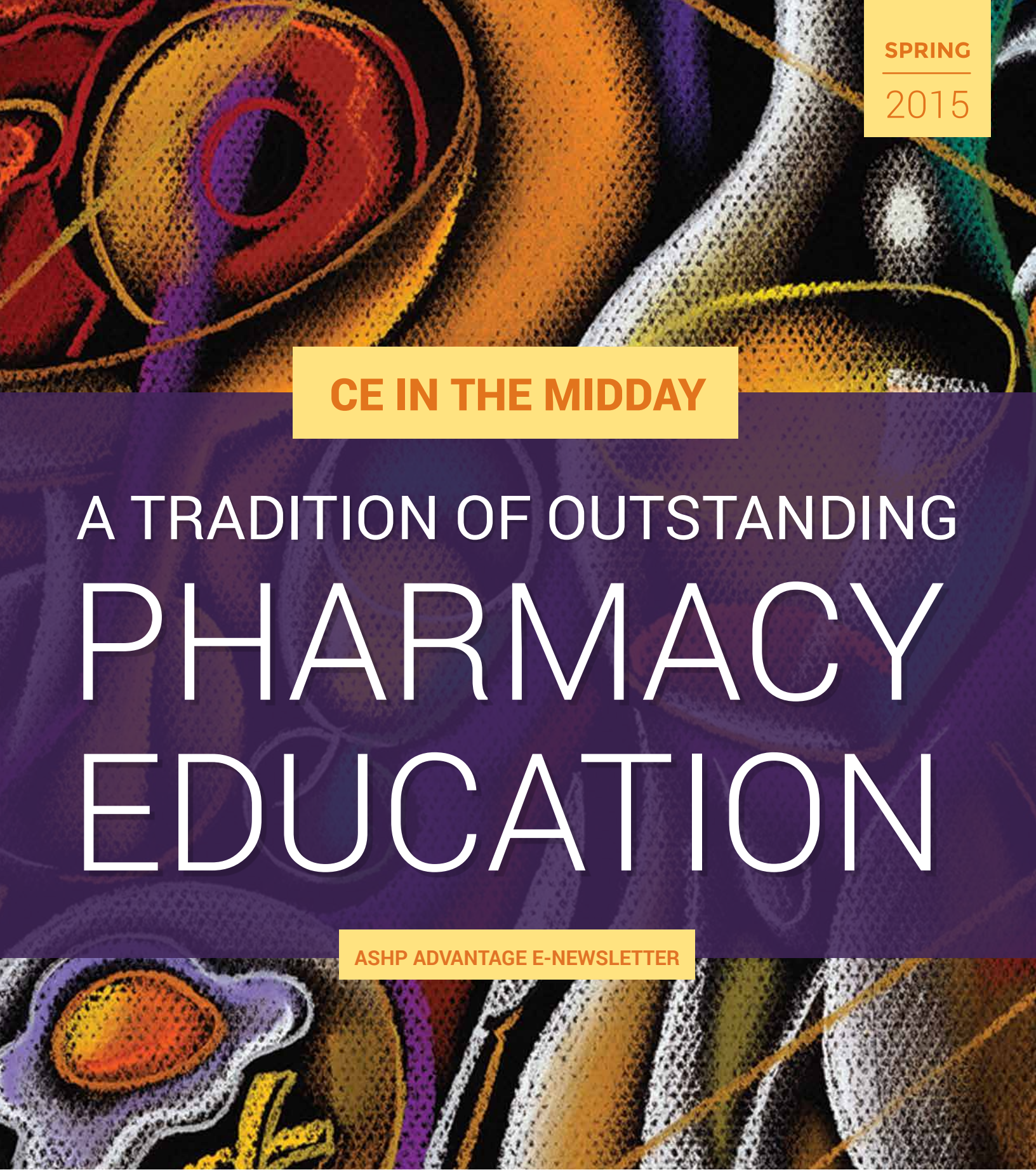

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ASHP ADVANTAGE E-NEWSLETTER

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To continue a tradition of outstanding pharmacy education, three CE in the Midday (formerly known as CE in the Mornings) topics were presented at the 49th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in early December 2014:

- Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist
- Management of Invasive Fungal Infections: Applying Evidence-based Strategies and Individualizing Antifungal Therapy
- New and Emerging Strategies for the Treatment of Advanced Melanoma

The programs were presented by nationally recognized experts. If you were unable to attend these programs, they are available on demand at the CE in the Midday web portal. Continuing pharmacy education credit (1.5 hours for each program) is available at no charge. Membership in ASHP is not required.

Selected unresolved issues and controversies in caring for patients with HIV in the inpatient and ambulatory care settings, managing invasive fungal infections, and treating advanced melanoma identified by Midyear Meeting attendees were addressed by the faculty in live Ask the Experts webinars conducted on March 5, 18, and 23, 2015, respectively. On-demand archived versions of the Ask the Experts webinars on invasive fungal infections and treatment of advanced melanoma will be available later in 2015. This newsletter summarizes recent developments in the use of immunotherapy for the treatment of melanoma.

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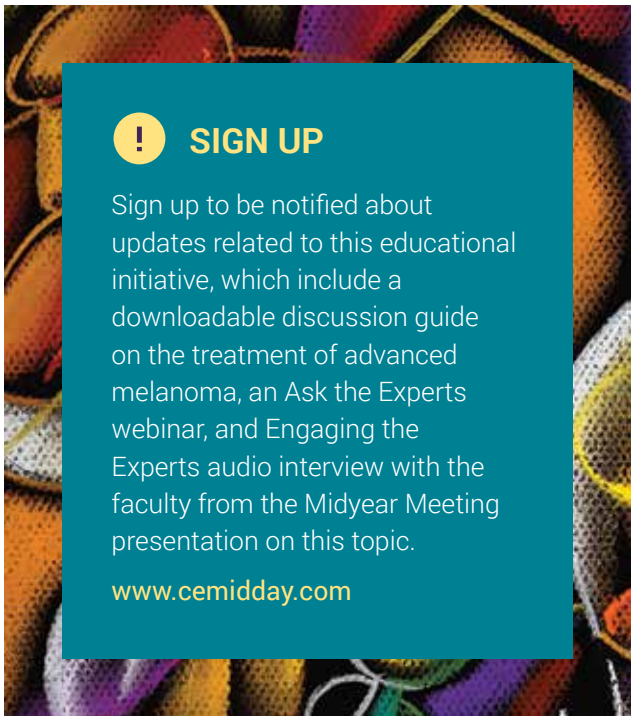

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Sign up to be notified about updates related to this educational initiative, which include a downloadable discussion guide on the treatment of advanced melanoma, an Ask the Experts webinar, and Engaging the Experts audio interview with the faculty from the Midyear Meeting presentation on this topic.

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Why focus on melanoma and the immune system?

Nearly 5 million Americans are treated for skin cancer at an estimated cost of $8.1 billion each year.[1] Melanoma accounts for the majority of skin cancer deaths but less than 2% of skin cancer cases.[2] The incidence of melanoma in the United States has increased dramatically over the past three decades.[2] Melanoma has been attributed to a combination of environmental and genetic factors, including exposure to ultraviolet radiation and mutations in genes associated with cellular proliferation, differentiation, and apoptosis (e.g., BRAF).[1,3] Melanoma is highly curable if it is diagnosed at an early stage, but the prognosis is poor for patients with advanced disease.[4]

The immune system plays an important role in detecting and eradicating tumor cells through surveillance activities. Melanoma may be the result of tumor cell avoidance of immune surveillance through various mechanisms. These mechanisms include producing immunosuppressive cytokines (e.g., tumor growth factor-β; interleukins-4, 6, and 10), increasing the number and function of immune suppressor cells (e.g., macrophages, regulatory T cells), changing cell signaling pathways that ordinarily lead to cancer cell death, limiting immune effector cell activity, and creating inhibitory checkpoints.[5] Activation of T cells with antitumor activity ordinarily plays an important role in preventing malignant transformation. The immune system has escape mechanisms designed to avoid an autoimmune response, and these escape mechanisms may be hijacked by tumor cells to serve as inhibitory checkpoints, circumvent the immune response to tumor cells, and allow tumor cell proliferation.[5]

Melanoma in patients with genetic mutations may be treated using targeted therapies (e.g., BRAF inhibitors). Drug development research has focused on immunotherapies for melanoma because of the role of the immune system and need for therapies for patients who lack genetic mutations. Cytotoxic T-lymphocyte antigen (CTLA)-4 is an important inhibitory checkpoint because it reduces T-cell activation and antitumor activity.[6] Drug therapies that inhibit CTLA-4 have been developed to reverse T-cell inhibition, thereby allowing T-cell activation and antitumor activity to predominate.

The programmed cell death protein-1 (PD-1) is an inhibitory T-cell receptor involved in another immunoregulatory negative checkpoint that affects tumor cell survival.[5,7] Drug therapies that inhibit PD-1 or its ligand PD-L1 have been developed to reduce T-cell inhibition (i.e., activate T cells to serve as anticancer effector cells).

Current Immunotherapies

Currently available immunotherapies for melanoma include interleukin-2 (IL-2), which is used for metastatic disease, and interferon alfa-2b (IFN) for use as adjuvant therapy in patients with localized or locally advanced disease.[8] Immune checkpoint inhibitors include the CTLA-4 inhibitor ipilimumab, which was approved in 2011 by the Food and Drug Administration (FDA) for treatment of patients with unresectable or metastatic melanoma, and the PD-1 inhibitors nivolumab and pembrolizumab.[9-11] Nivolumab and pembrolizumab were approved by FDA in late 2014 for treatment of patients with unresectable or metastatic melanoma if disease progression occurs following ipilimumab therapy and if the patient is BRAF V600 mutation positive, following treatment with a BRAF inhibitor (i.e., dabrafenib or vemurafenib).[10,11] In early 2015, nivolumab also was approved by FDA for the treatment of metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.[10]

High-dose IL-2 provides an objective response (i.e., complete or partial response) that is durable for 2.5 years and can be considered a cure in a limited number of patients with metastatic melanoma (10%).[12]

However, high-dose IL-2 is associated with substantial toxicity (especially hypotension). Its use is impractical because the drug must be administered in an inpatient setting where vital signs can be closely monitored and pressor agents can be administered in an intensive care unit (ICU) setting to maintain blood pressure. Systemic corticosteroid therapy cannot be used to manage toxicity from high-dose IL-2 because it can interfere with the activity of IL-2. Use of high-dose IL-2 is limited to selected patients with good organ function and performance status and no brain metastases at cancer centers where the staff are experienced with this therapy. Efforts to develop better tolerated IL-2-based regimens for treating melanoma have been unsuccessful.

Ipilimumab

Ipilimumab, a fully human IgG1 monoclonal antibody to human CTLA-4, is approved by FDA for administration to patients with metastatic or unresectable melanoma as a 3-mg/kg intravenous (i.v.) infusion over 90 minutes every 3 weeks for 4 doses.[9] It may be given on an outpatient basis. Durable improvements in overall survival were demonstrated in phase 3, randomized, double-blind, controlled studies of ipilimumab.[13,14] The most common adverse events in patients receiving ipilimumab are immune-related and involve the gastrointestinal (GI) tract (especially diarrhea), skin (e.g., pruritus, rash), liver (liver enzyme elevations), or endocrine system (e.g., hypophysitis, which is inflammation of the pituitary gland).[13,14] These adverse events usually are delayed and follow a pattern, with dermatologic adverse events manifesting 2 to 3 weeks after initiating therapy, GI and hepatic adverse events after 6 to 7 weeks of therapy, and endocrinologic adverse events after 9 weeks of therapy.[15] Ipilimumab is subject to FDA risk evaluation and mitigation strategy requirements because of the seriousness of its toxicity. Liver function, thyroid function, and blood chemistries should be evaluated before each ipilimumab dose. Patients receiving ipilimumab should be advised to notify their health care provider at the first sign of immune-related adverse events because the severity can escalate quickly if medical attention is not obtained promptly. Immune-related adverse events often resolve after the administration of systemic prednisone 1-2 mg/kg/day or its equivalent.[9] Topical corticosteroids may be used to treat dermatologic reactions. Infliximab has been used successfully to treat corticosteroid-refractory immune-related colitis associated with ipilimumab.[16]

A phase 3, randomized, double-blind study comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with unresectable or metastatic melanoma regardless of prior treatment is in progress.[17] Overall survival is the primary endpoint. The estimated study completion date is December 2016.

The results of a phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of ipilimumab as adjuvant therapy in 951 patients with stage III melanoma were reported at the 2014 American Society of Clinical Oncology Annual Meeting.[18] Adults with completely resected melanoma and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who were at a high risk of recurrence were stratified by stage (IIIA, IIIB, or IIIC) and region (North America, Europe, or Australia). The patients were randomly assigned to receive ipilimumab 10 mg/kg or placebo i.v. every 3 weeks for four doses, followed by a dose every 3 months for up to 3 years or until disease recurrence or unacceptable toxicity occurred. Placebo was used instead of IFN as an active control because IFN is not widely used for the treatment of melanoma in Europe. The primary endpoint was recurrence-free survival (RFS).

After a median follow-up time of 2.7 years, the RFS rate was significantly greater with ipilimumab than placebo, with a hazard ratio of 0.75 for recurrence (i.e., 25% reduction in risk of recurrence) from the use of ipilimumab ($p = 0.0013$).[18] The benefit from ipilimumab was consistent among subgroups, regardless of the presence of ulceration, which carries a poor prognosis. The 3-year RFS rate was 46.5% with ipilimumab and

34.8% with placebo. The median time to recurrence (i.e., local or regional disease, distant metastasis, or death) was significantly longer with ipilimumab (26.1 months) than placebo (17.1 months). Roughly half (52%) of 471 patients discontinued ipilimumab treatment because of adverse events. The most common grade 3 or 4 immune-related adverse events from ipilimumab were GI (15.9%), hepatic (10.6%), and endocrine (8.5%). The incidence of these adverse events was similar to that seen in patients with advanced melanoma receiving ipilimumab, except for a higher rate of endocrine events (e.g., hypophysitis) from adjuvant ipilimumab therapy. Whether ipilimumab is used as adjuvant therapy after surgery for stage III melanoma requires weighing the risk for disease recurrence and adverse events. A phase III study known as ECOG-E1609 comparing adjuvant ipilimumab 3 mg/kg and 10 mg/kg with high-dose IFN after surgery in patients with high-risk stage III or IV melanoma is in progress that should provide insight about whether the lower ipilimumab dosage provides the same benefit as the higher ipilimumab dosage with less toxicity.[19]

Anti-PD-1 Therapies

Although the PD-1 inhibitors nivolumab and pembrolizumab are approved by FDA for use in patients with advanced melanoma and disease progression after treatment with ipilimumab, all three agents are considered preferred options for treatment of advanced melanoma in recently updated guidelines from the National Comprehensive Cancer Network because of favorable responses observed from use of PD-1 inhibitors in this patient population.[8] Nivolumab was evaluated in a phase 1 dose-escalation study of patients with advanced malignancies, including 94 patients with advanced melanoma.[20] An objective response rate of 28% was observed in patients with advanced melanoma. No maximum tolerated dose was found. Thirteen (72%) of 18 patients with melanoma and an objective response who were treated for 1 year or longer had a durable response. The incidence of grade 3 or 4 toxicity was 14%. The most common treatment-related adverse events were fatigue, rash, and diarrhea.

A large randomized phase 3 study known as KEYNOTE-006 comparing pembrolizumab with ipilimumab in patients with unresectable stage III or IV advanced melanoma recently was stopped early because of a significant and clinically meaningful improvement in overall and progression-free survival from pembrolizumab compared with ipilimumab.[21,22] Two dosing regimens of pembrolizumab (10 mg/kg every 3 weeks and 10 mg/kg every 2 weeks) and four courses of ipilimumab 3 mg/kg every 3 weeks were used.

Temporary interruption or permanent discontinuation of nivolumab or pembrolizumab therapy in patients with melanoma may be needed if immune-related toxicity develops.[10,11] The decision to withhold or discontinue therapy is based on the severity of the toxicity. Therapy should be withheld from patients with:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Symptomatic hypophysitis from pembrolizumab only (e.g., unusual headache, extreme weakness, dizziness, fainting, vision changes)
- Grade 2 nephritis
- Creatinine >1.5 and ≤ 6 times the upper limit of the normal range (ULN) or >1.5 times baseline (from nivolumab only)
- Grade 3 hyperthyroidism (from pembrolizumab only)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 and ≤ 5 times ULN or total bilirubin >1.5 and ≤ 3 times ULN
- Any other severe or grade 3 treatment-related adverse reaction

Therapy may be resumed in patients whose adverse reactions recover to grade 0-1.[10,11]

Nivolumab and pembrolizumab should be permanently discontinued in patients with:[10,11]

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis, nephritis, or infusion-related reactions
- Grade 4 colitis
- Creatinine >6 times ULN
- AST or ALT > 5 times ULN or total bilirubin > 3 times ULN increase from baseline by ≥50% lasting for ≥1 week if liver metastasis is present and grade 2 AST or ALT elevation was present when pembrolizumab treatment began
- Inability to reduce the corticosteroid dose to ≤10 mg/day of prednisone by 12 weeks
- Persistent grade 2 or 3 adverse reactions that do not recover to grade 0 or 1 within 12 weeks after the last dose
- Any severe or grade 3 treatment-related adverse reaction that recurs

The similarity in dosing regimens for nivolumab (3 mg/kg i.v. over 60 minutes every 2 weeks) and pembrolizumab (2 mg/kg i.v. over 30 minutes every 3 weeks) raises concerns about the possibility of prescribing error. Health care providers should be educated about these differences and the proper dosing of these drugs.

Immune Checkpoint Inhibitors in Development

Several PD-1 immune checkpoint inhibitors are in development. Pidilizumab (also known as CT-011), a humanized IgG1 monoclonal antibody specific for PD-L1, has been evaluated in phase 2 studies of patients with metastatic melanoma and follicular lymphoma.[23,24] In an open-label study of 103 patients with metastatic melanoma who received 1.5 mg/kg or 6 mg/kg i.v. every 2 weeks for 27 doses, the overall 12-month survival rate was 64.5%.[23] The most common adverse events were fatigue (43%), diarrhea (22.5%), and arthralgia (21%), and the most common serious adverse events were pneumonia (5%) and dyspnea (3%).

In a phase 1 study of 207 patients with various advanced malignancies, including 55 patients with melanoma, an objective response was observed in 9 (17%) of 52 patients receiving a fully human IgG4 monoclonal antibody specific for PD-L1 known as BMS-936559.[25] The incidence of grade 3 or 4 toxicity was 5% in the entire study population.

In 35 patients with locally advanced or metastatic melanoma, an objective response was observed in 9 (26%) patients receiving an engineered human IgG1 monoclonal antibody product targeting PD-L1 known as MPDL-3280A.[26] The progression-free survival rate was 35% after 24 weeks. The incidence of grade 3 or 4 adverse events was 33%.

A phase 1 study of another engineered human IgG1 monoclonal antibody product targeting PD-L1 known as MEDI-4736 is under way in patients with advanced melanoma.[27]

Combination Therapy

Combining the CTLA-4 inhibitor ipilimumab with the PD-1 inhibitor nivolumab was explored in a phase 1 study of patients with stage III or IV melanoma.[28] Fifty-three patients received concurrent therapy with nivolumab and ipilimumab every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses and then maintenance therapy with both drugs every 12 weeks for up to eight doses. A dose-escalating regimen was used for nivolumab (0.3-10 mg/kg) and ipilimumab (1-10 mg/kg) in this concurrent regimen. Another 33 patients who previously had been treated with ipilimumab received nivolumab (1 mg/kg or 3 mg/kg) alone every 2 weeks for up to 48 doses as sequential therapy.

The objective response rate was 40% with the concurrent regimen, although it varied with the doses used and was as high as 53% in patients receiving the

maximum doses associated with an acceptable level of adverse events (nivolumab 1 mg/kg and ipilimumab 3 mg/kg).[28] By contrast, the objective response rate was 20% with the sequential regimen. The rate of objective response to the concurrent regimen did not vary based on expression of PD-L1. The incidence of grade 3 or 4 toxicity was 53% with the concurrent regimen and 18% with the sequential regimen. Rash and pruritus were the most common treatment-related adverse events from both regimens. Thus, concurrent therapy may be more effective than sequential therapy with a higher risk of toxicity.

Combining immunotherapy with targeted therapy for melanoma has been suggested for patients with unresectable or metastatic disease because of the depth of response and survival benefit observed from these therapies when used alone.[13,29] However, the efficacy and safety when these drugs are combined remain to be determined. A phase 1 study of a combination of ipilimumab and the BRAF inhibitor vemurafenib was terminated early because the combination caused substantial dose-limiting hepatotoxicity.[30] These two drugs should not be used concurrently outside of a clinical trial. The optimal combination of targeted and immune-based agents and dosing regimens for advanced melanoma remain to be determined.

Table 1
Acquisition Cost of Immunotherapies for Melanoma[9-12,a]

Agent	Dosage	Cost for 3 Months of Therapy ($)
High-dose IL-2	720,000 units/kg i.v. every 8 hr for 12 doses	44,352[b]
Ipilimumab	3 mg/kg i.v. every 3 weeks x 4 doses	155,129[c]
Nivolumab	3 mg/kg i.v. every 2 weeks	41,437[d]
Pembrolizumab	2 mg/kg i.v. every 3 weeks	41,434[e]

IL = interleukin; i.v. = intravenously

[a] Acquisition cost is based on the average wholesale price (AWP) for the most common or FDA-approved dosage and a patient weighing 80 kg, and it does not include the cost of supportive care for immune-related toxicity.

[b] The cost figure for high-dose IL-2 does not include the costs for hospitalization or supportive care. It is for one course of therapy based on an AWP of $133,057. Three courses is the average number for patients at Emory University.

[c] The cost figure for ipilimumab is based on use of one 200-mg and one 4-mg vial for each dose.

[d] The cost figure for nivolumab is based on use of two 100-mg vials and one 40-mg vial for each dose.

[e] The cost figure for pembrolizumab is based on use of two 100-mg vials for each dose.

Formulary Considerations

Table 1 illustrates the comparative acquisition costs for 3 months of treatment using currently available immunotherapies for melanoma. These costs do not reflect the cost of hospitalization for administration of high-dose IL-2 (e.g., an ICU stay for administration of pressor agents to maintain blood pressure during high-dose IL-2 therapy) or the costs of supportive care for immune-related toxicity from immunotherapies. The acquisition costs of the currently available immunotherapies are comparable, except for ipilimumab which is substantially more expensive than the other therapies.

Cost should be a consideration along with efficacy and safety in evaluating new therapies for inclusion in the institutional formulary and use in treating individuals with melanoma. Convenience, patient preference, and other considerations also may enter into formulary decisions about immunotherapies for melanoma. Many hospital formularies include both nivolumab and pembrolizumab. Pembrolizumab is preferred over nivolumab by many patients because of its less frequent administration (every 3 weeks for pembrolizumab and every 2 weeks for nivolumab).[11] Nivolumab is approved by FDA for patients with NSCLC as well as melanoma, so it is included in the formulary at institutions serving large numbers of patients with NSCLC.[10]

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Planned by ASHP Advantage and supported by an educational grant from Merck.

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