Systemic Therapy for Metastatic Melanoma in 2012: Dawn of a New Era

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Key Words

Metastatic melanoma, stage IV melanoma, ipilimumab, vemurafenib, BRAF, CTLA-4, interleukin-2

Abstract

The 10-year survival rate for patients with metastatic melanoma is less than 10%. Although surgery and radiation therapy have a role in the treatment of metastatic disease, systemic therapy is the mainstay of treatment for these patients. After decades of failed attempts to improve treatment outcomes, recent successes with ipilimumab and vemurafenib have ushered in a new era in systemic therapy. Both ipilimumab and vemurafenib are associated with significant improvements in overall survival of patients in randomized phase III trials, an end point that had proven elusive so far. These breakthroughs not only provide more treatment options for patients with melanoma but also spur the investigation of a new generation of drugs for cancer therapy in general. This article reviews both the current systemic treatment options for metastatic melanoma and promising investigational approaches. (*JNCCN* 2012;10:403–412)

Metastatic melanoma continues to be a challenging disease to treat, with an estimated 8790 deaths from melanoma in the United States in 2011.[1] The 10-year survival rate for patients with metastatic melanoma is less than 10%.[2] For more than 3 decades after its initial approval by the FDA in 1975, dacarbazine was considered the benchmark systemic therapy for this disease. High-dose interleukin-2 (HD IL-2), approved by the FDA in 1998 for metastatic melanoma, is associated with durable complete remission in a subset of patients, but the therapeutic efficacy of HD IL-2 is limited by treatment-associated toxicities and a lack of biomarkers predictive of response to therapy.

Numerous attempts to improve on the survival of patients with metastatic disease met with failure in the past, and a pressing need existed for successful new therapies. However, this changed recently with the successful investigations of ipilimumab and vemurafenib, with both therapies associated with significantly improved overall survival of patients with metastatic melanoma in phase III trials.[3,4] The FDA approval of these drugs for metastatic melanoma marks the dawn of a new era of systemic therapy for this life-threatening malignancy. Understanding of the biology of melanoma continues to increase steadily, and several other promising therapeutic approaches are currently under investigation. This article summarizes the available systemic therapies for melanoma, with a focus on ipilimumab and vemurafenib; discusses important considerations in selecting a treatment from the available options; and highlights some of the promising investigational approaches for this disease.

Therapeutic Options for Stage IV Melanoma

Although locoregional treatment modalities, such as surgery or radiation therapy, may provide palliation of symptoms caused by local tumor growth, the cornerstone of treatment for metastatic melanoma is systemic therapy to address the clinical and subclinical sites of metastases. Chemotherapeutic agents with modest antitumor efficacy in metastatic melanoma include

alkylating agents (dacarbazine, temozolomide, nitrosoureas), the microtubular toxins (paclitaxel) and platinum analogs. Combinations of cytotoxic agents may yield somewhat higher response rates than monotherapy but are associated with greater toxicity and do not extend survival significantly.[5] The success of HD IL-2 in inducing durable complete remission in some patients with metastatic melanoma has provided proof of concept for the field of immunotherapy and has fuelled extensive investigation of several immunotherapeutic approaches, including ipilimumab. However, the efficacy of HD IL-2 has been limited by the low objective response rate (ORR), treatment-associated toxicities, and paucity of predictive biomarkers. Biochemotherapy regimens that combine cytotoxic agents with interferon-α and/or IL-2 have sometimes been associated with higher ORR, but this approach did not result in reproducible significant improvement in overall survival when compared with chemotherapy alone.[6]

The various systemic therapies that have been used before 2011 are reviewed in detail elsewhere.[5] This article focuses primarily on the 2 most recently approved drugs, ipilimumab and vemurafenib.

Ipilimumab

Ipilimumab is a human monoclonal antibody that binds the cytotoxic T-lymphocyte antigen (CTLA)-4 molecule. CTLA-4 is expressed on activated T lymphocytes and counteracts positive costimulatory signals to these cells mediated through other T-cell receptors, hence acting as a negative regulator of T-cell activation.[7,8] CTLA-4 is also constitutively expressed on regulatory T cells that inhibit excessive immune stimulation. CTLA-4 blockade has been shown in preclinical models to augment T-cell immune responses and to induce major regressions and even cure established tumors.[9,10] These findings led to an extensive investigation of ipilimumab in several clinical trials in melanoma and other malignancies. The promising results of early-phase trials of ipilimumab were recently validated by the demonstration of improved survival of patients with advanced melanoma in 2 separate phase III trials.[3,11]

Phase III Trials of Ipilimumab

Ipilimumab Monotherapy for Previously Treated Melanoma: HLA-A*0201–positive patients (n = 676) who had received 1 prior systemic therapy for unresectable stage III or IV melanoma were randomly assigned into 3 groups in a 1:1:3 ratio to receive HLA-A*0201–restricted glycoprotein (gp)100 vaccine alone (n = 136), ipilimumab alone (n = 137), or ipilimumab plus gp100 vaccine combination therapy (n = 403).[3] Ipilimumab was administered intravenously at a dose of 3 mg/kg every 3 weeks for up to 4 doses (induction) without any maintenance dosing; however, patients were eligible for reinduction therapy (with 4 more doses) at disease progression after initial benefit. The results of the trial showed that the median overall survival was significantly improved in the ipilimumab groups (10 months) compared with the gp100 monotherapy group (6.4 months). However, combination therapy with ipilimumab plus gp100 was not associated with superior efficacy over ipilimumab monotherapy. Although the choice of the control group in this trial (minimally active gp100 vaccine monotherapy for 12 weeks instead of the usual second-line therapeutic approaches, such as paclitaxel-based regimens, that may result in disease stabilization in a subset of patients) may have exaggerated the true impact of ipilimumab on overall survival of patients with melanoma, the results nevertheless confirmed the clinical efficacy of ipilimumab as an active therapeutic agent for treatment of advanced melanoma.

These data contributed to the FDA approval of ipilimumab monotherapy for patients with unresectable or metastatic melanoma at 3 mg/kg for up to 4 doses. The patients in the ipilimumab monotherapy group were all previously treated (23% with IL-2 therapy) and had a mean age of 56 years; ECOG score of 0 (52%) or 1 (47%); mostly M1c disease (73%); normal (61%) or elevated (38%) lactose dehydrogenase (LDH) levels; and mostly absence of central nervous system metastases (90%). The best ORR (assessed at week 12 or later) in the ipilimumab monotherapy group was 11% (complete remission, 1.5%; partial response, 9.5%), and the disease control rate, which was defined as the proportion of patients with objective response or stable disease, was 28%. Although the ORR and complete remission rates were low, responses were mostly durable, with 60% of the responders maintaining the response beyond 2 years.

The spectrum of toxicities was consistent with earlier-phase studies of ipilimumab, with 60% of patients on ipilimumab monotherapy experiencing

immune-related adverse events (IrAEs); however, severe IrAEs (grade 3 or 4) were seen in only 15% of patients and included diarrhea/colitis (8%), endocrinopathy (2%), dermatologic toxicity (< 2%), and hepatic toxicity (< 1%). Most IrAEs had resolved by 6 to 8 weeks with appropriate immunosuppressive treatment (mostly glucocorticoids), although residual symptoms (e.g., vitiligo, endocrinopathy symptoms, rectal pain) were sometimes present in long-term survivors. Treatment-related mortality from IrAEs was low (1%) in this study.

Ipilimumab Plus Dacarbazine in Previously Untreated Melanoma: Patients with previously untreated metastatic melanoma (n = 502) were randomly assigned in a 1:1 ratio to dacarbazine (850 mg/m^2) plus ipilimumab (10 mg/kg) or to dacarbazine plus placebo. Ipilimumab or placebo could be given every 3 weeks for a total of 4 doses (induction therapy), and then every 12 weeks starting at week 24 (maintenance therapy) in eligible patients.[11] Dacarbazine could be given every 3 weeks through week 22. The efficacy results showed significant improvement in median overall survival in the ipilimumab/dacarbazine group (11.2 months) compared with the group receiving dacarbazine alone (9.1 months). Overall survival rates were also higher in the ipilimumab/dacarbazine group versus the dacarbazine group at 1 year (47% vs. 36%), 2 years (28% vs. 18%), and 3 years (21% vs. 12%) (hazard ratio for death, 0.72; *P* < .001). The best ORR in the ipilimumab/dacarbazine group was 15% (complete remission, 1.6%; partial response, 13.6%) and the disease control rate was 33% (compared with an ORR of 10% and a disease control rate of 30% in the dacarbazine group). Only 17% of patients received one or more maintenance dose in the ipilimumab group.

Grade 3 or 4 adverse events occurred in 56% of patients treated with ipilimumab plus dacarbazine, compared with 28% treated with dacarbazine (*P* < .001). The rate of grade 3 or 4 IrAEs in the ipilimumab/dacarbazine group was fairly high (38%). The frequency of certain IrAEs was different from that seen in the prior studies; specifically, the rate of grade 3 or 4 immune-mediated hepatitis was much higher (32%) and the rates of grade 3 or 4 gastrointestinal events (5%) and endocrinopathy (0%) were much lower than those observed in most prior studies of ipilimumab monotherapy at doses of 10 mg/kg or lower.

Important Considerations With Use of Ipilimumab

Optimal Dose: The optimal dose of ipilimumab (3 or 10 mg/kg) remains undefined. In a randomized phase II trial, 217 patients with advanced melanoma were randomly assigned to a fixed dose of ipilimumab of either 10 mg/kg, 3.0 mg/kg, or 0.3 mg/kg every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months.[12] The best ORRs were 11% (10 mg/kg), 4% (3.0 mg/kg), and 0% (0.3 mg/kg), respectively, (*P* = .0015, trend test), and the 2-year survival rates were 30%, 24%, and 18%, respectively. The rates of grade 3 or 4 IrAEs were 18% (10 mg/kg), 5% (3.0 mg/kg), and 0% (0.3 mg/kg), respectively. This trial suggested that both the antitumor efficacy and toxicity were dose-dependent; however, the small number of patients in each group precludes a definite conclusion on the optimal dose of ipilimumab. Although a prospective phase III trial to compare the 3.0 versus 10 mg/kg dose is warranted, the FDA-approved 3.0-mg/kg dose is currently recommended. Also, because of a lack of clear evidence of synergy between ipilimumab and dacarbazine and the atypical toxicities observed with the combination, combination therapy with dacarbazine plus ipilimumab is not currently recommended.

Use of Maintenance or Reinduction Dosing: Patients who seem to derive clinical benefit from the induction phase (ipilimumab administered every 3 weeks for a total of 4 doses) may potentially benefit from continuation of ipilimumab as maintenance therapy (administered every 12 weeks)[11] or from reinduction dosing at disease progression.[3] These strategies may potentially assist the host immune system in continually adapting to the tumor immune evasion mechanisms (e.g., altered antigen expression, production of immunosuppressive cytokines, T-cell exhaustion) that lead to acquired refractoriness to immunotherapy. In the phase III ipilimumab monotherapy trial, 6% of patients in the ipilimumab groups received reinduction therapy at disease progression after experiencing initial clinical benefit (partial response/complete remission/stable disease), and approximately two-thirds of these patients reexperienced an objective response or stabilization of disease.[3]

Compared with the potential advantage of the reinduction strategy in some patients, the relative benefits of using maintenance dosing have been more challenging to ascertain. This difficulty stems at least

partially from the observation that antitumor responses from ipilimumab can have a delayed onset and may continue to evolve several months after the induction phase.[13] Despite the use of maintenance therapy in several clinical trials of ipilimumab, the ORR has been uniformly low and the 2-year survival rate seems to be similar across various trials. Because of the lack of data showing an improvement in efficacy with maintenance dosing, the high cost of ipilimumab ($30,000 for each 3 mg/kg dose) and the potential risk of late-onset IrAEs, the routine use of maintenance dosing of ipilimumab is currently not recommended, although reinduction doses may be considered at disease progression in patients who have clearly benefitted from induction doses of ipilimumab.

Response Kinetics and Patterns: Responses to ipilimumab (and other immunotherapies) are usually delayed compared with cytotoxic chemotherapy. In ipilimumab monotherapy trials, objective responses usually have been identified 12 to 16 weeks into the therapy and have sometimes continued to improve beyond week 24.[3,11,14] The late-onset tumor regression with ipilimumab is especially important to consider in patients who are symptomatic or at the risk of experiencing symptoms. Also, infiltration of tumors by immune cells may result in transient inflammatory swelling of tumors, further predisposing patients to symptoms from tumors that are bulky or in critical locations (such as the central nervous system). This inflammatory swelling of tumors may also be mistaken for disease progression by conventional antitumor response assessment criteria (Response Evaluation Criteria in Solid Tumors [RECIST][15] or WHO[16]) and may lead to inappropriate discontinuation of an effective immunotherapy.[14] These observations led to the development of modified criteria for evaluating antitumor responses to immune therapy of solid tumors.[17] These criteria allow for continuation of immune therapy despite mild progression of existing lesions or appearance of isolated new lesions as long as the total tumor burden is not significantly increased.

Immune-Related Adverse Events: In addition to the more common IrAEs seen with ipilimumab (diarrhea/colitis, dermatitis, hepatitis, and hypophysitis), other immune toxicities have also been observed in clinical trials, including episcleritis/uveitis, secondary sarcoidosis, neuropathies (e.g., enteric neuropathy, myasthenia gravis–type syndromes), and pancre-

atitis.[18,19] A history of autoimmune diseases should be considered a relative contraindication to the use of ipilimumab, and therefore these patients have been excluded from most clinical trials of this agent because of the risks of exacerbating the underlying autoimmune disease and developing severe IrAEs. Algorithms have been developed for managing the more common IrAEs, and usually include the use of immunosuppressive treatments, such as glucocorticoids or infliximab in severe cases.[18] The severity and onset of IrAEs may be different for various dose levels, and close vigilance, prompt identification, and aggressive treatment of IrAEs are essential to prevent potentially life-threatening complications and long-term morbidity. Fortunately, the use of glucocorticoids for management of IrAEs does not seem to interfere with the clinical efficacy of ipilimumab in patients experiencing response.[12,20]

Vemurafenib

Vemurafenib (PLX4032) is a potent inhibitor of oncogenic BRAF kinase.[21] The RAS–RAF–MEK–ERK–MAP kinase signaling pathway mediates cellular responses to growth signals.[22] The *BRAF* gene codes for 1 of the 3 serine/threonine kinases of the Raf kinase family, which is regulated by the (upstream) Ras protein. Somatic missense mutations in the *BRAF* gene that result in constitutive activation of the kinase have been reported in 60% of cutaneous malignant melanomas.[23,24] Approximately 80% to 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (*BRAF* V600E), although other activating mutations have been found (e.g., *BRAF* V600K, *BRAF* V600R).[25] The absolute and relative frequencies of the different mutations of *BRAF* are age-dependent, with an inverse relationship between age and *BRAF* mutation rate and a higher proportion of V600K mutations in older patients.[26]

Earlier attempts to target BRAF in melanoma with sorafenib, a weak inhibitor of mutant BRAF kinase, were not successful.[27] In contrast to sorafenib, however, vemurafenib is more potent and selective, with marked antitumor effects against melanoma cell lines with the *BRAF* V600E mutation but not against cells with wild-type *BRAF*.[21,28] In a phase I study, vemurafenib was associated with impressive clinical efficacy in patients with melanoma with tumors that harbored the *BRAF* V600E mutation.[29]

This led to the phase III investigation of vemurafenib versus dacarbazine in previously untreated patients with metastatic melanoma harboring the V600E mutation.[4]

Phase III Trial of Vemurafenib

In the phase III trial by Chapman et al.,[4] 675 patients with previously untreated metastatic melanoma with the *BRAF* mutation as detected with the Cobas 4800 *BRAF* V600 Mutation Test (Roche Molecular Systems, Branchburg, NY), were randomly assigned to receive vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg/m² intravenously every 3 weeks). Patients in the vemurafenib group had a median age of 56 years, ECOG score of 0 (68%) or 1 (32%), mostly M1c disease (68%), and mostly elevated LDH (58%). In the interim analysis for overall survival, the hazard ratio for death in the vemurafenib group was 0.37 (*P* < .001). At 6 months, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group. The data for progression-free survival were more mature, and the estimated median progression-free survival was 5.3 months in the vemurafenib group versus only 1.6 months in the dacarbazine group. Most of the patients receiving vemurafenib had tumor regression; the confirmed ORR was 48% in the vemurafenib group versus 5% in the dacarbazine group (*P* < .001). Tumor regression occurred early in the vemurafenib group, with the median time to objective response being approximately 6 weeks. These efficacy data led to the FDA approval of vemurafenib for the treatment of patients with unresectable or metastatic melanoma harboring *BRAF* V600E mutations.

Adverse events associated with vemurafenib were mostly grade 1 or 2, and included arthralgia, rash, alopecia, fatigue, nausea, photosensitivity, headache, and hyperkeratosis. Some patients developed cutaneous neoplasms, such as squamous cell carcinoma (12%), keratoacanthoma (8%), and skin papillomas (18%). Dose interruptions and/or dose modifications (to 720 or 480 mg twice daily) were required in 38% of patients on vemurafenib.

Important Considerations in Use of Vemurafenib

BRAF *Mutation Testing*: Accurate determination of the *BRAF* mutation status in melanoma tumor samples is critical, because the efficacy of vemurafenib is restricted to patients whose tumors harbor activating *BRAF* mutations.[29] Also, the use of BRAF inhibitors in wild-type *BRAF* cells may lead to the paradoxical activation of the downstream MEK-ERK pathway, especially if a preexisting upstream activator (such as *RAS* mutation) is present in the cells.[30] The reported trials of vemurafenib have included only patients with melanoma tumors that harbor *BRAF* V600E mutation, as detected with the Cobas 4800 *BRAF* V600 Mutation Test using a real-time polymerase chain reaction (RT-PCR) assay.[4,29] However, a sizable portion (~10%–30%) of melanoma tumors with a *BRAF* V600 mutation have activating mutations in *BRAF* other than V600E, including most commonly V600K, and less commonly V600D or V600R.[25] The efficacy of inhibitors of the V600E mutant form of BRAF seems to be preserved in patients with melanoma harboring V600K mutations.[4,25] Important considerations in accurate molecular diagnosis in patients with melanoma also include adequate sampling of tumor tissue, specimen processing, tumor heterogeneity, and characteristics of the diagnostic assay.

***Dermatologic Toxicity*:** Vemurafenib and other BRAF inhibitors in clinical development have been associated with dermatologic toxicities that are not typically seen with other cancer therapies. These include rapid development of cutaneous neoplasms, such as squamous cell carcinoma and keratoacanthoma; the median time to onset of squamous cell carcinoma is approximately 8 weeks.[29] The finding of *RAS* mutations in most of these neoplasms may explain the rapid proliferation of these neoplasms on vemurafenib therapy, and is probably related to the aforementioned activation of the downstream ERK signaling by BRAF inhibitors in wild-type *BRAF* cells.[30] Fortunately, these neoplasms can usually be excised easily with negative margins and have low invasive or metastatic potential.[31] Besides the need for close dermatologic surveillance for neoplasms, patients must also be cautioned about the extreme photosensitivity associated with vemurafenib and should be advised to minimize ultraviolet exposure.

***Resistance to Therapy*:** A small proportion of patients with *BRAF* V600 mutant melanoma do not respond to vemurafenib.[29] The mechanisms of this intrinsic (or primary) resistance are not yet completely understood, although loss of the tumor suppressor PTEN (phosphatase and tensin homolog) has been implicated.[32] Also, despite the high ORR with vemurafenib in *BRAF*-mutant melanoma, the eventual disease progression in most patients has

been sobering. The duration of response has ranged from 2 to more than 18 months,[29] and the median progression-free survival has been only 5.3 months.[4] The mechanisms of acquired (or secondary) resistance continue to be elucidated at a rapid pace,[33] and may include 1) reactivation of the ERK-MAP kinase signaling caused by flexible switching between RAF isoforms,[34] upstream activating mutations in *NRAS*,[35] downstream activating mutations in *MEK*,[36] or (at least theoretically) amplification of "gatekeeper" mutations in *BRAF*, and/or 2) activation of alternative signaling pathways, such as increased platelet-derived growth factor receptor β signaling[35] or activation of PI3K/AKT signaling via increased levels of insulin-like growth factor receptor 1.[34] The therapeutic resistance in *BRAF*-mutant melanoma may signify an evolutionary adaptation of melanoma cells to BRAF inhibition, selection of already-resistant subclones within a heterogeneous tumor population, or (likely) both. Thorough understanding of the diverse resistance mechanisms will be critical to further improve the effectiveness of BRAF inhibition in patients with *BRAF*-mutant melanoma.

Choosing Among Systemic Therapy Options

The availability of ipilimumab and vemurafenib has raised several questions about the optimal timing and sequence in the use of various systemic therapies available for patients with melanoma. In the absence of clinical trial data that directly address these important questions, the unique characteristics of the various therapies, such as mechanism of action, treatment-associated toxicity, and antitumor efficacy, may help customize therapy to match the unique goals of care for individual patients. The authors propose the following general guidelines for choosing among the various available options:

- Participation in a well-designed clinical trial, when feasible, should be strongly considered for all eligible patients until the advent of "curative" systemic therapies for this fatal disease
- Metastatic melanoma is eventually fatal in most patients and durable complete remissions are uncommon. Immunotherapeutic approaches, such as HD IL-2, have resulted in durable complete remission in a small subset (~6%) of patients[37] and should be considered in patients with good performance status and adequate organ function. Ipilimumab has also been associated with long-term responses, although the rate of complete remission has been low (< 2%) in most trials.[3,11,12] When considering an immunotherapeutic option (such as HD IL-2 or ipilimumab) for the goal of a durable complete remission, the low objective response rates and the potential for delayed responses should be kept in mind, especially in patients with symptomatic or bulky metastases; these patients may experience worsening of symptoms and/or decline in the performance status because of the immune-mediated inflammatory swelling of tumors or, more commonly, disease progression.

- In patients who have ongoing (or impending) symptoms from bulky metastases or tumors in critical locations, initiating therapy with an agent that is most likely to result in rapid tumor regression may be more desirable. Tumor debulking from this type of therapy may allow not only quick palliation of symptoms but also subsequent consideration of an (immunotherapeutic) approach. Vemurafenib has been associated with high ORR in patients with *BRAF*-mutant melanoma, and may provide rapid palliation of symptoms in this population. However, because most patients eventually develop resistance to vemurafenib, close surveillance is necessary to identify disease progression early for timely intervention with an alternative systemic therapy (such as immunotherapy for the goal of durable complete remission). In patients with *BRAF* wild-type melanoma tumors, cytotoxic chemotherapy may provide rapid-onset palliation, although ORR has historically been low (~10%–30%).[5]

- Close vigilance for unexpected toxicities is warranted with the sequential use of various therapies, because the safety of sequential administration of certain drugs is currently not known. For example, use of HD IL-2 administered sequentially after ipilimumab was reported to potentially result in severe gastrointestinal toxicities, such as bowel perforation.[38] Novel combinations of available agents should only be used in the context of a clinical trial. Many important unanswered questions are being addressed in clinical trials, including optimal combinations or sequencing of molecularly targeted and immunomodulatory therapies.

Systemic Therapy for Metastatic Melanoma

Table 1   Novel Immunotherapeutic Approaches for Metastatic Melanoma

Therapeutic Approach (Mechanism of Action)	Drugs	Selected Clinical Trials and Results	Comments
Immune checkpoint blocking drugs result in immune stimulation through blockade of regulatory mechanisms that limit immune activation	Ipilimumab, tremelimumab (anti–CTLA-4 antibody) MDX-1106, MK-3475/SCH 900475, CT-011 (anti-PD-1 antibodies) MDX-1105 (anti-PD-L1 antibody)	Phase I trial of ipilimumab plus bevacizumab showed an ORR of 32%, 6-month PFS of 59%, and 1-year OS of 72%; toxicities were manageable[39] Phase I trials of MDX-1106[40] and MDX-1105 have shown good tolerability and preliminary evidence of efficacy in melanoma and other solid tumors Phase III trial of ipilimumab vs. placebo for adjuvant therapy of high-risk melanoma has completed accrual; another phase III trial comparing ipilimumab vs. interferon therapy (ClinicalTrials.gov identifier: NCT01274338) is ongoing for resected high-risk melanoma (including resected stage IV) Efforts to combine ipilimumab with other therapeutic approaches, (including vemurafenib, HD IL-2, and other cytokines [GM-CSF, IL-21]; adoptive cellular therapy; chemotherapy; and MDX-1106), are ongoing	Given the low ORR and DCR and the high cost associated with ipilimumab monotherapy, discovery of biomarkers that could be predictive of clinical benefit from ipilimumab should be prioritized Rational combinations involving ipilimumab should be pursued with the goal of increasing the rate of durable responses Patients whose disease does not respond or develops resistance to ipilimumab may benefit from other immune checkpoint blocking drugs
Adoptive cell therapy (ACT) involves administration of immune cells that have been processed ex vivo after isolation from peripheral blood mononuclear cells or tumor-infiltrating lymphocytes (TILs)		Pooled analysis of 3 trials using ACT with TILs was recently reported to have a high rate of durable CR (22%) and high ORR (56%) despite heavy pretreatment[41] Multiple other trials of ACT are currently ongoing	Key considerations to successful use of ACT include optimization of its various individual components such as (lymphodepleting) conditioning regimens, ex vivo processing (selection, expansion, stimulation), and use of cytokines or ipilimumab to increase the persistence and efficacy of transferred cells[42]
Novel cytokines with unique immunomodulatory properties may overcome the tumor immune evasion mechanisms Novel approaches to deliver cytokines preferentially to the tumors may lead to decreased systemic toxicity and better efficacy	Cytokines: • IL-12 • IL-15 • IL-21 Approaches: • Electroporative gene therapy (EGT) • ALT-801 (IL-2 fused to T-cell receptor specific for p53)	IL-21 monotherapy has led to objective responses in melanoma in various trials[43-45] A phase II randomized trial of IL-21 vs. dacarbazine in treatment-naïve patients with melanoma is ongoing A phase I trial of IL-15 is ongoing (ClinicalTrials.gov identifier: NCT01021059) Intratumoral delivery of IL-12 using EGT in a phase I trial was associated with high DCR (53%) and CR (16%)[46]; a phase II trial is being planned In patients with melanoma, ALT-801 has been associated with clinical efficacy and decreased toxicity (with outpatient administration) compared with HD IL-2[47]	The novel cytokines may address the limitations of HD IL-2, such as high toxicity and low ORR that may be related to paradoxical suppression of the immune system (through proliferation of T-regs or through activation-induced cell death) Novel ways to deliver cytokines may enhance the therapeutic index and may make cytokines more feasible for combination therapy with other approaches
Vaccination with tumor antigens aims at active in vivo expansion of cytotoxic T cells against tumor-specific antigens	Gp100 peptide vaccine MAGE-A3 ASCI vaccine	A phase III trial of gp100 vaccine plus HD IL-2 vs. HD IL-2 alone showed improvement in ORR and PFS[48] A phase III trial of MAGE-A3 vaccine vs. placebo for adjuvant therapy of high-risk melanoma (DERMA trial) has completed accrual Monotherapy with MAGE-A3 vaccine is also being tested for M1a melanoma (PREDICT trial)	Due to the low response rates usually associated with vaccine monotherapy, this approach will most likely be used as an adjunct to other therapies Low toxicity associated with most cancer vaccines is attractive for combination with other therapies

Abbreviations: CR, complete remission; DCR, disease control rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; HD IL-2, high-dose interleukin 2; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; T-reg, regulatory T cell.

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Future Directions

Despite the recent success, the overall prognosis of stage IV melanoma remains poor and much work is required to further improve outcomes. The approval of ipilimumab and vemurafenib has fueled investigation of other novel immunotherapy and chemotherapy agents for the treatment of advanced melanoma. Some of the promising immunotherapeutic and chemotherapeutic approaches are outlined in Tables 1 and 2, respectively.

A thorough understanding of the resistance mechanisms to current therapies is critical for successful incorporation of novel therapies and combinations in the treatment algorithms. Besides the

need to consolidate on the success of vemurafenib in *BRAF*-mutant melanoma, the biology of *BRAF* wild-type melanoma and noncutaneous melanoma types (such as ocular and mucosal melanoma) must be elucidated further. The development of brain metastases is a major cause of mortality and morbidity in patients with melanoma, and should be addressed specifically through coordinated multidisciplinary research.

The low ORR associated with immunotherapeutic interventions highlights the need to research biomarkers that can predict responses to avoid unnecessary toxicity and expense. Most importantly, the immune evasion mechanisms used by the tumors must be understood better to improve the rate of du-

Table 2 Novel Chemotherapeutic Approaches for Metastatic Melanoma			
Therapeutic Approach (Mechanism of Action)	**Drugs**	**Selected Clinical Trials and Results**	**Comments**
Kinase inhibitors disrupt signaling pathways by inhibition of specific kinases	Vemurafenib, GSK2118436 (V600 mutant *BRAF* inhibitors)	Trial to test safety and efficacy of vemurafenib in patients with brain metastases is ongoing (ClinicalTrials.gov identifier: NCT01378975)	Despite the high initial ORR with BRAF inhibitors, the durability of responses remains to be determined; hence, close surveillance for PD is recommended for all patients with rapid institution of salvage therapy at the early signs of resistance
	AZD6244, GSK1120212, TAK-733, MEK162 (MEK inhibitors)	MEK inhibitors have been associated with clinical responses in mutant *BRAF* and wild-type BRAF melanoma tumors	
	BKM120 (PI3K-inhibitor)	Several trials of MEK inhibitors as monotherapy or in combination with other chemotherapy agents (e.g., docetaxel, temsirolimus, AKT- and PI3K-inhibitors) are ongoing	Inhibitors of mutant BRAF, unlike MEK inhibitors, do not seem to affect the function of cytotoxic T lymphocytes and may be optimal partners with immunotherapy[50,51]
		A phase I/II study of combination of MEK and mutant BRAF inhibitors showed safety and efficacy of this combination in *BRAF*-mutant melanoma patients[49]; dermatologic toxicity was markedly decreased with the combination and clinical responses were seen in patients who had previously developed resistance to BRAF-inhibition alone	A combination trial of vemurafenib with ipilimumab is being planned

Rational combinations of targeted therapies that address the putative mechanism of resistance to monotherapies should be pursued |
Nab-paclitaxel is an albumin-bound, nanoparticle form of paclitaxel, a microtubular toxin		In a phase II trial, nab-paclitaxel monotherapy had an ORR of 22% and DCR of 48% in chemotherapy-naïve patients with metastatic melanoma[52]	Cytotoxic chemotherapy may be useful in patients with *BRAF* wild-type melanoma, and in *BRAF*-mutant melanoma that has progressed after vemurafenib
		A phase III trial of nab-paclitaxel vs. dacarbazine has completed accrual	
		In a phase II trial of nab-paclitaxel plus bevacizumab as first-line therapy for melanoma, the ORR and DCR were 36% and 80%, respectively[53]	

Abbreviations: DCR, durable complete remission; ORR, overall response rate; PD, progressive disease.

rable complete remission, which should be the desired benchmark of success in metastatic melanoma. Furthermore, the feasibility and safety of combining these emerging systemic therapies with locoregional treatment modalities, such as surgery or radiation therapy, must be investigated in a systematic manner to optimize the multidisciplinary management of melanoma. Lastly, the cost-effectiveness of all therapeutic advances must be examined critically in this era of burgeoning health care expenses.

Conclusions

A new era in the systemic therapy of metastatic melanoma has begun with the recent successes of ipilimumab and vemurafenib. However, several questions remain regarding the optimal timing and sequence of the currently available therapies, the mechanisms of resistance to various agents, and the identification of predictive biomarkers. Promising new immunotherapy and molecularly targeted therapy approaches are in development. Until curative therapies are available for this life-threatening disease, participation in well-designed clinical trials should be considered the standard of care.

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