

Melanoma: Understanding Relevant Molecular Pathways as Well as Available and Emerging Therapies

Trevor McKibbin, PharmD, MS, BCOP

There are 2 forms of skin cancer: melanoma and nonmelanoma, which includes basal cell carcinoma and squamous cell carcinoma. Melanoma is the rarest form of skin cancer, but it is more likely than other types of skin cancer to form metastases. The incidence of melanoma has been increasing, on average, about 1.4% annually in the United States over the last decade, partly because of a greater awareness of the disease.¹

A melanoma is a tumor that is produced by the malignant transformation of melanocytes that arise from the neural crest and migrate to the epidermis, uvea, meninges, and ectodermal mucosa.¹ Although melanomas typically occur on the skin, they can occur in other locations where neural cells migrate, such as the gastrointestinal tract or brain.² Melanoma is classified into 4 main types: superficial spreading, nodular, lentigo maligna, and acral lentiginous; there are also other rare forms.³⁻⁵

Acral lentiginous and other rare forms make up about 10% of melanoma cases, while the other 3 types make up 90% of all melanomas.³ Superficial spreading melanoma typically grows radially on the skin rather than deeper into the layers of the dermis. Nodular melanoma develops quickly; it affects the deeper layers of the skin and often is dark brown or black in color. Lentigo maligna melanoma is rarer; it is a slow-growing melanoma located in areas of pigmented skin called lentigo maligna. It is typically found in the elderly and is more prevalent on areas of the skin that are frequently exposed to the sun, such as the face. Acral melanoma is typically found on the soles of the feet, on the palms of the hands, close to the big toenail, or under nails. Although rare, acral melanoma is the most common type in darker-skinned individuals. Another rare form of melanoma is uveal (intraocular) melanoma, which makes up about 3% of all melanoma cases and occurs in the iris, ciliary body, and choroid of the eye.⁶

Abstract

Since 2011, 6 therapies, including cell signaling kinase inhibitors and immune checkpoint targeting antibodies, have been approved by the FDA for the treatment of melanoma. Due to advancements in research and a greater understanding of the role of the immune system in cancer as well as the molecular biology of melanoma tumors, novel therapies are emerging to combat and effectively manage melanoma tumors. Advances in research are resulting in prolonging rates of survival of patients with metastatic melanoma. Research is ongoing to gain deeper insight to discover (1) which patients are most likely to respond to and benefit from immunotherapy, (2) how to treat patients who have disease progression after treatment with targeted agents, and (3) how best to combine these approved immunologic therapies, targeted drugs, and emerging therapies, as well as their safety and efficacy.

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Statistics of Advanced/Metastatic Melanoma in the United States

Melanoma is the sixth most commonly diagnosed cancer in the United States, accounting for an estimated 4.5% of all newly diagnosed cancer cases annually. According to the National Cancer Institute, an estimated 73,870 new cases will have been diagnosed in 2015.¹ In its early stages, malignant melanoma is curable by surgical resection; the survival rate is 98.3% for these localized cases, decreasing to 63% for regional melanoma that has spread to lymph nodes.⁷

An estimated 4% of melanoma cases are classified as metastatic. Before the introduction of the newer immunotherapies and targeted oral agents to treat this disease, the median survival time for a patient with metastatic melanoma ranged from 6 to 9 months with treatment.⁷

Metastatic melanoma is among the most aggressive types of tumors; an estimated 9940 patients with metastatic melanoma will have died from this cancer in 2015. Melanoma accounts for an estimated 1.7% of all cancer deaths in the United States annually.¹

Melanoma is most prevalent in Caucasians and non-Hispanics and affects more men than women. It is most commonly diagnosed in patients aged 55 to 64 years.¹

Pathways to Management of Advanced/Metastatic Melanoma

In the last decade, basic and translational research have led to the development of therapies that target specific driver mutations and new classes of immunotherapy, yielding improved disease responses and prolonged survival. The knowledge of immune system signaling has fueled advances in immunotherapies. As a result, 3 immunotherapy antibodies and 3 oral, targeted agents have been approved since 2011 (see [Table 8-16](#)). In addition, mutations in multiple-signaling pathways have been identified that lead to aberrant signaling and tumor cell growth. Although metastatic melanoma remains a fatal disease with a high rate of mortality, the survival of patients with metastatic disease has improved because of these available therapies; a substantial portion of these patients now respond to treatment, and a minority have long-term, durable remission.^{17,18}

The most prevalent mutation in melanoma is in the BRAF gene, which encodes a serine/threonine kinase that activates the mitogen-activated protein kinase (MAPK)/ERK-signaling pathway.^{6,19,20} RAF itself is activated by the RAS oncogene and has the highest measured basal kinase activity of the RAF kinases, providing a possible rationale for the frequent mutation activation

of BRAF observed in melanoma and other human cancers.²¹ Just downstream of BRAF in this signaling pathway are the 2 MEK proteins—MEK1 and MEK2. The activated BRAF protein kinase phosphorylates and activates these 2 MEK proteins that then activate the downstream MAP kinases.²²

This RAS/RAF/MEK/MAP kinase pathway mediates the cellular responses to growth signaling, regulating proliferation and survival of melanoma tumor cells and those of other tumor types. This pathway is constitutively active in BRAF-mutated melanoma, resulting in unchecked cell division and angiogenesis as well as evasion of cellular senescence and apoptosis.^{23,24}

An estimated 60% of patients with melanoma have tumors that harbor a BRAF mutation. The most frequent mutation, found in about 90% of BRAF-mutated tumors, is a substitution of glutamic acid for a valine in codon 600 (V600E), followed by V600K (substitution of a lysine for a valine) and 2 relatively infrequent mutations, V600D and V600R.^{21,25} The frequent mutation of BRAF and its direct activation of the MEK protein provide the rationale for drugs targeting both of these proteins in melanoma.²⁶

Activating mutations in NRAS, a GTPase that also activates the MAPK/ERK-signaling pathway, are found in about 15% to 25% of patients with metastatic melanoma.²⁷ Mutations in NRAS are most frequent in exon 1 and 2 of the gene.²⁸ NRAS-mutated melanomas tend to be more aggressive than BRAF-mutated tumors, and pre-clinical studies show that the dependence of these tumors on NRAS makes it an attractive drug target.^{26,27,29}

C-KIT mutations have been identified in less than 10% of melanomas. Mutations in C-KIT are most often found in mucosal melanoma, particularly mucosal melanoma derived from genital regions, as well as in acral melanoma.^{30,31} The activating C-KIT mutations or C-KIT gene amplification have been found in about 39% of mucosal melanomas, 36% of acral melanomas, and 28% of melanomas in chronically sun-damaged skin.³² KIT is an essential gene for both the development and survival of melanocytes³³ and an oncogene also found mutated in other tumor types. C-KIT is a receptor protein tyrosine kinase with both extracellular and intracellular portions. C-KIT binds to the stem cell factor, facilitating growth of certain cell types. The most common C-KIT mutations are within the near-membrane region of the protein in exon 11.³⁴

Other rarer mutations have been identified, including mutations in the GNAQ, CDK4, and ERBB4 genes. The molecular signaling mechanisms of melanoma tumors continue to be studied.³⁵

■ **Table.** FDA-Approved Therapies for Metastatic Melanoma⁸⁻¹⁶

Agent	MOA	Indication	Accompanying Diagnostic	Approval Date
Alkylating Agents				
Dacarbazine (DTIC)	Cytotoxic, alkylating agent (IV)	Metastatic melanoma	N/A	1975
BRAF Inhibitors				
Vemurafenib (Zelboraf)	BRAF inhibitor (oral)	1L and 2L BRAF V600E-positive metastatic melanoma	cobas 4800, BRAF V600 Mutation Test	August 2011
Dabrafenib (Tafinlar)	BRAF inhibitor (oral)	1L and 2L BRAF V600E-positive metastatic melanoma	THxID BRAF assay	May 2013
MEK Inhibitors				
Trametinib (Mekinist)	MEK inhibitor (oral)	1L or 2L BRAF V600E- or V600K-positive metastatic melanoma only in those who have not received a prior BRAF inhibitor	THxID BRAF assay	May 2013
Combined Therapy				
Dabrafenib + Trametinib	BRAF inhibitor + MEK inhibitor	1L or 2L BRAF V600E- or V600K-positive metastatic melanoma only in those who have not received a prior BRAF inhibitor	THxID BRAF assay	January 2014
Interleukins				
High-dose Interleukin-2 (IL-2)	Interleukin (immunotherapy, IV)	Metastatic melanoma	N/A	1998
Anti-CTLA-4 Inhibitors				
Ipilimumab (Yervoy)	Anti-CTLA-4 antibody (immunotherapy, IV)	1L and 2L metastatic melanoma	N/A	March 2011
PD-1 Inhibitors				
Pembrolizumab (Keytruda)	Anti-PD-1 antibody (immunotherapy, IV)	2L positive in metastatic melanoma patients who have received therapy with ipilimumab or a BRAF inhibitor for BRAF-mutant positive patients	N/A	September 2014
Nivolumab (Opdivo)	Anti-PD-1 antibody (immunotherapy, IV)	2L positive in metastatic melanoma patients who have received therapy with ipilimumab or a BRAF inhibitor and ipilimumab for BRAF-mutant positive patients	N/A	December 2014

CTLA-4 indicates cytotoxic T-lymphocyte-associated antigen 4; IV, intravenous; L, line; MOA, mechanism of action; PD-1, programmed death-1.

Another potential therapeutic target for advanced melanoma is angiogenesis. As tumors advance, they require vasculature to sustain their growth, metastasize, and invade tissues. The ability to stimulate growth of host blood vessels to support the tumor comes from the release of growth factors for endothelial cells, which then stimulate blood vessel growth.³⁶ The development of a vascular

network correlates with progression of melanoma; a relationship between angiogenesis, inflammation, and metastasis has been found in melanoma.^{37,38} Melanoma cells produce and secrete vascular endothelial growth factor (VEGF), which is an important angiogenic factor and a signaling molecule that affects vascular permeability.³⁹ Factors related to angiogenesis, including VEGF-A, have

been shown to correlate with poor clinical outcomes and could predict survival in melanoma patients.⁴⁰ Earlier-stage patients who do not have an increase in levels of VEGF-A in their plasma are likely to have a remission.⁴¹ These studies and others provide the rationale for targeting angiogenesis as a potential therapy for melanoma.

Immunotherapeutic Pathways of Advanced/Metastatic Melanoma

Rare cases of spontaneous remissions in patients with metastatic melanoma are evidence that the immune system can respond to and eradicate melanoma.⁴² This hypothesis is further proven by the small subset of patients with advanced disease who respond to treatment with high-dose interleukin-2.⁴³ Both the innate and adaptive immune systems play a role in tumor cell immunosurveillance. Tumor cell antigens are either mutated proteins unique to tumor cells or proteins found on normal cells but produced in larger amounts by tumor cells. The adaptive immune system responds to both types of tumor antigens. Dendritic cells are activated when exposed to these antigens. These cells then present these tumor antigens to T and B cells. With the bound tumor antigen, the now activated T cells undergo clonal expansion and focus on the tumor to mount an antitumor response.⁴⁴ T-cell activation and expansion is partly mediated by molecules and receptors on immune cells as well as cells of the body. These receptor-molecule interactions can either be co-stimulatory or co-inhibitory. They function to make sure that T-cell responses are only mounted against foreign antigens and that these immune responses are short-lived.⁴⁵

Tumor cells have evolved ways to interact with these co-stimulatory and co-inhibitory receptors to dampen the immune system's ability to mount a tumor attack and avoid tumor surveillance. The regulatory co-inhibitory pathways that constrain the immune system's response to cancer are beginning to be well characterized. One such pathway is the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an immune checkpoint molecule expressed on tumor cells that binds to CTLA-4 receptors on T-cells to downregulate antitumor T-cell activation. Binding of CTLA-4 to CTLA-4 receptors competes with binding of ligands that activate cytotoxic T cells.^{45,46}

Another co-inhibitory pathway involves the programmed death-1 (PD-1) T-cell co-receptor and its 2 ligands, B7-H1/PD-L1 and B7-DC/PD-L2.⁴⁷ Research has demonstrated that tumor cells express PD-L1 to dampen the ability of T cells to mount an antitumor response.

CTLA-4 and PD-1 play different roles in regulating the T-cell-mediated adaptive immune system response. CTLA-4 is responsible for mediating early T-cell activation of naïve and memory T cells, lessening the T-cell signal and activity. In contrast, the role of PD-1 is to minimize the activity of T cells in the periphery during an inflammatory-based response to an infection or to limit autoimmunity, as PD-L1 and PD-L2 are both upregulated in response to inflammation.⁴⁷

Genetic and Other Testing in Patients With Advanced/Metastatic Melanoma

While next-generation sequencing studies have shown that melanoma harbors many genetic mutations, testing for the presence of genetic alterations in a patient's tumor is only useful when the mutation is actionable, meaning there is an approved drug or a drug in development that targets the mutation.

Laboratory tests have been developed to detect the presence of mutations from tumor biopsies.⁴⁸ These tests are performed before the start of first-line metastatic melanoma therapy; as BRAF and MEK inhibitors are now being tested in clinical trials as adjuvant therapies, the tests also may soon be performed for patients with stage III disease. Vemurafenib, a BRAF inhibitor, was approved by the FDA with a companion diagnostic, the cobas 4800 BRAF V600 Mutation Test, used to detect the presence of a BRAF V600 mutation. Dabrafenib, the second BRAF inhibitor approved, as well as trametinib, a MEK inhibitor, used either as monotherapies or in combination, also have a companion diagnostic called the THxID BRAF assay. These tests are able to detect V600E, V600K, and V600D substitution mutations in the BRAF gene with greater sensitivity than the Sanger sequencing technique.⁴⁹ In wild-type BRAF tumors, BRAF inhibitors enhance the activity of the MAP kinase pathway, and therefore tumor growth, making testing for the presence of BRAF mutations critical to determining appropriate therapy.⁵⁰

Clinicians can opt to test for the presence of an NRAS mutation using tumor biopsy before the start of any metastatic-indicated therapy, or only after the BRAF assay if the patient has BRAF wild-type disease, because NRAS targeted agents are still in clinical trials. Another testing option is the C-KIT mutation test, which can also be performed before the start of any therapy or if the patient is found to have BRAF wild-type disease. Patients with C-KIT mutations may be eligible to receive imatinib or dasatinib, both of which target the BCR/ABL kinase as well as C-KIT, and the Src tyrosine kinases.⁵¹

Targeted Therapies for Advanced/Metastatic Melanoma

The first orally-available, targeted agent approved by the FDA for the treatment of melanoma was vemurafenib in 2011. Vemurafenib, a selective BRAF kinase inhibitor, is approved for the treatment of patients with unresectable or metastatic melanoma who test positive for the BRAF V600E mutation. Vemurafenib is administered orally at 960 mg twice daily.⁹

Activity of vemurafenib in previously treated patients was tested in a 132-patient, randomized, phase 2 clinical trial of patients with BRAF V600E or BRAF V600K mutations. All patients in the trial had received at least 1 prior therapy for their advanced disease. After a median follow-up of 12.9 months, an independent review committee reported a response rate of 53%. Eight patients (6%) had a complete response and 47% had a partial response. Median duration of response was 6.7 months, and the majority of responses occurred within 6 weeks of therapy. However, some patients did not respond until after 6 months of treatment. Median overall survival (OS) was 15.9 months.⁵²

The benefits of vemurafenib for patients with metastatic melanoma were confirmed in the international, randomized BRIM-3 phase 3 trial of 675 BRAF V600E-positive patients as screened by the cobas 4800 BRAF V600 Mutation Test.^{52,53} Patients treated with vemurafenib had improved OS compared with those treated with the previous standard of care, dacarbazine (DTIC) at 1000 mg/m² intravenously every 3 weeks. Patients in the vemurafenib therapy arm had a 63% reduced risk of death from melanoma compared with those in the DTIC arm (hazard ratio, 0.37; $P < .001$). Patients in the vemurafenib arm were also 74% less likely to have tumor progression than those treated with chemotherapy. Median progression-free survival (PFS) was 5.3 months and 1.6 months in the vemurafenib and control arms, respectively.⁵¹

The most common low-grade (grade 1 and 2) adverse events (AEs) associated with the use of vemurafenib therapy included rash, arthralgia, photosensitivity, fatigue, alopecia, nausea, and vomiting. Cutaneous squamous-cell carcinomas (SCC), or keratoacanthomas, were diagnosed in 18% to 26% of patients receiving vemurafenib in both trials. High-grade AEs include arthralgia, rash, cutaneous SCC or keratoacanthoma, elevated liver enzymes, and photosensitivity reactions in at least 3% of patients.^{52,53} It is imperative that patients taking vemurafenib therapy be advised to avoid sun exposure.

The second BRAF inhibitor, dabrafenib, was approved in May 2013 by the FDA, along with trametinib, a MEK

inhibitor that is also used as monotherapy.¹⁰ Both agents were approved along with the THxID BRAF assay to test for BRAF mutation status. In a phase 3 clinical trial consisting of 250 melanoma patients with BRAF-mutated tumors, patients treated with 150-mg oral dabrafenib twice daily were 70% less likely to have disease progression than those treated with DTIC ($P < .0001$).⁴⁹ The estimated median PFS was 5.1 months in the dabrafenib arm, compared with 2.7 months in the DTIC arm. The most frequently reported AEs included hyperkeratosis, papillomas, palmar-plantar erythrodysesthesia, pyrexia, fatigue, headache, and arthralgia. Cutaneous SCC or keratoacanthoma occurred in 12 patients, basal cell carcinoma in 4 patients, mycosis fungoides in 1 patient, and new melanoma in 2 patients in the trial.⁵⁴

Trametinib, an oral MEK inhibitor, has also been shown to improve OS among patients with the BRAF V600E or V600K mutation. In a phase 3 randomized study of 322 patients who had not received a prior BRAF or MEK inhibitor therapy but could have received a prior biologic or chemotherapy, trametinib improved the median PFS by 3.3 months compared with DTIC (median PFS was 4.8 months and 1.5 months in the trametinib and DTIC arms, respectively). The risk of tumor progression or death was 55% lower in patients treated with trametinib compared with DTIC ($P < .001$). The most common AEs include rash, diarrhea, nausea, vomiting, fatigue, peripheral edema, alopecia, hypertension, and constipation. More severe AEs include cardiomyopathy (7%), interstitial lung disease (2.4%), central serous retinopathy (<1%), and retinal-vein occlusion (<1%).⁵⁵ Unlike treatment with BRAF inhibitors, trametinib does not cause cutaneous SCC.

Resistance to both BRAF and MEK inhibitor monotherapy eventually develops, and about half of patients typically experience disease progression 6 or 7 months after the start of treatment.^{52,54} Resistance to BRAF or MEK inhibitors is often through the reactivation of the MAP kinase pathway, including MEK mutations and novel mutations in the BRAF gene itself. Therefore, clinical trials have tested the combination of BRAF and MEK inhibitors, which in preclinical studies has been shown to more completely inhibit the MAP kinase pathway and delay the onset of resistance.^{56,57} Still, MAP kinase independent signaling through other receptor tyrosine kinases that fuel cancer growth has also been shown to develop.⁵⁶

The combination of dabrafenib and trametinib received an accelerated approval by the FDA in January 2014 based on response rates in a phase 2 open-label

trial of 247 patients with either BRAF V600E- or V600K-mutated disease. Patients received either dabrafenib alone or in combination with 1-mg or 2-mg trametinib twice daily. Patients treated with the combination had a 76% response rate compared with 54% with dabrafenib alone.⁵⁸ Median PFS was 9.4 months compared with 5.8 months in the dabrafenib-alone arm. Development of SCC was mitigated in patients treated with the combination compared with those treated with BRAF inhibitor monotherapy, reported as 7% versus 19%, respectively.⁵⁹ The incidence of cutaneous SCC, including keratoacanthomas, was 19% in patients treated with dabrafenib monotherapy, compared with 2% and 7% among those treated with the 2 dosing cohorts of dabrafenib plus trametinib ($P = .004$ and $P = .09$, respectively).⁵⁸ The most frequent AEs were mostly low grade, and included pyrexia and chills, fatigue, nausea, vomiting, and diarrhea. These results were subsequently confirmed in 2 large phase 3 randomized trials comparing dabrafenib plus trametinib to either dabrafenib or vemurafenib alone.^{18,59}

A phase 3 trial randomized 704 patients with metastatic melanoma and a BRAF mutation (V600E or V600K) to dabrafenib 150 mg orally twice daily with trametinib 2 mg orally once daily or vemurafenib 960 mg twice daily, with a primary end point of OS. A preplanned interim analysis led to discontinuation of the trial, with the combination of dabrafenib and trametinib significantly improving survival compared with vemurafenib alone (hazard ratio for death, 0.69 [$P = 0.005$] in the combination arm). PFS was 11.4 months in the combination group compared with 7.3 months in the vemurafenib group.^{58,59}

Two other BRAF-plus-MEK inhibitor combinations are also in development for BRAF V600-mutated metastatic melanoma. Vemurafenib plus the MEK inhibitor cobimetinib was evaluated in the phase 3 coBRIM trial, which was shown to reduce the risk of disease progression or death by 49% (hazard ratio, 0.51; $P < .0001$) compared with vemurafenib alone. The median PFS was 9.9 months and 6.2 months in the combination and control arms, respectively. The most common grade 3 or higher AEs in the combination arm were liver lab value abnormalities, elevated creatine phosphokinase, and diarrhea.⁶⁰ This combination is currently under review by the FDA.

A third BRAF (encorafenib, LGX818) plus MEK (binimetinib, MEK162) inhibitor combination is also being tested in a phase 3, randomized clinical trial.⁶¹ A different MEK inhibitor, selumetinib, is currently being tested in combination with dacarbazine for uveal melanoma in a phase 3, randomized clinical trial.⁶²

For C-KIT mutated tumors such as mucosal and acral melanomas, C-KIT inhibitors, including imatinib 400 mg orally twice daily, have been shown to be active, although responses may be short-lived.⁶³ For NRAS-mutated melanoma, MEK inhibitor monotherapy, as well as combinations, such as a MEK inhibitor plus a CDK inhibitor targeting cyclin D1/CDK4, are currently under investigation.^{64,65}

To target the angiogenesis process in melanoma, bevacizumab, the angiogenesis-inhibiting antibody, is currently being combined with vemurafenib and cobimetinib in a triple-combination, phase 2 clinical trial. This antibody is also being combined with ipilimumab, an immunotherapy antibody.^{66,67}

So far, the currently available targeted therapies have resulted in relatively rapid responses in patients with advanced melanoma. However, the drawback of targeted therapies is the development of resistance, even to combination therapies. Researchers are currently testing and developing combinations of targeted agents and immunotherapies, as well as triple combinations. A recent mouse model study showed that adding an immunotherapy to a regimen of a BRAF plus a MEK inhibitor improved anti-tumor activity, providing rationale for testing a similar triple combination in a human clinical trial.⁶⁸

Limitations of such targeted immunotherapy and triple combinations include the potential for higher toxicity that may not be tolerable for advanced melanoma patients. A phase 1 clinical trial combining vemurafenib plus ipilimumab was halted in 2013 because of a high incidence of liver toxicities. Grade 2 or 3 elevations of aminotransferase were seen in 4 of 6 patients treated in 1 cohort and in 3 of the first 4 patients in a second 6-patient cohort. The events resolved with treatment discontinuation or with initiation of glucocorticoids but resulted in the early termination of the trial.⁶⁹

Interleukins, Ipilimumab, Nivolumab, Pembrolizumab, and Combination Therapies

Immunotherapies for melanoma have been extensively studied because the tumors have a high number of mutations, providing a high immunogenic potential. In addition, melanomas typically have a relatively high number of tumor-infiltrating lymphocytes that have been activated against melanoma antigens.⁴³

The first immunotherapy for metastatic melanoma was approved in 1998, interleukin-2 (IL-2). Although the response rate with high-dose IL-2 is about 16%, when a response is elicited, it tends to be long-lasting and

durable. The use of IL-2, however, is limited to otherwise healthy patients because of the serious and sometimes life-threatening toxicity that can result from therapy. Patients must be in overall good physical condition and must have good cardiac, pulmonary, hepatic, and renal function. Some of the AEs associated with a high-dose IL-2 include low blood pressure, irregular heart rhythms, accumulation of fluid in the lungs, renal failure, hepatotoxicity, and high fever.⁷⁰

The first novel therapy approved for metastatic melanoma in over a decade, and the second immunotherapy approved for metastatic disease, was ipilimumab, an anti-CTLA-4 antibody.⁷¹ In March 2011, the FDA approved ipilimumab 3 mg/kg administered once every 3 weeks for a total of 4 doses as a single agent for both previously treated or treatment-naïve patients with metastatic or unresectable melanoma. A landmark phase 3 clinical trial randomized patients with metastatic melanoma to ipilimumab plus a glycoprotein 100 (gp100) vaccine, ipilimumab alone, or the gp100 vaccine alone, in a 3:1:1 ratio. The patients receiving ipilimumab had an improved OS compared with the gp100 peptide vaccine; the vaccine contributed no detectable benefit. Median OS was 10.1 months in the ipilimumab arm and was similar to the ipilimumab-plus-gp100 arm. Survival was significantly lower in the gp100 vaccine-only arm, at 6.4 months. The hazard ratio for death was 0.66 ($P = .003$) in the ipilimumab-plus-gp100 arm compared with gp100 alone. The response rate was 10.9% in the ipilimumab-treated arm.⁷²

Ipilimumab therapy causes grade 3 or 4 immune-related AEs (irAEs) in 10% to 15% of patients treated with ipilimumab—most often diarrhea, colitis, and endocrine-related events such as thyroid disorders, adrenal insufficiency, and inflammation of the pituitary (hypophysitis), which can cause hypopituitarism.⁷³ Patients treated with ipilimumab need to be carefully monitored before every dose for irAEs, which, if severe enough, may require the use of corticosteroids or infliximab, an anti-tumor necrosis factor (TNF)-alpha antibody. In some cases, temporary or permanent cessation of treatment may be warranted, and the irAEs are not necessarily indicative of a tumor's response to treatment. Biomarkers that can predict response to ipilimumab and other immunotherapies have not yet been identified, although it is an active area of research.⁷⁴

The so-called next-generation immune-checkpoint-inhibiting antibodies target either PD-1 or its ligand, PD-L1. Treatment with these newer antibodies results in fewer irAEs in patients than anti-CTLA-4 therapy.⁷³

Pembrolizumab, an anti-PD-1 antibody, was granted accelerated FDA approval in September 2014 for patients with unresectable or progressive metastatic melanoma, despite therapy with ipilimumab and, if BRAF V600-mutation positive, a BRAF inhibitor.¹⁵ Pembrolizumab is a human monoclonal antibody that binds to the PD-1 receptor, preventing it from binding to its ligands PD-L1 and PD-L2. Approval was based on a durable response rate in an international, open-label, randomized phase 1, dose-comparative trial. The overall response rate in the 173-patient trial was 26%. At the approved dose of 2 mg/kg every 3 weeks, 1 complete response and 20 partial responses occurred among 81 patients treated. Both BRAF-mutated and wild-type patients responded to treatment.⁷⁵

In a phase 3 international randomized clinical trial that compared responses to either pembrolizumab or ipilimumab, pembrolizumab resulted in improved response rates, which was 33.7% and 32.9% in the every-2-weeks and every-3-weeks pembrolizumab treatment arms, respectively, compared with 11.9% in the ipilimumab arm ($P < .001$ for both comparisons). Given the improved tolerability and responses, treatment with PD-1 antagonists may be considered first-line treatment in patients lacking BRAF mutations.⁷⁶

Common clinically important AEs associated with pembrolizumab include fatigue, pruritus, rash, arthralgia, and diarrhea, while common clinically important AEs for ipilimumab include pruritus, diarrhea, fatigue, and rash. The most commonly reported serious AEs that occur in 2% or more of patients include renal failure, pneumonitis, and cellulitis. Additional clinically significant irAEs with pembrolizumab include colitis, hypophysitis, hyperthyroidism, hypothyroidism, nephritis, and hepatitis; irAEs associated with patients treated with ipilimumab are colitis and hypophysitis.⁷⁷

The second anti-PD-1 antibody approved by the FDA, nivolumab, was the sixth new metastatic melanoma drug approved since 2011. Nivolumab, at a dose of 3 mg/kg every 2 weeks, was approved through an accelerated approval for second-line metastatic melanoma—those patients who did not respond to therapy with ipilimumab and/or a BRAF inhibitor in patients with BRAF-mutated melanoma.^{78,79} Nivolumab achieved a 32% overall response rate among 120 patients compared with 11% in patients treated with chemotherapy.⁷⁵ An estimated one-third of patients experienced a response lasting 6 months or longer. Grade 3/4 drug-related AEs occurred in 9% of patients treated with nivolumab compared with 31% of those treated with chemotherapy.⁷³

Nivolumab plus ipilimumab has also been tested in previously treated metastatic patients, based on preclinical data suggesting that the combination results in better treatment responses. The combination resulted in a 40% overall response rate when the therapies were given concurrently in a phase 1 dose-escalating trial of 53 patients. With the maximum dose, the overall response rate was 53%, including 3 complete responses among 17 patients. Patients responded quicker, by 12 weeks of therapy, compared with treatment with either agent alone. The 1-year survival rate was 85%. The most common AEs were elevated levels of lipase (13%), aspartate aminotransferase (13%), and alanine aminotransferase (11%).⁷⁸ In 2014, the updated 2-year survival rate with the combination was 79%.^{79,80}

In a randomized phase 2 trial of this immunotherapy combination, 61% of 72 patients with BRAF wild-type disease responded to the combination, including 22% who had a complete response, compared with 11% of the 37 patients treated with ipilimumab. Patients with BRAF-mutated disease had a 44% response rate to the combination, including 17% with complete responses.⁸⁰

The Checkmate 067 trial randomized 945 previously untreated patients to 1 of 3 arms: nivolumab alone (3 mg/kg every 2 weeks), ipilimumab alone (3 mg/kg every 3 weeks for 4 doses), or the combination of nivolumab (1 mg/kg every 3 weeks for 4 doses) and ipilimumab (3 mg/kg every 3 weeks for 4 doses) followed by nivolumab (3 mg/kg every 2 weeks). The combination led to an improvement in PFS to 11.5 months compared with 2.9 months with ipilimumab alone. Further, in PD-L1–negative tumors, PFS was longer with the combination (11.2 months) than with nivolumab alone (5.3 months). In PD-L1–positive tumors, PFS was similar at 14 months in the combination and nivolumab-alone groups and was 3.9 months with ipilimumab alone.⁸¹

MPDL3280A, an antibody targeted against PD-L1 is also being tested in patients with metastatic melanoma. In an initial phase 1 clinical trial, 26% of the 35 patients tested responded to therapy and drug-related AEs were similar to those seen with anti-PD-1 antibodies.⁸² MEDI4736, another anti-PD-L1 antibody, is currently under investigation in combination with dabrafenib and/or trametinib.⁸³

Immune checkpoint signaling pathways continue to be elucidated; novel immune checkpoint inhibitory and stimulating antibodies are entering phase 1 clinical trials that target pathways other than CTLA-4 and PD-1. These checkpoint proteins include indoleamine (2,3)-dioxygenase, which is involved in creating an immunosuppressive tumor

microenvironment for tumor growth; 4-1BB (CD137), a member of the TNF family and a co-stimulatory molecule that induces T-cell proliferation; CD27, which plays a crucial role in the activation pathway of lymphocytes; and OX-40, also a TNF receptor that acts as a co-stimulatory factor for T cells. Another is lymphocyte activation gene 3, which, like PD-1, acts as a T-cell inhibitory co-receptor. Antagonist and agonist antibodies to these immune checkpoint molecules are being tested as monotherapies and will also be tested in combination with anti-PD-1 agents.⁸⁴

CONCLUSION

Although melanoma has historically been a difficult-to-treat cancer and has had minimal responses when treated with chemotherapy, advances in research offer the healthcare industry some degree of hope, especially when melanoma is detected early. In the last 5 years, there have been tremendous developments in the availability of therapies for the treatment of metastatic disease. Ongoing research and advances in gaining a better understanding of the molecular pathways and underlying tumor growth, including growth signaling and immune modulation, continue to provide future options for patients.

Healthcare providers face various challenges when treating patients with melanoma, such as selecting the best treatment option and designing well-thought-out clinical trials combining the available agents for maximal therapeutic benefit and minimal toxicity issues. Responses to immunotherapy are often prolonged, but may be delayed, and severe autoimmune AEs can be difficult to manage. Although BRAF and MEK inhibitors have higher response rates and more rapid responses, the responses are less durable. Anti-CTLA-4 inhibitors, PD-1 inhibitors, and additional emerging treatments can potentially offer hope and prognosis in patients who may not be responding to other therapies. The expanding pipeline of advanced melanoma therapies and continued investment in the molecular biology of this disease should result in continued advancement of how to optimally treat patients with metastatic melanoma and improve their OS.

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Address correspondence to: trevor.mckibbin@emory.edu.

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