 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks. Promising antitumor activity (response rate of 38% across all doses) and acceptable safety were noted,[24] and the clinical benefit was further assessed in a subsequent expansion cohort. In this cohort, 173 patients with progressive, unresectable melanoma and who had received at least 2 prior doses of ipilimumab were randomized to receive pembrolizumab at 2 or 10 mg/kg every 3 weeks.[26] ORRs for both dose level groups were 26%. Median PFS was 22 weeks in the 2 mg/kg group, and 14 weeks in the 10 mg/kg group; estimated Kaplan-Meier PFS rates at 24 weeks were 45 and 37%, respectively. The majority of responses occurred by week 12, with the median duration of response not yet reached with a median follow-up of 8 months. Pembrolizumab was well tolerated and AE profiles were similar between the 2 dose groups. Drug-related AEs occurred in 82% of patients in both dose groups; the most common of any grade were fatigue, pruritus, and rash. Grade 3 or 4 AEs occurred in only 12% of patients, most commonly fatigue. Grade 3 or 4 immune-mediated adverse events occurred in only 3 patients: autoimmune hepatitis, maculopapular rash, and pancreatitis. This study is the largest reported trial of anti-PD-1 treatment in melanoma patients, and the first reported randomized comparison of an anti-PD-1 agent. Based on this study, the United States Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab in September 2014 for use in patients with unresectable or metastatic melanoma with progressive disease despite treatment with ipilimumab and a BRAF inhibitor (if BRAF V600 mutation positive).

Pidizilumab (CT-011) is a humanized monoclonal IgG1k antibody against PD-1. Two previous phase 2 studies in lymphoma showed clinical activity, thus a phase 2 study to investigate the safety and efficacy of pidilizumab in patients with metastatic melanoma was reported as an abstract at the ASCO 2014 Annual Meeting.[25] 103 patients were randomized to 2 dose levels (1.5 or 6 mg/kg) given every 2 weeks for 27 weeks. Although ORR was low at 6%, below response rates described in melanoma with other PD-1 antibodies, OS at 12 months was 65%. There were no significant differences in response rate or 12-month survival rate between the 2 dose levels, or between those who were ipilimumab naïve vs. ipilimumab treated. Treatment was well tolerated. Trials investigating the use of pidizilumab in other histologic tumor types (including pancreatic, prostate, and renal cell cancers) are ongoing.

PD-L1 antibodies

Two phase 1 trials of PD-L1 antibodies have demonstrated promising activity in advanced melanoma, albeit with generally lower response rates than PD-1 antibodies.

BMS-936559/MDX-1105 is a high-affinity, fully human, PD-L1-specific, immunoglobulin (Ig) G4 monoclonal antibody that inhibits the binding of PD-L1 to PD-1. Initial results from a phase 1 trial enrolling 207 patients with advanced solid tumors (including 55 with melanoma) demonstrated durable tumor regression (ORR of 6 to 17%) and prolonged disease stabilization (rates of 12 to 41% at 24 weeks). Of the 52 evaluable patients with melanoma, there were 9 objective responses and 3 achieved a complete response. Immune-related adverse events were observed in 39% of all patients, with grade 3 or 4 events noted in 9%. Events of note included colitis and infusion reactions. MPDL3280A is a human monoclonal antibody with an engineered Fc-domain targeting PD-L1. Initial results from a phase 1 study of 171 patients with advanced solid tumors showing an ORR of 21%.[26] PFS at 24 weeks was 44%. Patients with PD-L1-positive tumors showed an ORR of 39% and a progressive disease (PD) rate of 12%, while those with PD-L1-negative showed an ORR of 13% and a PD rate of 59%. Of all treated patients, 39% reported grade 3 or 4 adverse events; events noted include hepatitis, rash and colitis. These initial results were reported in the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting Abstracts, with additional updates to follow.

Other anti-PD-L1 drugs (MEDI4736, MSB0010718C) are being investigated for the treatment of melanoma in early phase trials (**Table 2**).

There is one antibody against PD-L2 currently in development: AMP-224. A phase 1 dose escalation and expansion trial investigating AMP-224 as monotherapy in advanced cancers has been completed and results are pending (**Table 3**).

Future directions

The PD-1 and PD-L1 antibodies appear to be more active and less toxic than ipilimumab, most likely due to the more tumor-specific pathway of immune system activation. Although

Table 2. Selected ongoing clinical trials of anti-PD-L1 for melanoma or including melanoma

Clinical Trials No.	Phase	Treatment Regimen	Population	Status
NCT02027961	1/2	MEDI4736 + dabrafenib + trametinib, or trametinib alone	Melanoma	Recruiting
NCT01693562	1/2	MEDI4736	Advanced solid tumors	Recruiting
NCT01938612	1	MEDI4736	Advanced solid tumors	Recruiting
NCT01975831	1	MEDI4736 + tremelimumab	Advanced solid tumors	Recruiting
NCT01656642	1b	MPDL3280A + vemurafenib	Melanoma	Recruiting
NCT01375842	1	MPDL3280A	Solid tumors or hematological malignancies	Recruiting[26]
NCT01633970	1	MPDL3280A + bevacizumab and/or with chemotherapy	Advanced solid tumors	Recruiting
NCT01988896	1	MPDL3280A + cobimetinib	Advanced solid tumors	Recruiting
NCT01772004	1	MSB0010718C	Solid tumors	Recruiting
NCT01943461	1	MSB0010718C	Advanced solid tumors	Recruiting
NCT00729664	1	BMS-936559/MDX1105	Advanced or recurrent solid tumors	Ongoing, not recruiting[31]

Table 3. Clinical trial of anti-PD-L2 including melanoma

Clinical Trials No.	Phase	Treatment Regimen	Population	Status
NCT01352884	1	AMP-224	Advanced solid tumor, cutaneous T cell lymphoma	Completed

results of head-to-head trials comparing anti-PD-1 and anti-PD-L1 vs. ipilimumab have not yet been reported, immune-related AEs also seem to be less prevalent than those reported for ipilimumab. Given the distinct activity and toxicity profiles of the PD-1 axis drugs and ipilimumab, it would be logical to combine these immunotherapies with other, less toxic systemic therapies or even with each other. Indeed, trials of nivolumab and ipilimumab given concurrently or sequentially are underway (**Table 1**). Data reported in July 2013 from a phase 1 trial of concurrent or sequential nivolumab and ipilimumab, in which 53 patients were given concurrent therapy, and 33 patients were given sequenced therapy. Concurrent therapy consisted of nivolumab and ipilimumab every 3 weeks for 4 doses, followed by nivolumab monotherapy every 3 weeks for 4 doses. Sequenced therapy consisted of patients previously treated with ipilimumab who then received nivolumab every 2 weeks for up to 48 doses. In the concurrent cohort, response rate across all dose levels was 40%. This activity was notable for the rapid and deep responses observed; responses often occurred by the time of first assessment at 12 weeks, and 1-year survival was 82%. Of note, toxicities were similar to those reported with ipilimumab monotherapy: 53% of patients reported grade 3 or 4 toxicities, most commonly asymptomatic elevations in aminotransferase and lipase. Pneumonitis and renal abnormalities were also reported, and 21% of patients discontinued treatment due to toxicities. In the sequenced groups, response rate across 2 dose levels of nivolumab was 20%, and was seen in patients with and without prior response to ipilimumab. Similar to the nivolumab monotherapy trial, grade 3 or 4 toxicity was 18%. Results from a phase 3 trial investigating nivolumab concurrent versus sequential ipilimumab are forthcoming.

The more tumor-specific pathway of immune activation with the PD-1 drugs has also resulted in efforts to find a potential biomarker to predict response. Tumor expression of PD-L1 may be a potential candidate: data from the initial nivolumab trial suggested that a lack of PD-L1 expression was associated with a lack of response. Nine of 25 patients with PD-L1 expression had treatment response, whereas zero of 17 patients that did not express PD-L1 showed lack of response. [22] Subsequent data suggested that metastatic melanoma patients who lacked PD-L1 expression their tumor could still respond to PD-1/PD-L1 inhibition, albeit at a lower rate. [26,27,28]

While these results showed the utility of PD-L1 staining, this may not yet be useful at the individual patient level since patients with PD-L1 negative tumors can have responses to treatment. Ongoing clinical trials that have collected pre-treatment tumor biopsies will be useful in future assessment of PD-L1 expression and correlations with tumor response.

To summarize, the existence of an adaptive immune response in melanoma is suggested by the tremendous clinical success of antibodies targeting the PD-1/PD-L1 axis. While this has revolutionized the treatment strategy for patients with advanced melanoma and has certainly influenced management strategies for other tumor types, there remains much work to be done. The median overall survival of patients with metastatic melanoma remains relatively short, and new drug combinations and development of new drugs are crucial to continued improvement in patient outcomes. Over the next few years, sequential and synchronous combinations of immunotherapies and targeted agents are poised to transform the landscape of melanoma treatment.

Disclosure of Potential Conflicts of Interest

K.T. has no conflicts of interest to declare. A.D. is the recipient of grants from Bristol-Myers Squibb, Genentech, Merck and Roche, as well as consulting fees/honoraria from Merck and Roche.

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