

By what way Physician can Enhance Outcomes in Patients with Metastatic Malignant Melanoma

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Abstract

Introduction: The incidence of malignant melanoma is increasing at a rate greater than any other human cancer. Although melanoma accounts for only 4 percent of all dermatologic cancers, it is responsible for 80 percent of deaths from skin cancer; only 14 percent of patients with metastatic melanoma survive for five years. The optimal therapy varies with the stage of the disease. Surgical excision is the treatment of choice for early disease, while some patients who are at high risk for developing metastatic disease (particularly those with stage II and III cancers may benefit from adjuvant therapy with interferon alfa (IFNa).(1) The management of patients with disseminated disease is a difficult problem. In carefully selected patients, excision of limited distant metastases can occasionally produce durable benefit. However, most patients with stage IV disease require systemic treatment. Traditional systemic treatment approaches include cytotoxic chemotherapy and immunotherapy. Several novel therapeutic approaches are under study, the most promising of which target specific molecular abnormalities that have been identified in melanomas. Molecularly targeted therapy for advanced melanoma will be reviewed here.(2)

Key Words: Malignant Melanoma, BRAF Mutation, Vemurafenib, Ipilimumab

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In carefully selected patients, excision of limited distant metastases can occasionally produce durable benefit. However, most patients with stage IV disease require systemic treatment. Traditional systemic treatment approaches include cytotoxic chemotherapy and immunotherapy.

Several novel therapeutic approaches are under study, the most promising of which target specific molecular abnormalities that have been identified in melanomas. Molecularly targeted therapy for advanced melanoma will be reviewed here.(2)

The aims of this review:

- Use current guidelines for workup and staging of melanoma to accurately diagnose advanced disease and plan appropriate therapy
- Apply a working knowledge of melanoma pathogenesis to prognosis and treatment strategies
- Develop individualized treatment plans for patients with metastatic melanoma and discuss with patients the benefits and risks of various immunotherapies, targeted therapies, and chemotherapies
- Recognize and effectively manage adverse effects of treatment, including immune-related adverse events
- Provide appropriate care and counsel for patients and their families

1-Initial workup for a patient with metastatic melanoma

Newly approved agents for patients with advanced unresectable or metastatic melanoma are dramatically changing the management paradigm for this malignancy. Importantly, the best management of individual patients with advanced melanoma begins with accurate assessment of the extent of disease.

Which of the following imaging methods would you recommend as routine evaluation for a patient with newly diagnosed metastatic melanoma?

- A. Computed tomography (CT) scan
- B. Positron emission tomography (PET) scan
- C. CT scan plus magnetic resonance imaging (MRI)
- D. PET scan plus MRI

Your answer: **D**

In the initial evaluation of patients for metastatic melanoma, most patients should have a CT scan to assess the extent of internal organ involvement. PET scans are useful for evaluating patients with disease limited to the extremities or as potential surgical candidates. Melanoma frequently metastasizes to the brain; an MRI of the brain is recommended for symptomatic patients such as those with seizures.

The panel of experts agreed that the recommended workup at baseline is a CT scan of the chest, abdomen, and pelvis. An MRI of the brain may or may not be appropriate, depending on the presence of symptoms or whether brain imaging is required by the patient's trial protocol. Some experts recommend a brain MRI even in the absence of symptoms, given the high incidence of brain metastases among these patients.(1) Still other experts recommend a baseline MRI that is only repeated if symptoms develop or if the patient is a part of a clinical trial.

Although the PET scan is gaining wider use, the panel recommends a CT scan for the majority of patients. The PET scan has limitations including inaccurate tumor size measurements and the risk of a false-positive result.(2) Moreover, changes in PET scans may not accurately reflect response to a therapy. For example, the BRAF inhibitor vemurafenib causes decreases in PET scan signals regardless of whether there is tumor shrinkage and disease improvement. The reason behind this effect is currently unknown.

Instances in which a PET scan may be useful include the following:

- A patient with primary melanoma in the foot or the leg and in whom there is suspected in-transit metastases in the legs.
- A patient with suspected metastases only in the bone. PET may be more sensitive in detecting bone metastases than other imaging modalities.
- A patient with stage III melanoma considering surgery.(2)

Scans should be repeated every 2-3 months, based on the patient's treatment regimen or protocol.

2. BRAF Mutation Testing in Metastatic Melanoma

Individualizing the management of patients diagnosed with metastatic melanoma requires oncologists to be knowledgeable regarding the clinical application of BRAF mutation testing.

Approximately how many of your patients with advanced melanoma do you test for BRAF V600 mutations?

- A. None
- B. A minority
- C. Approximately one half
- D. A majority
- E. All

Your answer: **D**

To provide appropriate care to patients with metastatic melanoma, it is essential to assess the BRAF mutation status of their disease. The new agent vemurafenib selectively inhibits the mutant BRAF kinase, providing significant clinical benefit only in those patients with advanced melanoma and this mutation. All of the expert panelists indicated that they now try to test all of their patients with metastatic melanoma for the BRAF V600E mutation. This activating mutation that drives disease progression is present in approximately one half of patients diagnosed with metastatic melanoma.(3) Thus, according to the panel, testing for the BRAF V600E mutation is now the standard of care for all patients with advanced unresectable or metastatic melanoma. As a result of the recent US Food and Drug Administration (FDA) approval of vemurafenib, the use of BRAF V600E mutation testing is certainly becoming more widespread. There is 1 FDA-approved test that was used in the clinical trials evaluating vemurafenib. (4, 5) Many pathology departments have already set up this assay. Alternatively, clinicians who do not have access to the approved test in their own institution can visit a Web site (<http://www.cobasbraftest.com>) and find the location of the nearest testing facility. The test uses unstained, formalin-fixed, paraffin-

embedded tissue slides prepared from biopsied tissue. A fresh biopsy is not necessary; archival slides from previous biopsies can be used for this test. Typically, for slides sent to a testing facility, the results are available within approximately 1 week.

Oncologists also need to know when it is appropriate to test for BRAF mutations during their patient's course of disease and how the test impacts the decision to initiate vemurafenib treatment.

In your current practice, when during a patient's course of care would you order a BRAF mutation test?

- A. At diagnosis of a primary melanoma lesion
- B. At diagnosis of stage IIIA (lymph node-positive) melanoma
- C. At initial diagnosis of metastatic melanoma
- D. Unsure

Your answer: **A**

BRAF mutation testing is important to identify appropriate patients with advanced unresectable or metastatic melanoma who are candidates for vemurafenib therapy. Earlier testing is currently not supported by clinical evidence and has the potential to be misleading as the disease progresses.

Currently, vemurafenib is only approved for patients with unresectable and metastatic melanoma. There are no data on the efficacy and safety of vemurafenib in earlier stages of the disease. Therefore, there is no need for BRAF mutation testing at the initial diagnosis of localized melanoma. However, the test should be done upon diagnosis of metastatic melanoma and can be performed on the formalin-fixed, paraffin-embedded tissue from the confirmatory biopsy as indicated above. The panel indicated that there is more uncertainty regarding the clinical use of BRAF testing in patients with stage III melanoma. In particular, many patients with stage IIIB and IIIC melanoma who have a high risk of recurrence are requesting the test to see whether vemurafenib will be an option for them, if needed. One panelist indicated they would only consider testing a patient with high-risk stage III disease that was unresectable or that was likely to progress to stage IV very quickly. Concerns raised regarding BRAF testing in stage III disease included the potential for discrepancy between the initial primary melanoma lesions and subsequent metastatic lesions that develop years later. This may reflect the relative quantity of tumor vs non-tumor DNA obtained from the biopsy of small primary lesions as found in stage IIIA disease as the assay sensitivity requires

that the tumor cells make up at least 5% to 10% of the sample in order to detect the mutation.(6) There is a greater concurrence in BRAF status in more advanced stage III disease and subsequent metastatic disease with the BRAF mutation status rarely changing over the course of disease.(7, 8) However, these discrepancies may also reflect heterogeneity of the primary melanoma, or the possibility that the metastatic melanoma arose from a separate, perhaps undetected, primary. This issue will require further investigation. For now, the panel supports the approach that clinicians should definitely assess a patient's BRAF mutation status upon an initial diagnosis of unresectable or metastatic melanoma.

A 53-year-old patient with extensive metastatic melanoma develops symptomatic disease and has a declining performance score. Would you initiate vemurafenib therapy before knowing the results of BRAF testing?

- A. Yes
- B. No
- C. Unsure

Your answer: **D**

Vemurafenib should not be given to patients until it has been established that they have a BRAF V600E mutation. Vemurafenib therapy is ineffective in patients without this mutation. Moreover, in addition to specific adverse effects, preliminary evidence suggests that vemurafenib can accelerate disease progression in some patients with melanoma that is BRAF wild type. All of the expert panelists agreed that obtaining results from BRAF mutation testing is essential before starting vemurafenib. There are several reasons for this. First, in the initial phase I study that evaluated vemurafenib antitumor activity in patients with various malignancies, no tumor responses were seen in patients with advanced melanoma and the wild-type BRAF gene.(9) Second, vemurafenib is associated with multiple adverse events including rash, fatigue, and the development of cutaneous squamous cell carcinomas (SCC).(10) Thus, treating patients with advanced melanoma harboring the wild-type BRAF gene would expose these patients to potential toxicities without any clinical benefit. Finally, there is consistent *in vitro* data showing that BRAF-targeted drugs such as vemurafenib activate the MAPK pathway in tumors with wild-type BRAF and can promote tumor growth.(6) Currently, there are no confirmed clinical characteristics that correlate with the presence of the BRAF mutation in patients with melanoma.

Initial data from an Australian patient cohort with metastatic melanoma suggest that the incidence of BRAF mutation in patients with melanoma decreases with increasing age.(11) However, this observation has not yet been verified in other studies.

3-Case Study: Initial treatment of BRAF mutation-positive metastatic melanoma

The best management of patients with previously untreated metastatic melanoma has been an important topic of discussion among melanoma experts. Consideration of individual patient and disease characteristics remains essential in the development of treatment decisions.

A 62-year-old patient with a previous history of melanoma comes in for a follow-up evaluation, which identifies 3 new lung lesions by CT scan. A biopsy confirms BRAF V600E mutation-positive metastatic melanoma. Which of the following treatment options would you recommend?

- A. Chemotherapy
- B. Interleukin (IL) 2
- C. Ipilimumab
- D. Vemurafenib
- E. Unsure

Your answer: **C**

For this patient with newly diagnosed metastatic melanoma with the BRAF mutation and a limited extent of disease, either ipilimumab or vemurafenib are reasonable options based on improved survival outcomes in large phase III trials. Additional clinical factors including age, comorbidities, and the presence or absence of symptoms are important considerations that influence the choice of first-line therapy. The expert faculty members were divided on the appropriate treatment approach for this patient, with 2 experts selecting ipilimumab and 1 expert choosing vemurafenib. The BRAF kinase inhibitor vemurafenib has become an important agent for the treatment of BRAF V600E mutation-positive metastatic melanoma. In the randomized, phase III trial of vemurafenib vs dacarbazine in patients with previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib was associated with a response rate of 48% with generally rapid tumor regressions.(5) In this study, the responses to vemurafenib were limited in duration with a median progression-free survival of 5.3 months. By contrast, ipilimumab, a CTLA-4-blocking monoclonal antibody that

enhances T-cell activation, induces responses in fewer patients.

In a phase III trial that enrolled previously treated patients with metastatic melanoma, ipilimumab as a single agent at a dose of 3 mg/kg resulted in an overall response rate of 11%.(12) Similarly, in a phase III trial that enrolled previously untreated patients with metastatic melanoma, ipilimumab at a dose of 10 mg/kg and combined with dacarbazine resulted in an overall response rate of approximately 15%.(13)

In addition, the tumor response induced by ipilimumab can be delayed following an initial increase in tumor volume or even the appearance of new lesions.

However, in contrast to vemurafenib, the tumor responses seen with ipilimumab are frequently durable. This was seen in both of the phase III trials of ipilimumab that reported improvements in 2-year overall survival to 23.5% from 13.7% in previously treated patients and to 28.5% from 17.9% in previously untreated patients with ipilimumab compared with the control arms. Moreover, ipilimumab offers the possibility of a sustained response off treatment, whereas vemurafenib needs to be continued indefinitely.

Based on these results, the panel suggested that ipilimumab may be preferable for selected patients, such as younger individuals, asymptomatic patients, or those with a limited extent of disease. The rapidity of disease progression and the possibility of future lines of therapy is also a consideration when selecting therapy for newly diagnosed metastatic melanoma. One expert explained that with vemurafenib, “a percentage of patients will progress so quickly that they will never receive ipilimumab.

If you start with ipilimumab, it is true that 60% of those patients will not have a benefit, but they will be able then to go on to vemurafenib if they have the BRAF V600 mutation, so they get 2 chances at an effective treatment.”

Vemurafenib may be the preferred treatment for patients with the BRAF V600E mutation and disease-related symptoms, extensive disease, or evidence of rapid disease progression especially if relief of pain or discomfort are important goals. The experts would not recommend chemotherapy using either dacarbazine or temozolomide as a first-line treatment for this relatively young patient with limited disease. However, the panel indicated that chemotherapy as first-line treatment may be appropriate for some patients who may not tolerate immunotherapy such as those with autoimmune

disorders or those who do not qualify for vemurafenib and therefore have limited options.

4-Initial treatment of BRAF wild-type metastatic melanoma

Approximately one half of patients with metastatic melanoma have a normal BRAF genotype. For this group of patients with newly diagnosed disease, consideration of individual patient and disease characteristics also remains essential in the development of optimal treatment decisions with immunotherapy or chemotherapy.

A 40-year-old patient with no previous history of melanoma presents with metastatic melanoma with 1 liver lesion and 2 lung lesions. The Eastern Cooperative Oncology Group performance score is 0, and a biopsy reveals BRAF wild-type disease. Which of the following treatment options would you recommend?

- A. Ipilimumab
- B. Vemurafenib
- C. IL-2
- D. Chemotherapy
- E. Unsure

Your answer: **A**

For this patient with newly diagnosed metastatic melanoma and a wild-type BRAF genotype, vemurafenib is not an option. In this case of a young and otherwise healthy patient with metastatic melanoma, immunotherapy using either ipilimumab or IL-2 are reasonable options based on evidence of durable responses in clinical trials.

All of the panel members agreed that immunotherapy is an appropriate strategy for this young and otherwise healthy patient with metastatic melanoma. Two of the experts on the panel indicated they would recommend ipilimumab rather than IL-2 based on similar overall response rates of 15% for both agents but a higher durable response rate for ipilimumab as well as better tolerability of ipilimumab than IL-2.^[12-16] Moreover, unlike IL-2, ipilimumab has demonstrated an overall survival benefit in randomized phase III trials as previously discussed.^[12,13] However, some experts would consider IL-2 for carefully selected patients, such as the patient described in this question. The criteria for identifying candidates for IL-2 therapy include a good performance score, excellent organ function, no extensive or active brain metastases, and patient motivation that generally selects for younger patients with metastatic disease. In addition, the data suggest that patients with lung-limited metastases are more likely to respond to IL-2 treatment.⁽¹⁷⁾ IL-2 is infused 3 times per day for up

to 28 doses in a course of therapy, causing activation of the patient's immune system. In the retrospective analysis reported by Atkins and colleagues,^(15, 16) 28% of responding patients remained progression free at a median follow-up of 62 months with no relapses reported in patients responding for longer than 30 months.

However, IL-2 therapy causes significant toxicity in almost all patients, including a capillary leak syndrome leading to hypotension and renal insufficiency potentially requiring hospitalization and, in some cases, intensive care treatment. Consequently, it is recommended that IL-2 therapy should be administered by experienced physicians and nurses with appropriate support.

The toxicities experienced by patients receiving IL-2 therapy subside quickly with the discontinuation of treatment unlike the toxicities associated with ipilimumab, which can last for weeks or months after treatment is stopped.

The use of IL-2 therapy for metastatic melanoma is likely to decline with the introduction of newer more effective and tolerable therapies, including ipilimumab and vemurafenib, as the panel noted that patients are less willing to undergo high-dose IL-2 therapy. The other treatment choices listed for this patient would not be appropriate according to the panel. Because this patient did not test positive for the BRAF V600E mutation, he is not a candidate for vemurafenib and would obtain no benefit from this agent while being exposed to potential adverse events and perhaps more rapid disease progression.

Chemotherapy would not be the first choice for this patient as immunotherapy has demonstrated the potential for a durable benefit. The panel recommended reserving chemotherapy for later lines of treatment in this case.

Finally, the panel noted that observation is not an option for this young, asymptomatic, and otherwise healthy patient with metastatic melanoma because this patient will eventually progress to life-threatening disease.

Observation may be considered for some elderly individuals with or without comorbidities and a limited life expectancy.

In particular, elderly patients with metastatic melanoma limited to soft tissue, lymph nodes, or perhaps the lung could have an indolent form of the disease.

One expert on the panel has followed this type of patient using performance score and scans every 2 or 3 months to assess the rate of disease progression. Some of these patients had indolent

disease and could be followed with close observation.

5- Managing adverse events with vemurafenib

Various adverse events are associated with vemurafenib treatment. Proper monitoring, including patient counseling, and the appropriate initiation of evidence-based management strategies are important to obtain the maximum benefit for patients receiving vemurafenib therapy.

A female patient with BRAF V600E mutation–positive metastatic melanoma is receiving vemurafenib. She has attained a partial response, but has grade 1 joint pain and fatigue. She also has a new skin lesion detected on exam; a biopsy reveals that the lesion is consistent with SCC. How would you proceed with this patient’s care?

- A. Continue vemurafenib as planned with excision of the SCC lesion
- B. Reduce the vemurafenib dose with excision of the SCC lesion
- C. Discontinue vemurafenib with excision of the SCC lesion
- D. Continue vemurafenib without excision of the SCC lesion
- E. Unsure

Your answer: B

Cutaneous lesions including keratoacanthomas and SCCs were the most common serious adverse events reported in patients treated with vemurafenib. In the clinical trial experience, no evidence of metastatic potential of the SCC lesions was reported, and the cutaneous lesions were managed with surgical excision without vemurafenib dosing modification. All of the experts on the panel recommended continuing vemurafenib as planned with surgical excision of the SCC lesion. Skin lesions, including keratoacanthomas and SCCs, are a primary adverse event associated with vemurafenib.(5)

Table- 1. Vemurafenib dosing modification for adverse events.

Grade 2 (intolerable)/grade 3 ■ 720 mg twice daily for first episode ■ 480 mg twice daily for second episode Grade 4 ■ 480 mg twice daily for first episode	Dose reduction (Interrupt treatment until resolution to grade 0-1)
Grade 2 (intolerable)/grade 3 ■ Third episode Grade 4 (any occurrence)	Discontinue therapy

In the phase III trial of vemurafenib vs dacarbazine as first-line therapy for patients with advanced unresectable or metastatic melanoma, 18% of vemurafenib-treated patients developed a cutaneous SCC, keratoacanthoma, or both. Grade 3 cutaneous SCC developed in 12% of patients; these lesions, which occur most often in the first 12 weeks of treatment, are usually self-limiting and can be cured with surgical resection.

Discontinuation of vemurafenib is not necessary. In the clinical trials of vemurafenib, the standard of care was to continue as planned with excision of the lesion and to follow patients with dermatological exams at 4- to 6-week intervals. No metastatic SCC lesion has been detected in the approximately 500 patients treated with this approach. Some patients developed multiple lesions, and thus, careful ongoing monitoring is essential. The most common adverse events aside from cutaneous events were arthralgia (21%), fatigue (13%), and photosensitivity skin reactions (12% grade 2/3). Less frequent vemurafenib-associated toxicities included grade 3/4 liver laboratory abnormalities and QTc prolongation.(18) To monitor for cardiac abnormalities, one expert on the panel recommended performing an electrocardiogram in the first few weeks of starting vemurafenib to ensure that the QT interval is not prolonged. Vemurafenib is also associated with hand-foot syndrome, which is characterized by an increase in keratinized skin on the hands or feet; this can become quite painful making it difficult for patients to walk. Hand-foot syndrome can be treated with topical keratolytics, including urea ointments or high-potency steroids. For patients who experience significant joint pain, management options include dose reductions or low-dose prednisone. In general, dose adjustments or the discontinuation of vemurafenib should be made according to established guidelines (Table- 1).

Managing Adverse Events With Ipilimumab

Ipilimumab is associated with a variety of potentially serious immune-related adverse events. These adverse events can be effectively managed with proper monitoring, patient counseling, and the appropriate initiation of evidence-based supportive care therapy allowing patients receiving ipilimumab to obtain the maximum clinical benefit.

A 47-year-old patient with metastatic melanoma is treated with single-agent ipilimumab following failure of dacarbazine. Two weeks after receiving the third dose, the patient develops

watery diarrhea (>6 episodes/day). There is no abdominal pain, no blood in the stools, and no evidence of a change in medications or diet.

Which of the following would you recommend to manage this patient's diarrhea?

- A. Initiate loperamide and notify if diarrhea continues
- B. Initiate intravenous methylprednisolone treatment
- C. Discontinue ipilimumab
- D. Emergency room gastrointestinal evaluation
- E. Unsure

Your answer: **A**

For this patient with a rapid onset of more than 6 daily bowel movements, it is important to obtain a quick response to reduce the inflammation and the potential for perforation. According to the Risk Evaluation and Mitigation Strategy program associated with ipilimumab, treatment should be discontinued for this patient and intravenous steroids should be initiated unless the bowel is perforated. Loperamide can be used for less-severe diarrhea, but patients should be monitored closely and steroid treatment initiated if the diarrhea continues. Ipilimumab is associated with the development of immune-related adverse events caused by the increase in T-cell activation. The most common immune-mediated adverse event is enterocolitis resulting in diarrhea, which occurs in approximately 35% of patients.(19) In the case of moderate enterocolitis, ipilimumab should be withheld, and antidiarrheal treatment should be administered.(19) If diarrhea persists for more than a week, systemic corticosteroids should be initiated at a dose of 0.5 mg/kg/day. If patients have 7 or more stools per day, methylprednisolone 1-2 mg/kg/day (or an equivalent dose of corticosteroids) should be started immediately, and ipilimumab should be permanently discontinued. Some of the panel experts suggested a more aggressive approach, with a lower threshold for starting intravenous steroids, in order to reduce the risk of continued bowel inflammation and bowel perforation. They suggested that loperamide could be considered for low-grade diarrhea, but for more severe diarrhea, or even for prolonged grade 1 diarrhea, intravenous steroids were recommended. Another option that was suggested for patients with 3 stools per day was the oral nonabsorbable steroid budesonide, switching to prednisone for approximately 4-6 weeks if the diarrhea does not resolve. The panel indicated that intravenous methylprednisolone should be administered for several days in the hospital until the diarrhea stops,

then tapering the steroids over 4-6 weeks to ensure that the diarrhea does not return. For cases in which steroids are ineffective, infliximab is an effective therapy in the vast majority of these patients. Because the enterocolitis and diarrhea associated with ipilimumab treatment is an immune-related adverse event, alternative approaches used to control diarrhea such as octreotide and gut microflora replacement do not have a role in the management of patients experiencing ipilimumab-associated gastrointestinal toxicity. Other immune-related adverse effects associated with ipilimumab include hepatotoxicity, endocrine toxicity (hypophysitis, thyroiditis), and dermatological toxicity, which are observed in fewer than 5% of the treated patients.(19) Serum chemistries including liver function (alanine aminotransferase, aspartate aminotransferase, and bilirubin) and thyroid function tests should be assessed before each dose and as medically necessary. If hepatotoxicity occurs and does not respond to systemic steroid treatment, the immunosuppressant mycophenolate can be used. Endocrine abnormalities can sometimes be difficult to detect, as they can present as nonspecific symptoms such as fatigue, or as hormonal changes in women. Oncologists may feel more comfortable having an endocrinologist follow the patient with them to address these adverse events. Another potential adverse event associated with ipilimumab is uveitis, which can typically be treated with topical steroidal eye drops. Therefore, patients should be monitored for the development of redness in the eye, which may suggest uveitis. Immune-related effects can also manifest as impaired kidney function and the presence of protein in the urine. The manufacturers of ipilimumab have developed a comprehensive Risk Evaluation and Mitigation Strategy program that clearly outlines the treatment related immune-mediated adverse events, providing a standard approach for the management of patients receiving ipilimumab. An important aspect of this program is the education of the patient regarding the various signs and symptoms of the adverse events associated with ipilimumab and maintaining close contact with the patient so that any adverse events can be quickly identified and appropriate management initiated (Table- 2).

6-Treatment of Metastatic Melanoma in the Salvage Setting

A majority of patients with metastatic melanoma will experience disease progression despite first-line therapy. The management of these patients is

also becoming more complex with increasing therapeutic options. In this setting, consideration of previous therapy along with other clinical factors is important to optimize an individual patient's outcome.

A 68-year-old woman with BRAF wild-type metastatic melanoma was previously treated with peginterferon for high-risk stage III disease with an ulcerated primary tumor. She initiates ipilimumab and has stable disease and mild abdominal discomfort. A scan after 8 months indicates disease progression with new lesions. Which of the following would you recommend for this patient now?

- A. Chemotherapy
- B. IL-2
- C. Vemurafenib
- D. Clinical trial
- E. Unsure

Your answer:

A clinical trial, if available, is a preferred option for patients who progress following initial therapy for metastatic melanoma according to guideline recommendations. High-dose IL-2 may also be an option for this patient depending on her overall health and whether she meets the criteria for IL-2 treatment. Chemotherapy is also an option with an increasing role in the salvage setting and a response rate of up to 30% for combination regimens. Vemurafenib should not be used in this patient with BRAF wild-type disease.

Table- 2. Signs of immune-related adverse events in patients receiving ipilimumab.

Physiologic system	Symptoms
Gastrointestinal tract	Diarrhea
	Pain
	Dark bloody stools
Skin	Rash (with or without itching)
	Blistering and peeling
	Oral sores
Liver	Jaundice
	Nausea/Vomitting
	Easier bleeding or bruising
Nervous system	Weakness in the extremities
	Numbness/tingling in the hands or feet
	Sensory changes
Endocrine	Headaches
	Fatigue
	Behavioral/mood changes
	Menstruation changes
Eyes	Dizziness/light-headedness
	Blurred vision or other vision problems
	Irritation (redness, pain)

Understanding what constitutes progression of patients receiving ipilimumab is an important factor in the management of patients treated with this agent. The timing of the tumor response to ipilimumab can differ from that commonly seen with other agents. Some patients may initially show stable disease or slight disease progression but still benefit from ipilimumab. Patients are usually scanned after completing all 4 doses of ipilimumab, typically at Week 12.

Even if patients show slight progression at this assessment, clinicians should consider continuing to observe the patient to allow time for slower responses. Some experts on the panel recommended repeating the scan 4-6 weeks later, depending on the results of the first scan. As long as the patient is not rapidly progressing, the panel suggested that observation could be continued with any benefits expected to be seen by Week 20.

A-Salvage Therapy After Ipilimumab

According to the panel, if the patient described in the preceding question had the BRAF V600E mutation, then vemurafenib would be an option. However, this patient has BRAF wild-type metastatic melanoma and, thus, is not a candidate for vemurafenib. The best approach for patients like this one after progression on ipilimumab is currently unclear. Some experts would consider IL-2 in this scenario based on the prolonged responses seen in some patients in clinical trials. But this would be an aggressive approach, and this 68-year-old patient may not be a suitable candidate for IL-2. In terms of sequencing of therapies, IL-2 may be more practical in the first-line setting. If IL-2 is not beneficial in the first-line setting, ipilimumab would certainly be an option afterwards based on the results of the phase III trial in previously treated patients which included patients who had received IL-2.(12) Clinical trials are particularly important for patients who progress on ipilimumab, and many ongoing trials are evaluating new approaches for patients with previously treated metastatic melanoma. Clinicians practicing at a site with no available clinical trials should consider contacting the nearest cancer center when considering treatment strategies for these patients. There is little guidance regarding reinduction therapy with ipilimumab, as reinduction is not included in the FDA-approved indication for the drug. However, in the pivotal phase III trial of ipilimumab, reinduction therapy did provide objective responses in several patients.(12) The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of

melanoma state that reinduction with ipilimumab may be considered for select patients who did not have significant systemic toxicity during prior ipilimumab and who relapse after attaining an initial clinical response or progress after having stable disease for longer than 3 months.(3) Some of the experts on the panel suggested that the decision for reinduction therapy with ipilimumab may depend on the duration and extent of response to ipilimumab. For a patient who had an objective response to ipilimumab for some time, then developed progression, the decision to reinduce with ipilimumab may be more straightforward. On the other hand, the use of ipilimumab reinduction in a patient who only attained stable disease with previous ipilimumab is more controversial, although it is included in the NCCN guidelines.(3)

B- Salvage Therapy After Vemurafenib

The best strategy for a patient with progressive disease on vemurafenib is not clear. It is currently not known if vemurafenib should be continued after progression, with the experts suggesting that the decision of whether to continue or discontinue the drug should be made on an individual basis. It was suggested that the approach may depend on the extent of the progression—if the patient is progressing at 1 site only, one approach may be to resect that area and continue the patient on therapy. In patients progressing at multiple sites, vemurafenib therapy is clearly failing, and patients need to start a different treatment such as ipilimumab, a clinical trial, or chemotherapy, depending on the patient's overall condition. The combination of ipilimumab and vemurafenib has not yet been evaluated, and the safety of this regimen is unknown. A phase I/II trial is evaluating vemurafenib plus ipilimumab in patients with BRAF V600E mutation-positive metastatic melanoma.(20) This approach is not currently recommended outside of a clinical trial.

C-Chemotherapy

With the introduction of new, more-effective first-line agents, chemotherapy is now used much less frequently by the experts on the panel in the first-line treatment of metastatic melanoma as indicated in the preceding discussions. In the panel's opinion, chemotherapy should generally be reserved for previously treated patients who have failed or are ineligible for ipilimumab, vemurafenib, IL-2, or a clinical trial. In particular, the panel cited patients with brain metastases and few other treatment options as possible candidates for first-line

chemotherapy. Dacarbazine and the orally available compound temozolomide have equivalent efficacy.(21, 22) Although some clinicians prefer dacarbazine, citing its lower cost, the faculty panel reported slightly greater use of temozolomide. Potential reasons for selecting temozolomide over dacarbazine included preference for an oral agent and a greater tolerance of temozolomide in older patients. Rietschel and colleagues(23) reported that an alternative dosing strategy for temozolomide, of 75 mg/m²/day for 6 weeks followed by a 2-week rest period every 8 weeks, is associated with equivalent efficacy but better tolerability compared with the standard dosing of 150-200 mg/m² for 5 continuous days every 4 weeks. In appropriate patients, combination chemotherapy may be preferable, as it is associated with a higher response rate than single agent chemotherapy. For example, a regimen of cisplatin/vindesine/dacarbazine is associated with an overall response rate of approximately 30%.(24) However, combination chemotherapy regimens are associated with greater toxicity, and thus, patients must be in better shape to tolerate the therapy.

The panel did not recommend combining chemotherapy with biologic agents (biochemotherapy) at this time, citing a lack of supporting evidence of benefit from multiple clinical trials, including a low response rate among previously treated patients and a lack of correlation between tumor response and survival in previously untreated patients.(25)

Ongoing Trials and Future Directions

Ongoing and planned clinical trials are continuing to evaluate new signaling pathway inhibitors for the treatment of metastatic melanoma, many with the goal of overcoming acquired resistance to single-agent vemurafenib.(26, 27)

These include other BRAF inhibitors; combination regimens with BRAF and MEK inhibitors; and a combination of vemurafenib plus inhibitors of the PI3-kinase pathway.

Additional immunotherapeutic agents are also being investigated. One agent that has generated recent interest in the melanoma community is the anti-PD-1 antibody MDX-1106. PD-1 is a negative regulatory molecule on T cells similar to CTLA-4, and thus, MDX-1106 has a mechanism similar to that of ipilimumab.

This agent has demonstrated response rates at least comparable to ipilimumab, and there appear to be fewer adverse effects.(28) An ongoing trial is

evaluating the efficacy and safety of ipilimumab plus MDX-1106.(29)

Finally, as indicated earlier, early-stage clinical trials are now beginning to evaluate the combination of signaling pathway inhibitors and immunotherapy in patients with advanced melanoma.(20)

Preclinical evidence suggests that this strategy may be promising as vemurafenib improves antigen-specific immune recognition by T cells in melanoma;(30) however, the safety of this approach can only be assessed with clinical trials.

Conclusion

The management of patients with metastatic melanoma is difficult. previously, the only approved therapies are immunotherapy with interleukin (IL)-2 and single agent cytotoxic chemotherapy. High-dose bolus interleukin (IL)-2 is associated with prolonged survival in a minority of carefully selected patients and may actually result in cure. This approach is associated with severe toxicity, however, and is only appropriate in carefully selected circumstances.(21, 22) Cytotoxic chemotherapy, using single agent dacarbazine, temozolomide, or fotemustine, has not been demonstrated to increase overall survival. The objective response rate with these agents is generally less than 20 percent, and most responses are of short duration. There has been no further improvement in results from combination chemotherapy or from regimens incorporation IL-2 or interferon alfa.(24) An understanding of the molecular pathogenesis has identified new targets for therapeutic intervention and may offer the opportunity for individualized patient therapy based upon the specific molecular abnormalities present in a particular tumor. In the mitogen-activated protein (MAP) kinase pathway. In this pathway, a number of cell surface tyrosine kinases can activate RAS, which sequentially activates BRAF, MEK, and ERK, leading to an upregulation of cyclin D1. Melanoma cells are dependent upon this pathway for their continued growth and survival.(26, 27) Activating mutations of BRAF, particularly the V600E mutation, are present in approximately one-half of patients with metastatic melanoma. Specific inhibitors BRAF, such as vemurafenib, have been highly active in this subset of patients in early clinical trials.(28) Responses have been seen in patients with visceral metastases and those who have previously been treated with other agents. Other potential targets associated with the MAP kinase pathway include MEK, which is downstream

from BRAF, and kit, which may activate Ras receptor at the cell surface.(30) Identification of specific mutations may allow effective individualization of therapy for smaller subsets of melanoma patients.

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