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.

**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 in enhanced tumor cell survival and diminished effectiveness of cytotoxic therapy.\(^2\) Bcl-2 is overexpressed in approximately 80% of melanoma.

**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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**References**


cell lines and has been associated with multidrug resistance in many types of cancer.\(^2,4\) 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.\(^5\) 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.\(^3\) 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\(^2\) i.v. every 21 days. Patients in the dacarbazine group received dacarbazine 1000 mg/m\(^2\) 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).\(^3\) The other secondary endpoints, durable response (i.e., duration of response > 6 months) and overall response, were also significantly better 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.\(^1,6\) 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.\(^7\) 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.\(^8,9\) 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.\(^10\) Sorafenib was subsequently evaluated as second-line therapy in a large phase III clinical trial, the results of which have been recently reported.\(^11\) 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.\(^12\) Dacarbazine was administered at a dose of 1 g/m\(^2\) 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; \(p = .393\)).\(^13\)

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).\(^13\) 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).\(^14\) 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.\(^15,16\) Two
SYMPOSIUM  Targeting

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%. 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%. 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%. The authors 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. 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 clinical trial 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. 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. 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-α. 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. 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. 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. 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. 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. HSPs are important in several immune processes, including transport of antigenic peptides, mediation of apoptosis, and binding of proteins. 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.

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. 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. All patients received HSPPC-96 in combination with interferon α 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. 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. The gp100 antigen vaccine has been administered in numerous studies in combination with a broad range of other immune-stimulating agents (e.g., interferon α, 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 cytokotoxic 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.

References


