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## Emerging strategies for the treatment of metastatic melanoma: The role of monoclonal antibodies in targeted immunotherapy

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# Emerging strategies for the treatment of metastatic melanoma: The role of monoclonal antibodies in targeted immunotherapy

## Introduction

VAN ANH TRINH AND JAMIE POUST

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**M**etastatic melanoma is the most serious form of skin cancer and among the most difficult to treat of all cancer types. Melanoma is responsible for more than 75% of all skin cancer deaths and is one of the most common of all cancers among young adults.<sup>1</sup> The incidence of melanoma in the U.S. grew rapidly during the 1970s, at an annual rate of approximately 6%, and continues to increase at a rate of approximately 3% per year.<sup>1</sup> In 1973, the incidence of melanoma was 5.7 per 100,000 population; by 2002, the incidence had increased to 17.2 per 100,000.<sup>2</sup> When detected early, the prognosis for patients with melanoma is generally favorable, and surgical excision is often curative for patients with early lesions. The 5-year survival rate is approximately 90% for patients with early melanoma and thin lesions

(<1.5 mm), and is progressively lower for patient with thicker lesions.<sup>2</sup> However, despite a trend toward the earlier recognition of melanoma over the last several decades and the adoption of interferon  $\alpha$  as adjuvant therapy following surgery, mortality for patients with advanced disease has not decreased significantly since the 1970s.<sup>2</sup>

The management of metastatic melanoma presents many challenges for patients and health care professionals. Metastatic melanoma remains highly resistant to cancer therapy and response rates to most therapeutic options continue to be very low. Even the most active cytotoxic chemotherapy agent, dacarbazine, is associated with an overall response rate (complete plus partial responses) of only approximately 20%. Dacarbazine is associated with

many adverse events, including anorexia, nausea, vomiting, myelosuppression, local tissue damage caused by extravasation, and flu-like symptoms.<sup>3</sup> Long-term survival without disease recurrence is attained by fewer than 10% of patients who receive dacarbazine or interleukin-2, the only other FDA-approved agent for metastatic melanoma.<sup>4,5</sup> Combining cytotoxic chemotherapy and biologic therapy has resulted in increased response rates in some studies, but this approach is associated with increased toxicity and has not been clearly shown to improve overall survival.<sup>4,5</sup> Therefore, new treatment options are needed to improve treatment outcomes for patients with metastatic melanoma, and especially to extend long-term survival.

Several new strategies are currently being examined for patients

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ing the Hematology/Oncology Pharmacy Association Annual Meeting in Anaheim, California, and supported by an educational grant from Bristol-Myers Squibb. Drs. Trinh and Poust received honoraria for their participation in the symposium and for the preparation of this article. Drs. Trinh and Poust report having no significant financial relationship with any commercial entity related to this activity.

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with metastatic melanoma. Some of these approaches include targeted drug therapy via inhibition of signal transduction pathways, monoclonal antibodies, and vaccinations. Targeted drug therapy by inhibiting Bcl-2, which inhibits apoptosis, may increase sensitivity to chemotherapy.<sup>6</sup> Mutations in RAF kinase are associated with suppression of apoptosis and cell proliferation.<sup>7</sup> Sorafenib, an inhibitor of RAF kinase, is currently being evaluated as a potential therapeutic target for this pathway. Monoclonal antibodies targeting specific cell-surface receptor molecules or other targets have emerged as important potential treatments for patients with a variety of cancer types. The development of therapeutic monoclonal antibodies against cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) has been described as a promising approach for patients with melanoma.<sup>8</sup> CTLA-4 is a naturally occurring cell-surface protein that is expressed primarily by activated T cells. Upon exposure to antigens, CTLA-4 suppresses T-cell activation and promotes peripheral tolerance to self antigens.<sup>9</sup> Monoclonal antibodies against CTLA-4 enhance T-cell activation and stimulate T-cell responses against tumor cells. Two monoclonal antibodies against CTLA-4—ipilimumab and tremelimumab—are being evaluated in phase III clinical trials for metastatic melanoma. In early studies, these agents have induced tumor regression in some patients. The adverse event profiles associated with these monoclonal antibodies are distinct from conventional chemotherapy agents, and include inflammatory responses that may reflect an autoimmune process. These inflammatory responses may

be most pronounced among patients who have the best response to treatment.<sup>10,11</sup> Another novel approach to melanoma treatment is vaccines against melanoma-related antigens or vaccines that contain heat shock proteins.

Oncology pharmacists are uniquely positioned to collaborate with oncologists and other members of the health care team to develop comprehensive treatment plans for patients with melanoma. It is therefore essential that oncology pharmacists possess the information needed to evaluate novel therapies for melanoma and to educate patients and other health care professionals about the efficacy and safety characteristics of these emerging treatment options. The articles in this supplement provide pharmacists with an update and overview of the role of therapeutic monoclonal antibodies and other novel approaches to the treatment of patients with metastatic melanoma. The first article reviews the impact of metastatic melanoma and the current chemotherapy, immunotherapy, and biochemotherapy strategies that are used in the treatment of these patients are described. In the second article, recent research that has examined the efficacy and safety of monoclonal antibody therapy for metastatic melanoma is discussed, as are other treatments that are in development, including melanoma vaccines, antisense oligonucleotides to interrupt the production of cancer-related proteins, and the use of targeted biologic therapies that modulate specific cell pathways of growth or survival.

At the conclusion of this activity, readers should be able to discuss the current approaches to melanoma

therapy, as well as the success rates and limitations of these treatments. Readers should also be able to explain the rationale for the use of monoclonal antibodies and other targeted biologic therapies in melanoma care, and integrate these new treatments into melanoma management strategies as part of a clinical trial or as they are made available.

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# Current management of metastatic melanoma

VAN ANH TRINH

**M**elanoma is a type of cancer that originates in melanocytes, which are pigment-producing cells primarily located in the skin. In rare cases, melanoma may originate in other pigmented tissues, such as the mucosa (mucosal melanoma) or the eye (ocular melanoma). Melanoma accounts for approximately 3% of all cancer cases, but is especially likely to metastasize, and the death rate of metastatic melanoma is among the highest of all cancers.<sup>1</sup>

Although many new treatments for metastatic melanoma have been introduced over the last several decades, and dozens of clinical trials have been conducted to examine the efficacy and safety of these new options, it is clear that systemic therapies have done little to significantly improve long-term survival for patients with melanoma. This observation is illustrated by the results of a meta-analysis of more than 15,000 patients who were treated at the John Wayne Cancer Institute that examined the overall survival rates of patients with melanoma during three time periods: 1971–1978, 1979–1986, and 1987–1993.<sup>2</sup> The survival times for the patients in all 3 of these eras were virtually indistinguishable, suggesting that the introduction of new therapies had no discernable impact

**Purpose.** Metastatic melanoma and current treatments are reviewed.

**Summary.** Despite the many advances in cancer treatment that have occurred over the last several decades, the prognosis for patients with advanced melanoma remains poor. The 5-year survival rate for patients with distant metastases is less than 10%. For these patients, surgery and radiation therapy are primarily used to palliate symptoms. Most patients with advanced melanoma receive systemic therapy. Single-agent cytotoxic chemotherapy with dacarbazine is the standard of care in community practice, although the response rate is generally low and few patients attain complete remission. Temozolomide is an orally active congener of dacarbazine that is at least as effective as dacarbazine when used as single-agent cytotoxic therapy. Low-dose extended temozolomide regimens may provide greater antitumor efficacy. Combinations of dacarbazine or temozolomide with other cytotoxic therapies have not markedly improved patient survival. Newer agents (e.g., lomeguatrib and decitabine) have

been developed to overcome mechanisms of drug resistance. Biotherapy using high-dose interleukin-2 has been shown to induce durable responses lasting 5 years or more in some patients, although the overall response rate is not substantially better than that with dacarbazine. Interferon  $\alpha$  is also used for the treatment of metastatic melanoma, despite lack of approval by the FDA for this indication. Some evidence suggests that combining chemotherapy and biotherapy agents (biochemotherapy) increases the rate of treatment response but does not significantly extend overall survival.

**Conclusion.** New strategies are needed to improve treatment response rates and duration of overall survival in patients with metastatic melanoma.

**Index terms:** Antineoplastic agents; Dacarbazine; Decitabine; Interferon alfa; Interleukin 2; Lomeguatrib; Melanoma; Neoplasm metastasis; Radiation; Resistance; Surgery; Temozolomide

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on patient survival over the 22-year period studied.

Considerable recent research has focused on new treatment options to improve response rates and extend survival for patients with melanoma. This article provides an overview of the impact and current management

of metastatic cutaneous melanoma. An accompanying article describes the efficacy and safety of new treatment options that have recently been developed for the treatment of advanced melanoma. Extracutaneous forms, such as mucosal or ocular melanoma, are beyond the scope of

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this article, but have been recently reviewed.<sup>3</sup>

**Epidemiology and staging of melanoma**

According to the American Cancer Society (ACS), more than 62,000 new cases of melanoma are reported each year in the U.S.<sup>4</sup> For 2008, the ACS estimates that melanoma will account for 8420 deaths (5400 men and 3020 women). The true incidence of melanoma may be considerably greater than this because many cases are treated in outpatient settings and are not included in estimates of cancer prevalence or mortality. Melanoma is the sixth most common cancer diagnosis among men and the seventh most common among women,<sup>4</sup> but is second only to adult leukemia in terms of years of life lost. Melanoma is the leading cause of cancer death among women between 25 and 35 years old, and the second leading cause of cancer death (following breast cancer) in women between the ages of 30 and 35. The incidence of melanoma increased exponentially during the second half of the 20th century, from a rate of approximately 2 cases per 100,000 population in 1950 to nearly 18 cases per 100,000 population by the mid 1990s.<sup>5</sup> The death rate during this period increased linearly, from less than 1 per 100,000 in 1950 to approximately 3 per 100,000 by the 1990s. The incidence of melanoma in men increased more rapidly than any other type of cancer; in women, the increase in melanoma incidence was second only to lung cancer.

As with any cancer, the prognosis and treatment plan for patients with melanoma are determined by the cancer stage at presentation. In 2002, The American Joint Committee on Cancer (AJCC) made several critical revisions to the standard staging system for melanoma, including the incorporation of revised clinical and pathological prognostic factors.<sup>6</sup> Four stages of melanoma have been

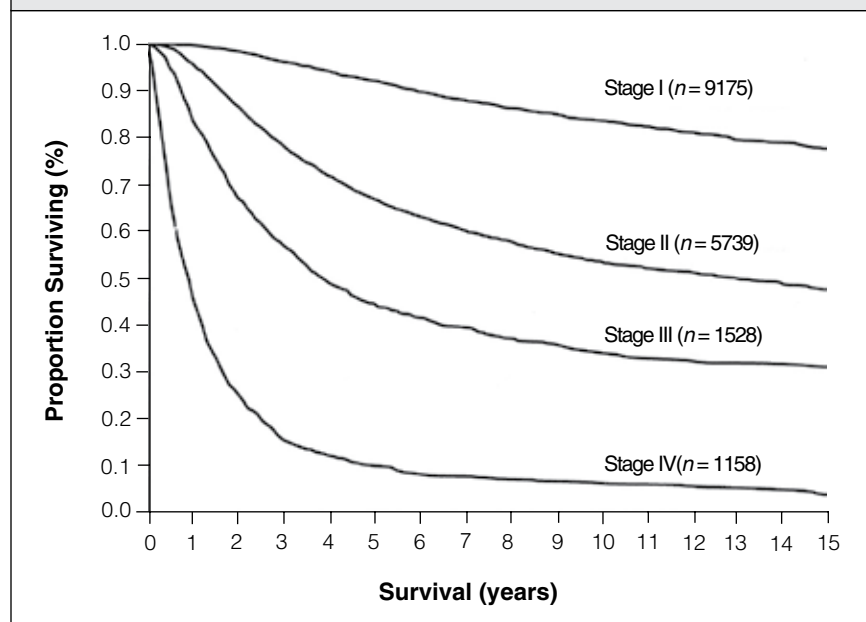
defined: stages I and II represent localized disease, stage III indicates more advanced disease involving regional nodal metastases, and stage IV disease indicates the presence of distant metastases. At the time of initial presentation, approximately 85% of patients have localized disease, 10% have regional nodal involvement, and 5% have distant metastases.<sup>7</sup>

As shown in Figure 1, melanoma stage at presentation is a critical determinant of the patient's prognosis.<sup>6</sup> The prognosis for patients with localized disease is influenced by two principal factors—tumor thickness and the presence or absence of ulceration of the primary lesion. Patients with stage I disease who have melanoma lesions of 1-mm thickness or less and without ulceration have a relatively good prognosis. The long-term survival rate for these individuals is approximately 90% or more. However, for patients with stage II disease—characterized

by thicker or ulcerated melanoma lesions—long-term survival drops sharply, to approximately 30–40% after 10 years. For stage III disease, long-term prognosis varies considerably depending on the size and number of nodal metastases. The 10-year survival rate may exceed 60% for individuals with stage III disease who have only a single nodal micrometastasis, but decreases to approximately 15% for patients with multiple affected lymph nodes and macroscopic metastases. Finally, patients with stage IV melanoma have the worst prognosis. More than 90% of these patients die within 2–5 years from the initial diagnosis. The median survival for patients in this group is measured in months rather than years.

Several factors influence the prognosis for patients with metastatic melanoma.<sup>6</sup> The AJCC melanoma staging system classifies individuals with metastatic disease into three subcategories on the basis of the site

**Figure 1.** Cutaneous Melanoma: 15-Year Survival by Stage. Fifteen-year survival curves comparing localized melanoma (stages II and I), regional metastases (stage III), and distant metastases (stage IV). The numbers in parentheses are patients from the AJCC melanoma staging database used to calculate the survival rates. The differences between the curves are significant ( $p < .0001$ ). AJCC = American Joint Committee on Cancer. Reprinted with permission from reference 6.



of metastasis and the presence of elevated serum lactate dehydrogenase (LDH). Individuals in the M1a group are those with distant skin, subcutaneous, or nodal metastases and normal LDH concentrations. The 10-year survival rate for these individuals is approximately 16%. For individuals in the M1b group, which is characterized by lung metastases and normal LDH, the 10-year survival rate is approximately 2–3%. For patients with M1c metastatic melanoma, which is defined as all other visceral or distant metastases, the 10-year survival rate is approximately 6%. All patients with elevated LDH above the upper limit of normal are classified as M1c regardless of the specific sites of distant metastases. During the first year after the diagnosis of metastatic melanoma, the likelihood of survival is somewhat higher for patients with involvement of the skin or lung (approximately 60%) than for patients with metastasis of other visceral sites (approximately 40%). After the first year, the likelihood of survival decreases most rapidly for patients with lung metastases. By the second year after diagnosis, the survival rate is 37% for patients with involvement of the skin, compared with approximately 23% for patients with metastases of the lungs or other visceral sites.

### Management of metastatic melanoma: single-agent chemotherapy

Management options for patients with metastatic melanoma include surgery, radiation, and systemic medications.<sup>8</sup> In general, surgery and radiotherapy are primarily used to palliate symptoms, although surgery may be performed with curative intent when the metastatic disease is solitary or limited and complete surgical resection is possible. Appropriate surgical intervention in this subgroup of patients has been shown to improve survival in several case series.<sup>9–11</sup> Patients with extensive un-

resectable stage IV melanoma, and those who have poor performance status and are too weak to tolerate systemic therapy, should be managed with the best supportive care. Most patients with stage IV disease receive some form of systemic therapy, and many systemic treatment options are available. Patients should be encouraged to participate in clinical trials that are examining new treatment strategies for melanoma. When this option is not available, systemic therapy options include dacarbazine or temozolomide, high-dose interleukin-2 (IL-2), and biochemotherapy combining IL-2 with dacarbazine or temozolomide.

Dacarbazine remains the standard of care in community practice for the treatment of metastatic melanoma, and it has been considered the benchmark for evaluating the efficacy of new treatment regimens in clinical trials. However, the response rate with dacarbazine is modest at best. The overall response rate is less than 20%, and fewer than 5% of patients achieve complete remission.<sup>12</sup> Despite this low response rate, dacarbazine was approved by the FDA for the treatment of metastatic melanoma in 1976, a decision that reflects the dire prognosis and the low activity of other chemotherapy agents for these patients. Dacarbazine is usually administered as either an intravenous (i.v.) infusion of 250 mg/m<sup>2</sup> for 5 days, or 850 to 1000 mg/m<sup>2</sup> as 1 dose with the cycle repeating every 21 days. An important potential limitation of dacarbazine is that hepatic metabolism of dacarbazine is required to yield the active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC). The usefulness of dacarbazine may therefore be limited in patients with liver metastases. Dacarbazine does not cross the blood-brain barrier, and is therefore ineffective for treating brain metastases. Finally, dacarbazine requires repeated i.v. administration, which is often less convenient for patients.

Temozolomide has been developed to help overcome some of the limitations of dacarbazine.<sup>13</sup> Temozolomide is an orally active congener of dacarbazine that is converted to MTIC at physiologic pH. The oral bioavailability of temozolomide is nearly 100%, and the agent is able to cross the blood-brain barrier and act on central nervous system metastases. Temozolomide is not FDA-approved for the treatment of metastatic melanoma, although it is widely used in clinical practice as a replacement for dacarbazine, especially for patients with brain metastases. The most commonly used dosing schedule calls for administration of 150 to 200 mg/m<sup>2</sup> daily for 5 days, with the cycle repeating every 28 days. The efficacy and safety of temozolomide were directly compared with dacarbazine in a large randomized phase III clinical trial of approximately 300 patients with metastatic melanoma who were not previously treated with chemotherapy and who were free of brain metastases.<sup>14</sup> Patients were randomized to treatment with temozolomide (each cycle consisting of temozolomide 200 mg/m<sup>2</sup> orally for 5 days, with the cycle repeated every 4 weeks) or dacarbazine (250 mg/m<sup>2</sup> i.v. for 5 days, repeated every 3 weeks). Baseline demographic and clinical characteristics, including the sites of metastases, were well balanced between the two groups. For the primary study end point of overall survival, temozolomide was associated with a trend toward better survival, although the difference between the groups was not statistically significant. The median survival time was 7.7 months for the temozolomide group versus 6.4 months for the dacarbazine group. Median progression-free survival was significantly longer with temozolomide (1.9 months) than dacarbazine (1.5 months; *p* = .012). The trial investigators concluded that temozolomide is at least as effective

as dacarbazine for the treatment of advanced melanoma.

Subsequent research demonstrated that the activity of temozolomide is schedule dependent, which led to the development of a low-dose extended schedule in which patients were treated at a dose of 75 mg/m<sup>2</sup> per day for 6 weeks, followed by 2 weeks of rest, with the cycle repeated after a total of 8 weeks.<sup>15</sup> This schedule increased total drug exposure by a factor of nearly 3, and also resulted in depletion of the DNA repair protein O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT), which is a major mechanism of tumor resistance to dacarbazine or temozolomide. Low-dose temozolomide regimens have also been shown to suppress angiogenesis.<sup>16</sup> On the basis of these potentially attractive characteristics, the effectiveness of low-dose, extended temozolomide is being compared with dacarbazine in an ongoing phase III clinical trial. One potential limitation of this approach has been the risk for severe lymphopenia, which in some cases has resulted in serious opportunistic infections, such as *Pneumocystis jiroveci* pneumonia and varicella zoster.<sup>17</sup>

### Combination chemotherapy

Several studies have evaluated whether combination chemotherapy regimens that include temozolomide or dacarbazine would result in higher response rates among patients with metastatic melanoma. The two most commonly used combination chemotherapy regimens are cisplatin/vinblastine/dacarbazine (CVD) and cisplatin/carmustine/dacarbazine/tamoxifen (CBDT). Initial phase I and phase II trials that examined these combination regimens produced very promising results, with especially high tumor response rates. However, response to chemotherapy in patients with metastatic melanoma is generally partial or transitory, and the results of subsequent confirmatory

phase III studies have been disappointing.<sup>18</sup> Buzaid and colleagues compared the efficacy and safety of single-agent dacarbazine versus combination chemotherapy using CVD in 91 patients with metastatic melanoma.<sup>19</sup> Although the response rate was higher for the combination regimen than for single-agent dacarbazine (24% versus 11%), all of the responses were partial, and the median duration of survival was not markedly better with combination therapy than with monotherapy (6.6 months versus 5.3 months). Chapman and colleagues compared the combination of CBDT versus single-agent dacarbazine in 226 patients, with similar results.<sup>20</sup> There was no difference in response rates with combination chemotherapy (18.5% versus 10.2%,  $p = 0.09$ ), but the responses were again all partial, and the median duration of survival was similar for the two groups (6.3 months versus 7.7 months for the dacarbazine and combination regimens, respectively). In addition, the combination regimens were associated with significantly greater toxicity than single-agent chemotherapy.

Temozolomide and dacarbazine have also been combined with several newer chemotherapy agents, including lomeguatrib (an inhibitor of MGMT), decitabine (a hypomethylating agent), oblimersen sodium (a Bcl-2 antisense oligonucleotide), and sorafenib (an inhibitor of the enzyme RAF kinase).<sup>21-23</sup> Lomeguatrib has been developed to overcome intracellular mechanisms that decrease the effectiveness of alkylating chemotherapy agents. As noted previously, MGMT is a DNA repair protein that is a significant factor in the development of resistance to some cytotoxic therapies. Lomeguatrib is a low-molecular-weight pseudosubstrate that binds to and inactivates MGMT.<sup>24</sup> Initial dose-finding studies of lomeguatrib in combination with temozolomide have suggested that a five-day lomeguatrib treatment

regimen is well tolerated, but that MGMT levels recover rapidly after the completion of lomeguatrib and temozolomide coadministration.<sup>22</sup> These investigators suggested that continued lomeguatrib after temozolomide is completed may be required in order to maintain MGMT depletion. Extended-dosing regimens of lomeguatrib will be evaluated in future clinical studies. Decitabine has been developed to reactivate naturally occurring tumor-suppressing genes that have been inactivated by the process of DNA hypermethylation, which is common in many types of cancer.<sup>25</sup> One target of DNA hypermethylation in cancer is the mismatch repair (MMR) system, a family of proteins that help to repair errors that occur during DNA replication.<sup>26</sup> When an alkylating lesion escapes the surveillance of MGMT, it is subsequently identified by the MMR pathway, activating apoptotic cell death. In other words, a competent MMR pathway is required for temozolomide-induced cytotoxicity. Suppression of this pathway by hypermethylation of the promoter region is therefore another important mechanism of acquired tumor resistance to temozolomide. Decitabine is a hypomethylating agent that restores the activity of the MMR pathway, resulting in increased response to temozolomide. Studies examining the combination of decitabine and temozolomide are in progress.

### Biologic therapy for metastatic melanoma

High-dose bolus IL-2 is another FDA-approved option for the treatment of metastatic melanoma. Each treatment cycle consists of IL-2 at a dose of 600,000 to 720,000 units per kg of body weight by short i.v. infusion every 8 hours for a maximum of 14 doses.<sup>27</sup> Treatment cycles may be repeated at intervals of approximately 10 days. High-dose IL-2 is associated with considerable toxicity and requires intensive patient monitoring

(typically in an intensive care unit). The effectiveness of this strategy was described in a case series of 134 patients with metastatic melanoma, in which 9 patients (7%) attained complete responses and another 14 patients (10%) attained partial responses (5.9 months).<sup>28</sup> Although this overall response rate of 17% appears to be modest and generally similar to the response rate obtained with dacarbazine, IL-2 was approved by the FDA for the treatment of metastatic melanoma in 1998 in part because IL-2 can produce durable responses in some patients. As shown in Figure 2, approximately 60% of patients who attained a complete response with high-dose IL-2 exhibited continued, durable responses that lasted five years or more.<sup>29</sup> The potential for this strategy to induce long-term survival provided the basis for FDA approval for high-dose bolus IL-2, despite the fact that this

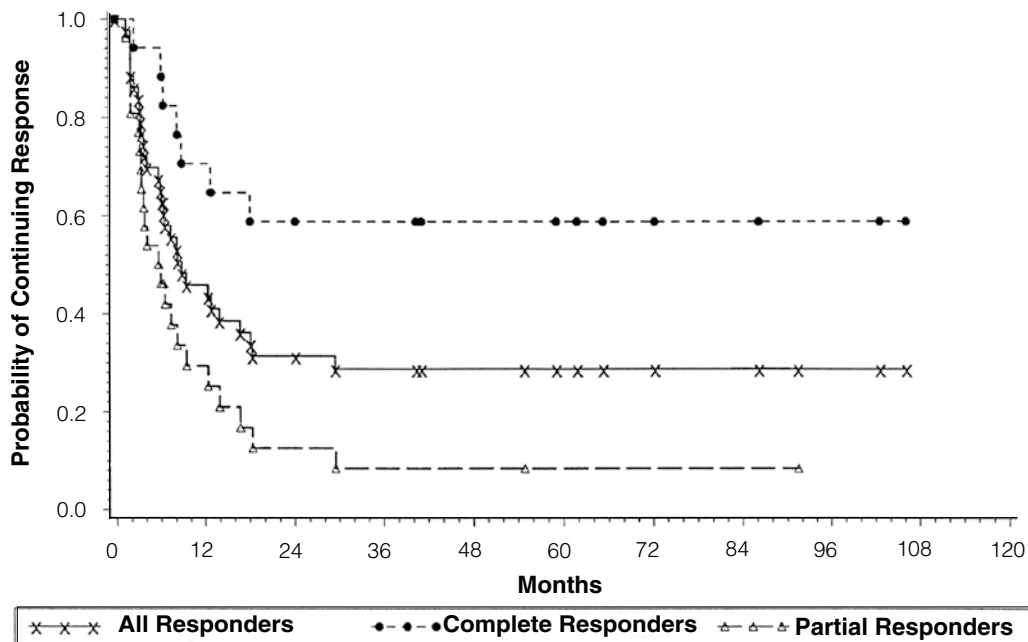
approach has not been evaluated in randomized controlled trials.

A second biologic agent, interferon (IFN)  $\alpha$ , is also used for the treatment of metastatic melanoma, although it is not approved by the FDA for this indication. IFN $\alpha$  possesses modest activity against metastatic melanoma when administered as a single agent, with reported response rates of approximately 10–15% and a complete response rate of approximately 5%.<sup>30,31</sup> The antitumor efficacy of IFN $\alpha$  is highest when administered chronically at doses of 10 million to 50 million units/m<sup>2</sup> by subcutaneous injection three times per week. IFN $\alpha$  is primarily used as one component of combination therapy. Ongoing clinical trials are evaluating the efficacy of long-acting pegylated IFN $\alpha$  in patients with metastatic melanoma.

Biologics and cytotoxic chemotherapy agents act by different

mechanisms of action, which has prompted many researchers to combine them—an approach that has been referred to as biochemotherapy. Phase II clinical trials using various biochemotherapy regimens have reported generally favorable outcomes, with response rates of approximately 50–60% and median survival times of approximately 11 to 12 months.<sup>32</sup> However, in several phase III clinical trials that have examined various biochemotherapy regimens, the addition of IL-2 and IFN to chemotherapy did not significantly increase response rates, and most have found no significant differences between chemotherapy and biochemotherapy groups for the median duration of survival.<sup>33–35</sup> Two meta-analyses have examined the efficacy of biochemotherapy by combining the results from several controlled clinical trials. The authors of both analyses concluded that biochemotherapy

**Figure 2.** Durable Responses with IL-2. Kaplan-Meier plots of response durations for patients who achieved a complete response, a partial response, or any response. IL = interleukin. Reprinted with permission from reference 29.



regimens have the potential to significantly increase response rates compared with chemotherapy alone, but they do not appear to improve overall survival.<sup>36,37</sup>

**Conclusions**

Metastatic melanoma is among the most deadly of all cancer types. Current treatment regimens have not markedly improved the five-year survival rate since the 1970s, which remains approximately 6%. Dacarbazine has long been used to treat metastatic melanoma and is still considered the standard by which other therapies are evaluated, despite its low response rate and inability to penetrate the central nervous system. Other chemotherapy options, such as temozolomide or combination regimens, have produced some gains in the proportion of patients who respond to therapy, but have not improved overall survival. Biotherapy with IL-2 also produces a relatively modest response rate, but has the potential to produce durable responses in some patients. Novel treatment strategies are required to further enhance the treatment response and improve survival for patients with metastatic melanoma.

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## Targeting metastatic melanoma

JAMIE POUST

The long-term prognosis for patients with metastatic melanoma remains poor despite decades of basic and clinical research to develop new treatment strategies. Many new medications are now in development that may significantly improve the likelihood of survival for those with metastatic melanoma. Results from several important clinical trials of these agents have recently been reported. These novel therapies act by several different mechanisms, including modulation of immune function, suppression of angiogenesis, and the activation of intracellular signaling pathways that initiate apoptosis. Many of these emerging therapies target specific molecular pathways that critically affect the survival, progression, and function of tumor cells.<sup>1</sup>

### Bcl-2 antisense therapy

The initiation of apoptotic cell death is regulated by the release of cytochrome C and other chemical mediators from mitochondria. Bcl-2 is a protein inhibitor of apoptosis that prevents the release of mitochondrial cytochrome C, resulting

**Purpose.** New medications and combination treatment strategies for patients with metastatic melanoma are discussed.

**Summary.** Bcl-2 is an inhibitor of apoptosis that is overexpressed in approximately 80% of melanoma cell lines and is believed to contribute to the development of resistance to cytotoxic chemotherapy in patients with melanoma. Oblimersen, an antisense oligonucleotide that stops the translation of Bcl-2 mRNA to protein, significantly improved progression-free survival when administered in combination with dacarbazine. Overall survival was significantly improved in patients with low levels of serum lactate dehydrogenase (LDH), but not in patients with elevated LDH. RAF proteins are a family of serine/threonine kinases that regulate many aspects of cellular function. RAF mutations occur in 70% of melanoma cell lines. Although RAF kinases are thought to be important in the pathogenesis of melanoma, RAF inhibition with sorafenib has not significantly improved survival in patients with advanced disease. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is a naturally occurring inhibitor of T-cell function that prevents the complete activation of T cells upon exposure to antigens by antigen-

presenting cells. Two monoclonal antibodies to CTLA-4 (tremelimumab and ipilimumab) have been developed to promote T-cell activation in melanoma and other types of cancer. Phase I and phase II clinical trials of these agents in patients with metastatic melanoma have demonstrated promising effects on tumor progression, with objective response rates of approximately 20% and sustained responses in some patients. Several vaccines have been developed to stimulate immune system responses against melanoma. Despite promising early findings with polyvalent melanoma vaccine and with vaccine containing heat shock proteins, results with these agents in larger clinical trials have been disappointing.

**Conclusion.** Ongoing clinical trials continue to evaluate these and other novel approaches to the treatment of metastatic melanoma.

**Index terms:** Antineoplastic agents; Dacarbazine; Ipilimumab; Mechanism of action; Melanoma; Neoplasm metastasis; Neoplasm vaccines; Oblimersen; Site of action; Sorafenib; Tremelimumab; Vaccines

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in enhanced tumor cell survival and diminished effectiveness of cytotoxic therapy.<sup>2,3</sup> Bcl-2 is overexpressed in approximately 80% of melanoma

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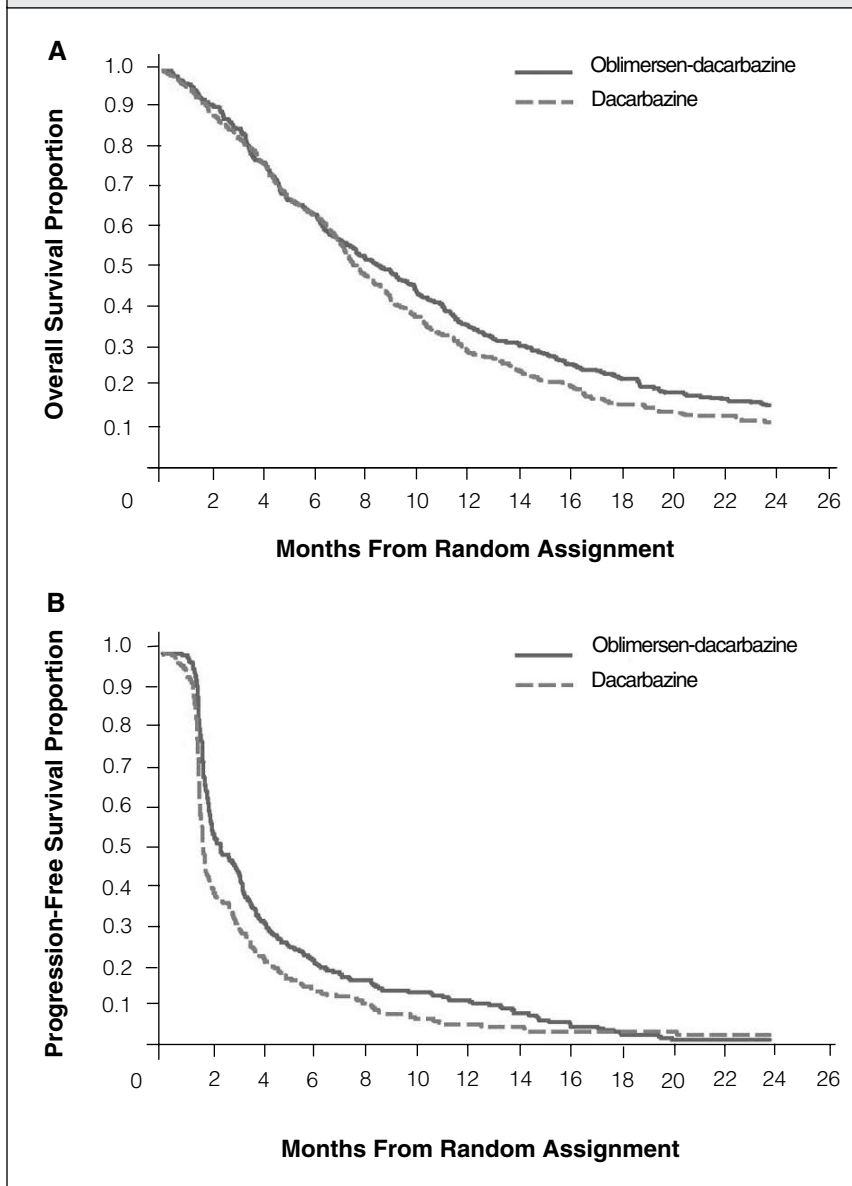
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cell lines and has been associated with multidrug resistance in many types of cancer.<sup>2,4</sup> Oblimersen is an antisense oligonucleotide that binds to the first 6 codons of Bcl-2 mRNA and blocks the translation of Bcl-2 mRNA to protein.<sup>5</sup> By suppressing the production of Bcl-2 protein, oblimersen may increase sensitivity to chemotherapy and enhance chemotherapy-induced apoptosis.

The efficacy and safety of oblimersen were examined in a double-blind clinical trial in which 771 patients with unresectable stage III or stage IV melanoma were randomized to treatment with oblimersen plus dacarbazine or single-agent dacarbazine.<sup>3</sup> Patients in the combination group received oblimersen 7 mg/kg per day by continuous intravenous (i.v.) infusion on days 1 through 5, followed by dacarbazine 1000 mg/m<sup>2</sup> i.v. every 21 days. Patients in the dacarbazine group received dacarbazine 1000 mg/m<sup>2</sup> i.v. every 21 days. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, overall and durable response rates, and duration of treatment response. Baseline demographic and disease characteristics were similar for the two groups, including the proportion of patients with distant metastatic disease, the types of treatments used previously, and the number of cycles of dacarbazine used during the study. The median duration of survival was greater with combination therapy (9 months) than with dacarbazine alone (7.8 months), although the difference between groups was not statistically significant. For the secondary endpoint of progression-free survival, the median survival time was significantly greater for the combination treatment group (2.6 months) than for dacarbazine monotherapy (1.6 months;  $p < .001$ ; Figure 1).<sup>3</sup> The other secondary endpoints, durable response (i.e., duration of response > 6 months) and overall response, were also significantly better

**Figure 1.** Oblimersen: Clinical Efficacy. Kaplan-Meier estimates of (A) overall survival (median overall survival, 9 months for oblimersen-dacarbazine versus 7.8 months for dacarbazine;  $p = .077$ ; HR = 0.87; 95% CI, 0.75–1.01) and (B) progression-free survival (median progression survival, 2.6 months for oblimersen-dacarbazine versus 1.6 months for dacarbazine;  $p < .001$ ; HR = 0.75; 95% CI, 0.63–0.88): intent-to-treat analysis ( $n = 771$ ). CI = confidence interval; HR = hazard ratio. Reprinted with permission from reference 3.



with combination therapy than with dacarbazine alone.

The investigators performed an additional analysis in which patients were subdivided on the basis of high serum lactate dehydrogenase (LDH) at baseline, which is an independent predictor of poor prognosis. In this

analysis, oblimersen was associated with significantly increased overall survival in patients who did not have elevated serum LDH at baseline (median survival, 11.4 versus 9.7 months;  $p = .02$ ). No benefit was observed in the subset of patients with elevated baseline LDH. On the basis of these

observations, a new clinical trial has been developed to prospectively examine the efficacy of oblimersen and dacarbazine specifically in patients without elevated LDH at baseline. Oblimersen is also being examined in combination with other cytotoxic agents and investigational therapies.

### RAF kinase inhibition

RAF proteins are a family of serine/threonine kinases that regulate cell proliferation, differentiation, and survival.<sup>2,6</sup> RAF mutations are associated with suppression of apoptosis and continuous cell proliferation. Mutations of one RAF isoform (B-RAF) occur in as many as 70% of melanoma cell lines, including 31% of primary melanomas and 57% of metastatic melanomas.<sup>7</sup> Sorafenib is an inhibitor of RAF kinase that promotes tumor cell apoptosis, but it also acts as other protein kinases, including factors that stimulate angiogenesis.<sup>8,9</sup> In an initial phase I/phase II clinical trial of sorafenib in combination with carboplatin/paclitaxel for patients with melanoma, approximately 85% of patients exhibited partial response, complete response, or stable disease.<sup>10</sup> Sorafenib was subsequently evaluated as second-line therapy in a large phase III clinical trial, the results of which have been recently reported.<sup>11</sup> A total of 270 patients with advanced melanoma who had progressed on dacarbazine and temozolomide were treated with a combination of carboplatin and paclitaxel, and were randomized to oral sorafenib 400 mg twice daily or placebo for 18 out of every 21 days. Patients with active brain metastases at baseline were excluded from the study. Baseline characteristics of the two groups were similar, and the patients were well matched with regard to metastases, LDH level, and prior adjuvant treatment. The study primary endpoint of progression-free survival was similar for both treatment groups (median, 17.4 weeks versus 17.9 weeks for the

sorafenib and placebo groups, respectively;  $p = .492$ ). Several secondary outcomes were also similar for the two treatment groups, including time to progression, objective response rate, duration of response, and overall survival.

A randomized, double-blind phase II clinical trial examined dacarbazine, which is currently considered the standard of care in patients with metastatic disease, in combination with sorafenib or placebo in 101 patients with advanced melanoma.<sup>12</sup> Dacarbazine was administered at a dose of 1 g/m<sup>2</sup> i.v. every 21 days, and sorafenib at a dose of 400 mg orally twice per day continuously until disease progression or intolerable toxicity. The primary endpoint of progression-free survival was greater with sorafenib and dacarbazine (21.1 weeks) than with dacarbazine and placebo (11.7 weeks), although the difference was not statistically significant ( $p = .068$ ). Secondary endpoints included overall survival and time to progression. The two groups did not differ significantly in overall survival. As shown in Figure 2, median time to progression was significantly longer with sorafenib (21.1 weeks) than placebo (11.7 weeks;  $p = .039$ ).<sup>12</sup>

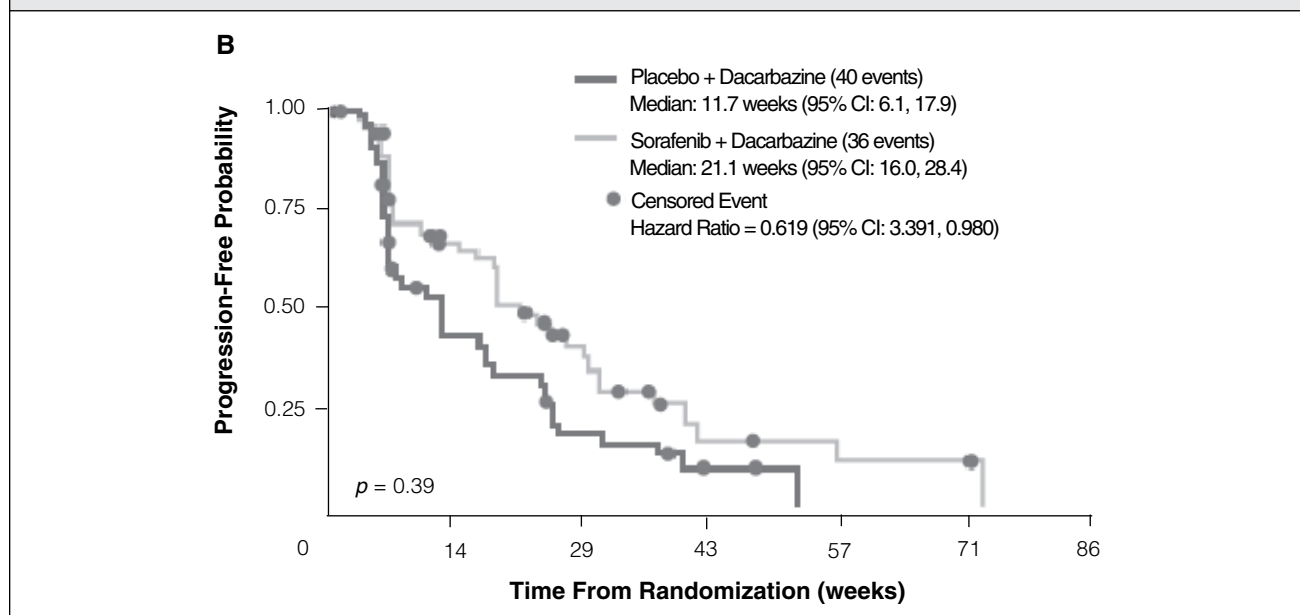
The results of these studies demonstrate that although RAF kinases appear to play an important part in the pathophysiology of melanoma, RAF inhibition has not yet translated into a survival benefit in patients with advanced disease. Ongoing clinical trials are examining sorafenib in combination with other treatments, including temozolomide, nanoparticle paclitaxel, and other multitargeted agents.

### CTLA-4

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a cell-surface molecule that is expressed primarily on T cells, is an important modulator of T-cell activity and proliferation. The complete activation of T cells in response to tumor cells requires two

distinct cell signals between T cells and antigen-presenting cells (APCs). Signal 1 is the presentation of tumor cell antigens to T-cell receptors by APCs; signal 2 (also referred to as the T-cell costimulatory signal) is the interaction between a second set of cell-surface proteins that are present on T cells (CD28) and on APCs (B7).<sup>13</sup> If antigen presentation occurs without the costimulatory signal, T cells become desensitized to the presented antigen and do not replicate or secrete inflammatory cytokines upon subsequent reexposure to the antigen (a condition that is referred to as T-cell anergy).<sup>14</sup> CTLA-4 is structurally similar to CD28 and competes with CD28 for B7 binding sites. The result of this competitive binding is inhibition of T-cell activation and proliferation, suppression of interleukin-2 (IL-2) secretion, and an immune environment that is conducive to the proliferation of tumor cells. These observations suggest that treatment strategies that block the engagement of CTLA-4 and B7 would promote T-cell activation and proliferation and suppress tumor growth. Two monoclonal antibodies against CTLA-4, tremelimumab (CP-675206) and ipilimumab (MDX-010), have been developed for the treatment of melanoma and are currently being evaluated in clinical trials.

Several phase I and phase II clinical trials have examined tumor response rates in patients with metastatic melanoma who were treated with tremelimumab or ipilimumab in combination with other agents. Although these studies represent relatively early stages of clinical testing in small numbers of patients, preliminary findings have been very encouraging, with reported response rates greater than 20% in several studies. One study of tremelimumab in 90 previously treated patients with metastatic disease reported a complete response rate of 3.3%, a partial response rate of 4.4%, and stable disease in 28.9% of the patients.<sup>15,16</sup> Two

**Figure 2.** Time to Progression (Independently Assessed). CI = confidence interval. Reprinted with permission from reference 12.

clinical trials of ipilimumab in combination with cancer peptide vaccination in previously treated patients have been reported. In the first study, a total of 56 patients with progressive stage IV melanoma despite prior therapy received ipilimumab every three weeks. Ipilimumab produced complete responses in two patients (3.6%) and partial responses in five patients (8.9%), for a total objective response rate of approximately 13%.<sup>17</sup> The second study examined 14 previously treated patients with progressive stage IV melanoma. Ipilimumab was associated with two complete responses (14.3%) and one partial response (7.1%), for a total objective response rate of approximately 21%.<sup>18</sup> A third study examined ipilimumab at varying doses from 0.1 mg/kg to 3 mg/kg every three weeks. All of the patients also received IL-2 at a dose of 720,000 IU/kg every 8 hours for a maximum of 15 doses. These investigators reported complete responses in 3 of 36 patients (8.3%) and partial responses in 5 of 36 patients (13.9%), for a total objective response rate of 22%.<sup>19</sup> The au-

thors of this study concluded that the addition of IL-2 to ipilimumab did not appear to substantially increase the objective response rate beyond the rate that would be expected with ipilimumab alone, on the basis of previous clinical studies. These clinical trials of CTLA-4 blockers have also generally reported relatively long durations of stable response, for up to 35 months.<sup>15,17</sup> The response rates, which are similar to current standard of care and long duration of response with these agents, has generated considerable interest in their use in the treatment of metastatic melanoma. Larger clinical trials of these agents are ongoing. Currently, a phase III clinical trial that is examining the efficacy of ipilimumab in combination with dacarbazine should help to refine the role of CTLA-4 in the treatment of metastatic melanoma. A phase III study that compared single-agent tremelimumab to dacarbazine or temozolomide was discontinued in April 2008 when an interim analysis concluded that the drug was not superior to conventional cytotoxic chemotherapy. Other clinical trials

are ongoing to evaluate both of these agents in combination with tumor vaccines or with other novel cancer therapies.

CTLA-4 antibodies produce several immune-mediated adverse events that are distinct from the typical adverse events associated with conventional cancer treatments. Many of these adverse effects are autoimmune in nature. Antibodies against CTLA-4 may cause autoimmune-mediated adverse events by promoting the activation of self-reactive T cells.<sup>20</sup> In phase I and phase II studies of tremelimumab, the most common grade 3/4 or serious adverse events included dermatitis and diarrhea. Serious adverse events observed in phase I or phase II clinical trials of ipilimumab have included colitis, enterocolitis, and dermatitis. Less common adverse effects that have been described with these agents include autoimmune thyroiditis, adrenal disease, or hepatitis.<sup>21,22</sup> In the clinical studies reported to date, patients who have experienced grade III or grade IV autoimmune toxicities have also been most likely to ex-

hibit tumor regression and increased time to relapse. The timing of adverse effects is variable and may occur several months after the cessation of treatment. These immune-mediated adverse events are generally treated with high-dose corticosteroids. The immune-suppressing effects of corticosteroid therapy do not appear to negate the beneficial effects of blocking CTLA-4. At the conclusion of corticosteroid therapy, the corticosteroid dose should be tapered very gradually to avoid a flare of autoimmune disease activity. Another option for the treatment of enterocolitis is infliximab, a monoclonal antibody against the proinflammatory cytokine tumor necrosis factor- $\alpha$ . The American Society of Clinical Oncology provides several resources for patients and health care professionals that may be helpful in the management of treatment-related adverse effects in patients with melanoma.

### Melanoma vaccines

Melanoma vaccines are another immune-mediated therapy that has been studied for the treatment of melanoma. Vaccines have been designed to stimulate the immune system and the formation of antibodies against antigens that are present on melanoma cells. Several different methods of vaccine development have been described. Individualized vaccines may be developed using the patient's own melanoma cells, or vaccines may be developed from a combination of several melanoma-associated antigens. Tumor vaccines have been evaluated for several different cancer types, but few studies have described marked improvement in outcomes with this approach.

A polyvalent melanoma cancer vaccine has been developed to stimulate an antitumor response that is mediated by cytotoxic T cells, resulting in inhibition of tumor cell proliferation and increased tumor cell death.<sup>23</sup> The vaccine components include whole irradiated

heterologous melanoma cells from three allogenic tumor cell lines that together express more than 20 tumor-related or melanoma-related antigens.<sup>24</sup> A phase III clinical trial of this polyvalent vaccine began in 1998, and the results of a third interim analysis of this study were reported.<sup>25</sup> Patients with stage III ( $n = 1160$ ) or stage IV ( $n = 496$ ) melanoma, with no evidence of residual disease after surgical resection, were randomized to melanoma vaccine or placebo. Following an initial 5-dose induction phase, patients received vaccine or placebo monthly during the first year, every other month during the second year, and every 3 months during years 3, 4, and 5. In addition, all of the patients were treated with the tuberculosis vaccine bacillus Calmette-Guerin (BCG) as an adjuvant for the first two vaccine doses. BCG is a nonspecific immune-stimulating agent that has been used to treat superficial bladder cancer, and it has also been explored for the treatment of melanoma and other tumor types.<sup>26,27</sup> This study was terminated prematurely after an interim analysis reported a low probability that the vaccine would significantly improve outcomes. For patients with stage III disease, the median duration of overall survival was actually longer with placebo (67.8 months) than with vaccine (59.1 month;  $p = .04$ ). For other outcomes, including the likelihood of five-year disease-free survival, the two treatments did not differ significantly from one another.

Another approach to melanoma vaccination is to incorporate heat shock proteins (HSPs), which are produced in all cell types and are unregulated under conditions of stress, into a vaccine.<sup>28</sup> HSPs are important in several immune processes, including transport of antigenic peptides, mediation of apoptosis, and binding of proteins.<sup>29</sup> Autologous HSP-peptide complex 96 (HSPPC-96) is

an investigational tumor vaccine that has been evaluated for the treatment of melanoma. HSPPC-96 consists of tumor-derived HSPs linked to tumor antigens, resulting in a vaccine that is specific both to the patient and the tumor type from which the antigens were derived.<sup>30,31</sup>

In a phase I clinical trial of 45 patients with stage IV melanoma, patients received either 5 mg or 50 mg of HSPPC-96, by either subcutaneous or intradermal injection, once weekly for 4 weeks.<sup>32</sup> All the patients had undergone surgical resection for melanoma; 11 patients were disease free after surgery and 34 had residual disease. Among the patients with residual disease, two exhibited complete responses and three exhibited stable disease. The duration of complete response was more than 450 days. No grade III or grade IV toxicities were observed. A subsequent phase II clinical trial was conducted in 28 patients with stage IV melanoma who had undergone surgery, nearly all of whom had previously received chemotherapy or biotherapy.<sup>33</sup> All patients received HSPPC-96 in combination with interferon  $\alpha$  and granulocyte macrophage colony-stimulating factor to stimulate immune function. Of 18 patients who were considered evaluable, two were disease free after surgery and one of these patients remained free of melanoma for 419 days. For the other 16 evaluable patients with residual disease after surgery, 10 had stable disease that lasted between 97 and 372 days. Treatment was well tolerated, and no significant toxicity was observed with HSPPC-96 vaccination.

These early results were considered promising, and a larger phase III clinical trial was initiated.<sup>34</sup> In this study, 322 patients with stage IV melanoma were randomized to treatment with HSPPC-96 or to the treating physician's choice of other therapy, including IL-2, dacarbazine, temozolomide, or tumor resection.

For the primary endpoint (median survival time), patients in the vaccine group tended to do worse than patients in the physician's choice group, although the difference was not statistically significant (281 days versus 322 days;  $p = .078$ ). Patients with M1a or M1b disease survived longer with HSPPC-96 than with physician's choice, although these trends were not statistically significant. For patients with M1c disease, survival time was significantly worse for patients who received HSPPC-96 than physician's choice (226 versus 299 days;  $p = .015$ ). As a result of this disappointing outcome the trial was also discontinued.

Vaccination with gp100 is a third potential option for melanoma vaccine development—gp100 is a melanoma-associated antigen that, when formulated as a vaccine, stimulates cytotoxic T cells via a specific human leukocyte antigen receptor.<sup>35</sup> The gp100 antigen vaccine has been administered in numerous studies in combination with a broad range of other immune-stimulating agents (e.g., interferon  $\alpha$ , dendritic cells, and CTLA-4). More than 50 clinical trials evaluating gp100 in various clinical settings are ongoing.

### Conclusions

Current management options for metastatic melanoma employing cytotoxic chemotherapy or immune therapy are effective for some patients, but have not substantially improved long-term survival. Several new and potentially curative treatments are currently being evaluated in clinical trials, although it is not yet clear how these new agents will be incorporated into clinical practice. Bcl-2 inhibition via antisense technology has improved clinical outcomes in some studies, and appears to be especially effective in patients who do not have elevated LDH concentrations. Future clinical trials will continue to refine the role of Bcl-2 inhibition in different patient

subgroups. RAF kinase clearly has an important role in melanoma, but it has proven difficult to significantly alter the course of the disease using medications that target this system. Blockers of CTLA-4 stimulate T-cell activation and proliferation and have been shown to induce durable responses in some patients with progressive metastatic melanoma despite prior therapy. Vaccines have generated considerable interest for the treatment of metastatic melanoma, but clinical studies conducted over the last 10 years have generally been disappointing. Ongoing studies continue to examine the potential role of vaccines in melanoma in combination with other therapies.

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## Emerging strategies for the treatment of metastatic melanoma: The role of monoclonal antibodies in targeted immunotherapy

Article 204-000-08-009-H01P

Qualifies for 1.5 hours (0.15 CEUs) of continuing-education credit

### Learning objectives

After studying these articles, the reader should be able to

1. Identify current treatment options for patients with metastatic melanoma.
2. Summarize the data from recent clinical trials evaluating chemotherapy, biochemotherapy, and immunotherapy for metastatic melanoma.
3. Define the rationale for targeted therapy in the treatment of metastatic melanoma.
4. Develop strategies to integrate monoclonal antibodies into the management of metastatic melanoma.

### Self-assessment questions

For each question there is only one best answer.

1. A meta-analysis of outcomes among patients with metastatic melanoma found that between 1971 and 1993, the median survival time increased by approximately
  - a. 0 percent.
  - b. 6 percent.
  - c. 12 percent.
  - d. 18 percent.
2. A predictor of poor prognosis is elevation of
  - a. Creatine kinase.
  - b. Lactate dehydrogenase.
  - c. Aldehyde dehydrogenase.
  - d. Aspartate aminotransferase.
3. Melanoma is the leading cause of cancer death among women between the ages of
  - a. 65 to 75.
  - b. 55 to 65.
  - c. 45 to 55.
  - d. 25 to 35.
4. For patients who present with stage IV melanoma, the percentage who will die within two to five years from the initial diagnosis is approximately
  - a. 90%.
  - b. 80%.
  - c. 70%.
  - d. 60%.
5. A major mechanism of drug resistance in patients who receive cytotoxic chemotherapy is
  - a. 5-(3-methyl-1-triazeno)imidazole-4-carboxamide.
  - b. RAF kinase.
  - c. O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT).
  - d. Bcl-2 antisense oligonucleotides.
6. In patients with metastatic melanoma, biologic therapies have produced response rates of approximately
  - a. 2–3%.
  - b. 10–20%.
  - c. 25–35%.
  - d. 45–50%.
7. Meta-analyses of patients with metastatic melanoma have found that biochemotherapy is associated with
  - a. Improved response rates.
  - b. Higher survival rates.
  - c. Elevated LDH.
  - d. Serious opportunistic infections.
8. An inhibitor of apoptosis that prevents the release of cytochrome C from mitochondria is
  - a. C-fos.
  - b. Bcl-2.
  - c. Nitric oxide.
  - d. Matrix metalloprotease 9.
9. Serine/threonine kinases that regulate cell proliferation, differentiation, and survival are
  - a. ICAMs.
  - b. Luciferins.
  - c. Endonucleases.
  - d. RAF proteins.
10. Antigen presentation without the presence of T-cell costimulation results in
  - a. An allergic reaction.
  - b. Decreased T-cell replication.
  - c. Increased T-cell cytokine production.
  - d. Transient T-cell hypersensitivity.
11. In clinical trials of antibodies against cytotoxic T-lymphocyte antigen 4, tumor regression and increased time to relapse were most likely to occur in patients who

- a. Were pretreated with H<sub>1</sub> blockers.  
 b. Had stage III melanoma.  
 c. Had poor performance status.  
 d. Experienced autoimmune toxicities.
12. A hypomethylating agent that results in increased response to temozolomide is  
 a. Tamoxifen.  
 b. Dacarbazine.  
 c. Cisplatin.  
 d. Decitabine.
13. A biologic therapy that is associated with considerable toxicity, and requires intensive patient monitoring (typically in an intensive care unit), is  
 a. Interferon  $\alpha$ .  
 b. Interleukin (IL)-2.  
 c. Sorafenib.  
 d. Oblimersen.
14. By suppressing the production of Bcl-2 protein, a drug that may increase sensitivity to chemotherapy and enhance chemotherapy-induced apoptosis is  
 a. Interferon  $\alpha$ .  
 b. IL-2.  
 c. Sorafenib.  
 d. Oblimersen.
15. An inhibitor of RAF kinase that promotes tumor cell apoptosis, but which also acts as other protein kinases, including factors that stimulate angiogenesis, is  
 a. Interferon  $\alpha$ .  
 b. IL-2.  
 c. Sorafenib.  
 d. Oblimersen.
16. An orally active congener of dacarbazine that is converted to MTIC at physiologic pH is  
 a. Lomeguatrib.  
 b. Oblimersen.  
 c. Tamoxifen.  
 d. Temozolomide.
17. To maintain MGMT depletion after temozolomide treatment is completed, Ranson, Hersey, and Thompson et al. suggest continuing with  
 a. Decitabine.  
 b. Lomeguatrib.  
 c. Sorafenib.  
 d. Oblimersen.
18. Phase II clinical trials using various biochemotherapy regimens for metastatic melanoma have reported median survival times of approximately  
 a. 3 to 4 months.  
 b. 11 to 12 months.  
 c. 15 to 20 months.  
 d. 2 to 3 years.
19. One year after a diagnosis of metastatic melanoma, the likelihood of survival decreases most rapidly for patients with metastases of the  
 a. Lung.  
 b. Brain.  
 c. Liver.  
 d. Spleen.
20. In patients who received HSPPC-96 vaccine, survival time was worse for the vaccinated patients than for a control group among patients with disease at stage  
 a. M1a.  
 b. M1b.  
 c. M1c.

## AJHP Continuing Education

Supplement: Emerging strategies for the treatment of metastatic melanoma:

The role of monoclonal antibodies in targeted immunotherapy

ACPE #: 204-000-08-009-H01P

CE Credit: 1.5 hours (0.15 CEU)

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