Ipilimumab

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J Adv Pract Oncol
2011;2:323–332

Although it is responsible for only 5% of all skin cancers (both benign and malignant), melanoma accounts for the majority of skin-cancer–related deaths in the United States. The incidence of melanoma has been increasing over the past 3 decades. In 2011, approximately 70,230 new cases of melanoma are predicted to be diagnosed (American Cancer Society, [ACS], 2011). Risk factors for melanoma include having a light complexion that sunburns easily or that does not tan, multiple abnormal moles or dysplastic nevi, inherited genetic mutations, family history, previous melanoma, and sun exposure (Coit et al., 2011). The use of tanning beds is also associated with increased risk of melanoma (Woo & Eide, 2010). A meta-analysis done by a group from the World Health Organization shows a 15% increased risk of melanoma with the use of tanning beds and a 75% increased risk with first exposure to tanning beds prior to 35 years of age (IARC Working Group, 2007; Woo & Eide, 2010).

Deaths due to melanoma have decreased since the 1990s in younger people (less than 50), remained stable in women older than 50 years, and risen by approximately 1.1% per year in men older than 50 years (ACS, 2011). However, outcomes in patients with metastatic melanoma treated with chemotherapy or immunotherapy are poor, with a median survival of 6 months for patients with stage IV disease (Davis, Kotapati, Mitra, & Iloeje, 2008). An estimated 8,700 people will die from melanoma in 2011 (American Cancer Society, 2011).

Recommendations for first- and second-line treatment can been found in guidelines from the National Comprehensive Cancer Network (NCCN, 2011). Dacarbazine, considered standard of care for treatment with a chemotherapeutic agent, has historically yielded response rates of 10% to 20% and a median response duration of 3 to 4 months (Coit et al., 2011, Serrone et al., 2000). Temozolomide, high-dose interleukin-2 (IL-2), and paclitaxel with or without cisplatin or carboplatin yield similar response rates (Coit et al., 2011). Current NCCN guidelines have added ipilimumab (Yervoy) for the treatment of advanced or metastatic melanoma, and rate the drug higher than dacarbazine with regard to evidence for appropriateness of use (NCCN, 2011). Ipilimumab is the first agent to demonstrate a longer overall survival in patients with metastatic melanoma (Hodi et al., 2010; Robert, 2011).

Pharmacology

Ipilimumab is a recombinant, human monoclonal IgG1 antibody that increases the natural antitumor response of the immune system. The

drug binds to the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), a downregulator of T-cell activation. By binding to CTLA-4, ipilimumab blocks interaction with CD80 and CD86, leading to increased T-cell activation and proliferation, as well as increased endogenous production of IL-2 (Culver et al., 2011; Thumar & Kluger, 2010). Activity of ipilimumab in patients with melanoma is thought to be through this T-cell immune response in which there is increased recognition of tumor antigens with resultant tumor shrinkage. This action of ipilimumab on the immune response also contributes to autoimmune-type adverse events (ATAEs) observed with this agent (Thumar & Kluger, 2010). The most severe ATAEs include enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy (Bristol-Myers Squibb, 2011c).

Clinical Trials

Clinical trials of ipilimumab for the treatment of metastatic melanoma have included administration of the agent alone or in combination with vaccines, chemotherapy, or immunotherapy such as IL-2 (Agarwala, 2010; Weber, 2009). A phase I trial of ipilimumab in combination with a vaccine of peptides from the gp100 melanoma-associated antigen (gp100 vaccine) was conducted in patients with resected stage III or IV melanoma (Sanderson et al., 2005). The study demonstrated a maximum tolerated dose of 1 mg/kg, as defined by the study protocol (three of five patients experienced dose-limiting toxicities at the 3-mg/kg dose). However, a targeted trough level of 10 μg/mL, the level needed to inhibit CTLA-4, was achieved by administering a dose of 3 mg/kg. Dose-limiting toxicities in this study were grade 3 diarrhea or abdominal pain. At 28.5 months, 12 of the 19 patients had relapsed disease. This, as well as other studies, confirmed a dose of at least 3 mg/kg to be used in subsequent clinical trials, both as monotherapy and in combination with other agents (Maker et al., 2005; Maker et al., 2006; Phan et al., 2003; Thumar & Kluger, 2010; Weber et al., 2008).

There was some evidence in this study that patients observed to have side effects related to the autoimmune mechanism of the drug had a better outcome, and that more patients were observed to have ATAEs in the higher-dose cohorts (Sanderson et al., 2005). All of the patients (100%) in the 3-mg/kg cohort were observed to have ATAEs. Of the eight patients enrolled in any of the cohorts that were observed to have ATAEs, three (37%) relapsed at the last date of follow-up. Eleven patients were observed not to have experienced ATAEs, with nine (82%) reported to have relapsed by the last date of follow-up. Other studies have also alluded to a relationship between ATAE, dose, duration of treatment, and response (Attia et al., 2005; Bouwhuis et al., 2011; Downey et al., 2007; Weber et al., 2008).

Multiple studies have reported on the outcomes of patients with metastatic melanoma treated with ipilimumab at doses of 3 mg/kg and higher (see Table 1). Overall, the phase II studies of single-agent ipilimumab demonstrated higher response rates, prolonged disease response, and increased incidence of ATAEs with higher doses of ipilimumab. A phase II study that evaluated the combination of ipilimumab and dacarbazine demonstrated activity in patients with untreated, unresectable metastatic melanoma with progressive disease (Hersh, 2011). Patients randomized to the combination arm also reported ATAEs that were considered expected and manageable.

Phase III Studies

Two phase III studies have been published. The pivotal study leading to approval of the drug was a randomized, double-blind, double-dummy trial conducted in 676 previously treated patients with unresectable stage III and IV melanoma (Hodi et al., 2010). Prior therapy could have included, as monotherapy or in combination, agents such as dacarbazine, temozolomide, fotemustine, or carboplatin, or prior treatment with IL-2. Patients were randomized in a 3:1:1 ratio to receive ipilimumab 3 mg/kg and gp100 vaccine (n = 403), ipilimumab 3 mg/kg and placebo gp100 vaccine (n = 137), or placebo ipilimumab and gp100 (n = 136) vaccine every 3 weeks for four doses (weeks 1, 4, 7, and 10). The primary endpoint was amended to overall survival of patients treated with ipilimumab and gp100 vaccine compared to survival of patients treated with gp100 vaccine alone. Secondary outcomes included overall survival of patients treated with ipilimumab alone compared to patients treated with gp100 vaccine, overall survival of patients treated with ipilimumab and gp100 vaccine compared to patients treated with ipilimumab alone, response rate (sum proportion of patients with com-

Table 1. Clinical Trials of Ipilimumab in the Treatment of Metastatic Melanoma

Study design	Treatment groups[a]	Efficacy	Safety	Reference
Phase I/II	A–SD to 20 mg/kg (n = 30) B–MD to 5 mg/kg (n = 34) C–MD to 10 mg/kg (n = 24)	***RR[b] (DCR)*** A–2.9% (13.3%) B–2.9% (14.4%) C–8.7% (39.1%) ***DCR ≥ 24 wk*** A–8.8% B–6.7% C–34.7%	***Grade 3/4 AEs*** A–13.3% B–20.6% C–25% ***Grade 4 AEs (only observed in Group C)*** Colitis (n = 1, 4.2%) Diarrhea (n = 1, 4.2%) GI perforation (n = 1, 4.2%)	Weber (2008)
Phase II	A–0.3 mg/kg (n = 72) B–3 mg/kg (n = 72) C–10 mg/kg (n = 73) Induction: every 3 wk for 4 cycles Maintenance: every 3 mo	***RR[b] (DCR)*** A–0% (13.7%) B–4.2% (26.4%) C–11.1% (29.2%) ***DCR ≥ 24 wk*** A–0% B–3% C–7%	***Most frequent grade 3/4 ATAEs*** A–None B–Diarrhea, vomiting, pruritus, rash, fatigue, colitis (1.4% each) C–Diarrhea (14%), pruritus, fatigue, colitis (2.8% each)	Wolchok (2010)
Phase II	A–10 mg/kg (n = 155) Induction: every 3 wk for 4 cycles Maintenance: every 3 mo	***RR[b] (DCR)*** A–5.8% (27%) Median OS: 10.2 mo 12-mo survival: 47.2% 24-mo survival: 32.8%	***Grade 3/4 AEs*** GI 8.4% Liver 7.1% Skin 3.2% Endocrine 1.3% Other 2.6%	O'Day (2010)
Phase II	A–3 mg/kg every 3 weeks + gp100 vaccine (n = 54) B–3 to 9 mg/kg every 3 weeks ± gp100 vaccine (n = 85)	***RR[b]*** A–13% B–19% Median PFS, all patients (responders): 2.9 (30.6) mo Median OS, all patients (responders): 15.7 (not yet reached) mo	***Grade 3/4 ATAEs (n = 139)*** Enterocolitis 17% Hypophysitis 9% Dermatitis 6% Arthralgia, uveitis (2% each) Alveolitis, hepatitis, episcleritis, nephritis (1% each)	Downey (2007)
Phase II	A–3 mg/kg every 4 wk for 4 doses (n = 37) B–3 mg/kg every 4 wk for 4 doses + DTIC 50 mg/m^2/day × 5 days for up to 6 courses (n = 35)	***RR[b] (DCR)*** A–5.4% (21.6%) B–14.3% (37.1%) ***DCR ≥ 24 wk*** A–10.8% B–5.7% ***Median OS*** A–11.4 mo B–14.3 mo	***Grade 3/4 AE*** — ***A*** — ***B*** Fatigue — 0 — 5.7% Nausea — 0 — 2.9% Pyrexia — 0 — 2.9% Rash — 2.6% — 2.9%	Hersh (2011)
Phase III	A–3 mg/kg every 3 wk for 4 treatments + gp100 (n = 403) B–3 mg/kg every 3 wk for 4 treatments (n = 137) C–gp100 alone (n = 136)	***RR[b] (DCR)*** A–5.7% (20.1%) B–10.9% (28.5%) C–1.5% (11%) B vs. C for RR, $p = .001$ B vs. C for DCR, $p < .001$ ***Median OS (PFS)*** A–10.0 (2.76) mo B–10.1 (2.86) mo C–6.4 (2.76) mo ***Rate of survival at 24 mo*** A–21.6% B–23.5% C–13.7%	***Grade 3/4 ATAE*** — ***A*** — ***B*** — ***C*** Dermatologic — 2.4% — 1.5% — 0 GI — 5.8% — 7.6% — 0.8% Endocrine — 1.1% — 3.8% — 0 Hepatic — 1.1% — 0 — 2.3% Other — 1.3% — 2.3% — 0.8%	Hodi (2010)
Phase III	Induction: Treatment on weeks 1, 4, 7, and 10 A–10 mg/kg + DTIC 850 mg/m^2 (n = 250) B–DTIC 850 mg/m^2 (n = 252) Maintenance: Treatment every 12 wk A–10 mg/kg B–Placebo	***RR[b] (DCR)*** A–15.2% (33.2%) B–10.3% (30.2%) Hazard ratio for disease progression 0.76, $p = .006$. ***Median OS (duration of response)*** A–11.2 (19.3) mo B–9.1 (8.1) mo Hazard ratio for death 0.72, $p > .001$ ($p = .03$)	***Grade 3/4 ATAE*** — ***A*** — ***B*** Rash — 1.2% — 0 Hepatitis — 1.2% — 0 Pruritus — 2.0% — 0 Colitis — 2.0% — 0 Increased AST — 17.4% — 0.4% Increased ALT — 20.7% — 0.8%	Roberts (2011)

Note. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATAE = autoimmune-type adverse event; DCR = disease control rate; DTIC = dacarbazine; GI = gastrointestinal; MD = multiple dose; OS = overall survival; PFS = progression-free survival; RR = response rate; SD = single dose.
[a]Dosing is for ipilimumab treatment groups unless otherwise specified.
[b]Response rate = Sum of the percent assessed to have achieved complete or partial response.

plete or partial response), duration of response, and progression-free survival.

Median overall survival was 10 months for patients treated with ipilimumab and gp100 vaccine, 10.1 months for patients treated with ipilimumab alone, and 6.4 months for patients treated with gp100 vaccine alone. The hazard ratio for death was 0.68 ($p < .01$) for patients treated with ipilimumab and gp100 vaccine compared to gp100 vaccine alone, 0.66 ($p = .03$) for patients treated with ipilimumab alone compared to gp100 vaccine alone, and 1.04 ($p = .76$) for patients treated with ipilimumab and gp100 vaccine compared to ipilimumab alone. Survival rates at 12, 18, and 24 months were reported for patients in each group. The 12-month overall survival for patients in the ipilimumab and gp100 vaccine group, the ipilimumab alone group, and the gp100 vaccine group were 43.6%, 45.6%, and 25.3%, respectively. The 18-month overall survival rates were 30%, 33.2%, and 16.3%, respectively. The 24-month overall survival rates were 21.6%, 23.5%, and 13.7%, respectively. Response rates were 5.7% for patients treated with ipilimumab and gp100 vaccine, 10.9% for patients treated with ipilimumab alone, and 1.5% for patients treated with gp100 vaccine alone. Nine of 16 patients (60%) maintained their response for at least 2 years in the ipilimumab alone treatment group compared to 4 of 23 patients (17.4%) in the ipilimumab and gp100 vaccine group. None of the patients in the gp100 vaccine alone group maintained a response for at least 2 years. The study concluded that ipilimumab significantly improves overall survival compared to the gp100 vaccine in patients previously treated for metastatic melanoma.

The second phase III trial combined ipilimumab with dacarbazine for use in patients with previously untreated metastatic melanoma (Robert et al., 2011). Patients were randomized, in a double-blind fashion, to be treated with ipilimumab 10 mg/kg and dacarbazine 850 mg/m^2 or dacarbazine 850 mg/m^2 and placebo at weeks 1, 4, 7, and 10. Treatment with dacarbazine was continued every 3 weeks through week 22. Patients with a response or stable disease at week 24 could continue treatment with ipilimumab or placebo every 12 weeks until progression or until they were no longer able to tolerate treatment. The primary endpoint was also amended in this study from progression-free survival to overall survival. Secondary endpoints included progression-free survival, response (proportion of patients with a complete or partial response), time to response, duration of response, and safety.

Median overall survival was significantly longer in patients treated with ipilimumab and dacarbazine compared to dacarbazine and placebo (11.2 months compared to 9.1 months). The hazard ratio for death with ipilimumab and dacarbazine compared to dacarbazine and placebo was 0.72 ($p < .001$). The 12-, 24-, and 36-month survival rates for patients treated with ipilimumab and dacarbazine were higher compared to patients treated with dacarbazine and placebo: 47.3% vs. 36.3%, 28.5% vs. 17.9%, and 20.8% vs. 12.2%, respectively. There was no significant difference between treatments with respect to response rate and disease control rate (DCR). Response rate (and DCR) was 15.2% (33.2%) in the ipilimumab and dacarbazine group compared to 10.3% (30.2%) in the dacarbazine and placebo group. Duration of response was 19.3 months in patients treated with ipilimumab and dacarbazine compared to 8.1 months in patients treated with dacarbazine and placebo ($p = .03$). Risk of progression was reduced by 24% in patients treated with ipilimumab and dacarbazine compared to patients treated with dacarbazine and placebo ($p = .006$). Therefore, there was an improvement in survival in patients with untreated metastatic melanoma who received treatment with ipilimumab and dacarbazine.

Many of these trials reported on the observation that some patients continued to respond after completion of treatment. One of the studies where this phenomenon was observed was the pivotal phase III study of ipilimumab with or without gp100 vaccine or gp100 vaccine alone in patients with previously treated metastatic melanoma (Hodi et al., 2010). This study reported an improvement in disease after week 24 in both of the ipilimumab treatment groups. Three patients were observed to improve from progressive to stable disease, five patients improved from stable disease to partial response, and four patients improved from partial response to a complete response. Of 31 patients treated with reinduction therapy, an additional 21 patients were observed to respond (stable disease, partial response, or complete response).

These types of observations led one researcher to conclude that patients observed to have sta-

ble disease or even progressive disease that does not significantly affect performance status may benefit from continued treatment (Weber, 2009). They also recommended the use of response criteria, which considers the differences between more rapid tumor shrinkage or response observed with traditional chemotherapeutic agents and the delayed immune-related response. Criteria would include disease assessments conducted later in the course of therapy (i.e., week 12 instead of week 6 or 8), and new disease would not necessarily be classified as disease progression unless it affects performance status or total increase in disease exceeds a predetermined amount, such as 30% increase compared to baseline (Weber, 2009). These observations and recommendations differ from the dosage regimen in the package insert, which recommends that a total of four doses of ipilimumab be administered (Bristol-Myers Squibb, 2011c). The differences between the experts' recommendations and the package insert still need to be resolved.

Adverse Effects

Ipilimumab carries a black box warning on the label indicating that patients receiving the drug are at risk for ATAEs due to the mechanism of action of the drug and the activation and proliferation of T-cells. The drug also has a risk evaluation and mitigation strategy (REMS) in place to ensure prescribers are aware of the risks associated with ipilimumab therapy (Bristol-Myers Squibb, 2011a). The REMS and its components are further discussed in the Implications for the Advanced Practitioner section of this article. The rationale for the black box warning and the REMS has to do with the adverse events observed in clinical trials. Table 1 lists grade 3 and 4 adverse events observed in clinical trials, with the majority considered immune-related. Additional details regarding the frequency and types of ATAEs observed in the phase III trials are outlined below.

In the pivotal phase III trial, grade 3 or 4 immune-related adverse effects were observed in 10% to 15% of patients treated with ipilimumab and in 3% of patients treated with gp100 (Hodi et al., 2010). Organ systems affected by the immune-related adverse effects were dermatologic, gastrointestinal, endocrine, and hepatic. The most commonly observed immune-related adverse effects (all grades) in patients treated with ipilimumab alone were diarrhea (27.5%), pruritus (24.4%), rash (19.1%), and colitis (5.3%). Common adverse events (all grades) observed in patients treated with ipilimumab alone, not considered immune-related, included fatigue (42%), nausea (35.1%), decreased appetite (26.7%), vomiting (23.7%), and constipation (20.6%). Median time to resolution of grade 2, 3, or 4 immune-related adverse effects in the ipilimumab treatment group was 4.9 weeks (95% CI, 3.1 to 6.4). A total of 14 deaths were judged as related to the study drug. Of the 14 deaths, 7 were considered immune-related, with 5 of the 7 deaths due to colitis or bowel perforation.

In the second phase III study of ipilimumab combined with dacarbazine in patients with previously untreated metastatic melanoma, grade 3 or 4 immune-related adverse events were observed in 38.1% of patients treated with the combination of ipilimumab and dacarbazine and 4.4% of patients treated with dacarbazine alone (Robert et al., 2011). Organ systems affected by immune-related adverse events were the same as in the previous phase III study, with the most commonly observed immune-related adverse events (all grades) in patients treated with ipilimumab and dacarbazine being diarrhea (32.8%), increases in alanine aminotransferase (29.1%) and aspartate aminotransferase (26.7%), pruritus (26.7%), rash (22.3%), colitis (4.5%), and hepatitis (1.6%). Pyrexia, an adverse event not considered immune-related, was observed in more than a third of patients treated with ipilimumab and dacarbazine (36.8%). This trial included a maintenance phase in which patients randomized to the ipilimumab and dacarbazine could continue to receive ipilimumab (blinded therapy) every 12 weeks. The most common adverse effects observed in this group of patients were rash (25.6%), pruritus (16.3%), diarrhea (14.0%), nausea (7.0%), and fatigue (9.3%). None of the patients died due to immune-related hepatitis or colitis during the study.

SEE PAGE 304

Use your smartphone to access reports on the phase III Hodi et al. and Robert et al. studies, as well as the REMS materials necessary for ipilimumab prescribers.

Treatment of the majority of adverse effects associated with ipilimumab therapy is aimed at the immune system (Bristol-Myers Squibb, 2011a, 2011b, 2011c). Table 2 summarizes recommendations for treatment of the most common ATAEs associated with ipilimumab therapy. Baseline assessments, including thyroid and liver function tests, as well as assessment of disease states such as enterocolitis, endocrinopathy, and neuropathy, should be done prior to treatment with ipilimumab. Patients should be closely monitored for neuropathies and any adverse events affecting the skin, GI tract, liver, or endocrine system. Ipilimumab therapy should be permanently discontinued with any severe reaction and prednisone 1 to 2 mg/kg/day, or an equivalent corticosteroid, should be administered until resolution of the adverse event (i.e., grade 1 or better for enterocolitis). The corticosteroid should then be tapered over at least 1 month. According to the package insert, ipilimumab should also be discontinued in patients who cannot tolerate a corticosteroid taper to an equivalent of prednisone 7.5 mg per day or in those patients who cannot complete a full treatment course within 16 weeks of the first ipilimumab dose (Bristol-Myers Squibb, 2011). Symptomatic treatment, such as antidiarrheals or topical steroids, can be used to treat adverse events considered less severe. However, treatment with systemic corticosteroids should be initiated in patients experiencing persistent adverse effects, such as diarrhea lasting for longer than 1 week. In these cases, the recommended oral dose of prednisone is 0.5 mg/kg/day. Treatment of immune-related adverse effects with corticosteroids has not been observed to impact response to treatment (Downey et al., 2007; Wolchok et al., 2010).

Other modalities for the treatment of immune-related adverse events have been used. Infliximab (Remicade) has been used for treatment of patients with enterocolitis unresponsive to corticosteroids (Hodi et al., 2010). The phase III study of ipilimumab and dacarbazine noted that five patients were given mycophenolate mofetil for treatment of immune-related hepatitis (Robert et al., 2011). Supportive treatment for other immune-related adverse effects should be considered. For example, treatment for patients with endocrinopathies should include, along with initiation of corticosteroid therapy, hormone replacement therapy. Although most immune-related adverse effects were observed during treatment, there is a risk that they could occur after treatment discontinuation (Bristol-Myers Squibb, 2011c). Therefore, monitoring for immune-related adverse effects should continue after completion of therapy.

Role in Melanoma Therapy

The US Food and Drug Administration (FDA)-labeled indication for ipilimumab is for the treatment of unresectable or metastatic melanoma, and the recommended treatment regimen is 3 mg/kg IV every 3 weeks for a total of four doses (Bristol-Myers Squibb, 2011). Results of the phase III studies reported statistically significant prolongation of survival (Hodi et al., 2010; Robert et al., 2011). See Table 3 for dosage and administration guidelines for ipilimumab. Considering the observed improvement in survival compared to dacarbazine, ipilimumab will likely be used as first-line treatment in combination with dacarbazine as well as in patients who have failed other therapy.

Although immune-related adverse effects are treatable with corticosteroids and supportive care, the risk of suffering from a severe immune-related reaction may exclude certain patients from treatment. The NCCN, in its compendium, gives some consideration to performance status in its recommendations for use of ipilimumab as a single agent. The NCCN notes that patients with disseminated recurrence or metastatic disease, "with good performance status," should be considered candidates for single-agent therapy (NCCN, 2011). Recommendations for therapy in combination with dacarbazine have not yet been added to the compendium.

The FDA gives a dosing regimen that only includes a total of four doses of ipilimumab (Bristol-Myers Squibb, 2011c). Maintenance therapy and response after discontinuation of therapy are not addressed in the label. Both phase III studies allowed continued use of ipilimumab, past the four induction doses (Hodi et al., 2010; Robert et al., 2011). Patients with previously treated metastatic melanoma were allowed reinduction if they progressed after being assessed as having stable disease for 3 months after the week 12 disease assessment or if they had a confirmed partial or complete response (Hodi et al., 2010). Patients with previously untreated metastatic melanoma who received the combination of ipilimumab and

Table 2. Common Autoimmune-Type Adverse Events and Recommended Treatment

Adverse event	Severity	Symptoms	Recommendation
Dermatologic	Moderate	Rash covering ≤ 50% of body	Stop ipilimumab temporarily and evaluate for other causes. Start corticosteroids (either topical or systemic) if no improvement within 1 week of stopping ipilimumab therapy. Restart ipilimumab if patient is able to tolerate taper to equivalent of ≤ prednisone 7.5 mg
	Severe	SJS, TEN, rash with full thickness dermal ulcers, rash with areas of necrosis, bullous lesions, or bleeding	Discontinue ipilimumab Systemic corticosteroids equivalent to prednisone 1–2 mg/kg/day Start 1-mo taper when rash is controlled
Endocrine	Moderate and severe	Generalized symptoms such as fatigue, headache, hypotension, abnormal thyroid function tests	Stop ipilimumab temporarily in symptomatic patients. Evaluate thyroid, pituitary, adrenal function. Systemic corticosteroids equivalent to prednisone 1–2 mg/kg/day Consider hormone replacement therapy Restart ipilimumab once symptoms are alleviated and if patient is able to tolerate taper to equivalent of ≤ prednisone 7.5 mg
Enterocolitis	Moderate	4 to 6 BM/day more than BL, abdominal pain, blood, or mucus in stool	Stop ipilimumab temporarily and evaluate for other causes of diarrhea. Start antidiarrheals. *For ongoing symptoms (> 1 week)* Systemic corticosteroids (equivalent to prednisone 0.5 mg/kg/day) until improved or resolved. Begin steroid taper and monitor for any worsening in symptoms. Restart ipilimumab if patient is able to tolerate taper to equivalent of ≤ prednisone 7.5 mg
	Severe, uncomplicated	≥ 7 BM more than BL	Discontinue ipilimumab Systemic corticosteroids equivalent to prednisone 1-2 mg/kg/day
	Severe, complicated	Dehydration, bleeding, sigmoidoscopy shows severe colitis	Inpatient admission to correct hydration, electrolytes. Consider bowel rest and TPN. If event is not due to bowel perforation, IV corticosteroids (see below if no response)
	Severe, steroid refractory	No/partial improvement in symptoms or relapse while receiving corticosteroids	Infliximab 5 mg/kg, may repeat every 2 wk if necessary Add tacrolimus or rapamycin if no/limited response to infliximab
Hepatic	Moderate	AST/ALT > 2.5 to 5 times ULN Total bilirubin > 1.5 to 3 times ULN	Stop ipilimumab temporarily while cause is determined Monitor liver function more frequently until event is resolved
	Severe	AST/ALT > 5 times ULN Total bilirubin > 3 times ULN	Discontinue Ipilimumab Evaluate for other causes, such as infection or malignancy Monitor liver function more frequently Systemic corticosteroids equivalent to prednisone 1–2 mg/kg/day. Start 1-mo taper when patient shows continued improvement or improvement to baseline.
Neurologic	Moderate	Neuropathies, muscle weakness not interfering with ADLs	Temporarily stop ipilimumab until event is resolved or symptoms are back to baseline Symptomatic treatment
	Severe	Symptoms interfere with ADLs or are life-threatening Guillain-Barré syndrome, myasthenia gravis	Discontinue ipilimumab Systemic corticosteroids equivalent to prednisone 1–2 mg/kg/day

Note. ADLs = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; BM = bowel movement; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TPN = total parenteral nutrition; ULN = upper limit of normal.
Information from Bristol-Myers Squibb (2011b), Thumar & Kluger (2010).

Table 3. Dosage and Administration of Ipilimumab

Dose	3 mg/kg IV
Schedule	Every 3 weeks for a total of 4 doses
Preparation	1. Take vials out of the refrigerator for 5 min before preparing infusion 2. Inject required volume of drug into an IV bag of 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, to a final concentration between 1 and 2 mg/mL 3. Mix the IV solution by gently turning the bag 4. The diluted solution can be kept at room temperature (20°–25°C) for up to 24 hours
Administration	1. Administer ipilimumab over 90 min IV through a sterile, nonpyrogenic, low-protein binding in-line filter 2. Flush the line with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, after each dose 3. Do not mix or administer with other medications

Note. Information from Bristol-Myers Squibb (2011c).

dacarbazine were allowed maintenance therapy with ipilimumab every 12 weeks until disease progression or until the patient no longer tolerated treatment. Off-label use will likely occur with patients receiving additional drug as part of a maintenance regimen or for reinduction. Considering the high cost of the agent (approximately $30,000/dose), it is difficult to predict how the health-care system will respond to additional demand for the agent, outside the package insert–labeled regimen.

Other strategies and new agents are being investigated for the treatment of metastatic melanoma. Results of studies combining ipilimumab with temozolomide (Patel et al., 2011), fotemustine (Di Giacomo et al., 2011), and bevacizumab (Avastin; Hodi et al., 2011) were recently presented. Additionally, the *BRAF* inhibitor vemurafenib (Zelboraf) was recently approved for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutations (Genentech, 2011). A recently published phase III trial randomized 675 patients with previously untreated, unresectable stage IIIC or stage IV melanoma with the *BRAF* V600E mutation to treatment with either vemurafenib or dacarbazine (Chapman et al., 2011). Overall survival at 6 months was 84% in patients treated with vemurafenib and 64% in patients treated with dacarbazine. Treatment with vemurafenib was associated with a 63% reduction in risk of death and a 74% reduction in risk of either death or disease progression compared to dacarbazine ($p < .001$ for both endpoints). Vemurafenib is an oral agent, dosed twice daily. Treatment with vemurafenib was well tolerated, with the most common grade 2 or 3 adverse events being dermatologic reactions (rash [18%], pruritus [7%], hyperkeratosis [6%]), arthralgias (21%), and fatigue (13%). Cutaneous squamous cell carcinoma, keratocanthoma, or both were observed in 18% of patients treated with vemurafenib. Acquired resistance to the agent has been identified as a potential problem, with the mechanism of resistance and strategies to overcome resistance currently being investigated (Smalley & Sondak, 2010; Solit & Rosen, 2011). The role of ipilimumab in combination with other agents, such as various chemotherapy agents or *BRAF* inhibitors, will further shape treatment and expectations for survival in this population.

Implications for the Advanced Practitioner

Ipilimumab has been shown to provide a survival advantage and will be useful in patients with metastatic melanoma. However, there are risks associated with use of the drug, especially with regard to ATAEs. The Communication Plan outlined in the REMS includes a letter to prescribers that includes information regarding the incidence, type, severity, and management of immune-related adverse effects due to ipilimumab and an adverse reaction management guide. An adverse effects checklist is also available. Information in the Communication Plan is to be periodically updated, with updated materials sent to prescribers. Written communications are fol-

lowed up by phone calls and visits from company representatives to further discuss monitoring and treatment of adverse effects. The goal is for the advanced practitioner to be familiar with necessary monitoring for immune-related adverse effects and to be able to initiate corticosteroids or other supportive therapy early in the course of the event.

Early recognition and treatment of immune-related adverse effects is essential. Although the majority of adverse events were reported while the patient was being treated, some adverse events occurred after treatment was discontinued. Therefore, monitoring should continue even after withdrawal from treatment. Patients should be informed of the importance of early recognition of potential immune-related adverse effects. They should understand that changes from baseline, such as changes in bowel habits or abdominal pain or cramping, should be reported to their prescribers. Other signs of immune-related adverse events can include detection of a rash, itching, yellow skin or eyes, numbness or tingling in hands or feet, and unsteadiness. Patients should understand that prescribers should be contacted for any of these sorts of symptoms, and that symptomatic management without contacting the prescriber is discouraged.

Summary

Treatment with ipilimumab has been reported to prolong survival in patients with metastatic melanoma. An unfortunate consequence to this agent's pharmacology is that significant immune-related adverse effects are common with administration. These adverse effects typically occur during treatment, but can occur after treatment has been discontinued. Immune-related adverse events primarily involve the skin, GI tract, endocrine system, or liver. Early recognition and treatment of immune-related adverse events will be crucial in the care of these patients.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES

Agarwala, S. S. (2010). Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: Cytotoxic T-lymphocyte antigen-4 blockade in advanced melanoma. *Melanoma Research 20*(1), 1–10. doi:10.1097/CMR.0b013e328333bbc8.

American Cancer Society. (2011). Melanoma skin cancer. Atlanta: American Cancer Society. Retrieved from http://www.cancer.org/acs/groups/cid/documents/webcontent/003120-pdf.pdf.

Attia, P., Phan, G. Q., Maker, A. V., Robinson, M. R., Quezado, M. M., Yang, J. C.,...Rosenberg, S. A. (2005). Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *Journal of Clinical Oncology 23*(25), 6043–6053.

Bouwhuis, M. G., ten Hagen, T. L. M., Suciu, S., & Eggermont, A. M. M. (2011). Autoimmunity and treatment outcome in melanoma. *Current Opinion in Oncology, 23*(2), 170–176. doi:10.1097/CCO.0b013e328341edff

Bristol-Myers Squibb. (2011a). BLA 125377 YERVOY (ipilimumab) injection, for intravenous infusion human cytotoxic T-lymphocyte antigen-4 (CTLA-4)-blocking monoclonal antibody. Risk evaluation and mitigation strategy (REMS). Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377_REMS.pdf.

Bristol-Myers Squibb. (2011b). Yervoy immune-mediated adverse reaction management guide. Retrieved from http://www.yervoy.com/hcp/safety-education-outreach.aspx.

Bristol-Myers Squibb. (2011c). Yervoy package insert. Retrieved from www.yervoy.com.

Chapman, P. B., Hauschild, A., Robert, C., Haanen, J. B., Ascierto, P., Larkin, J.,...McAuthur, G. A. (2011). Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine* (Epub ahead of print). doi:10.1056/NEJMoa1103782.

Coit, D. G., Andtbacka, R., Bichakjian, C. K., Carson, W. E., Daud, A., Dilawari, R. A.,...Urist, M. M. (2011). Melanoma: Clinical practice guidelines in oncology. Version 1.2012. Retrieved from www.nccn.org.

Culver, M. E., Gatesman, M. L., Mancl, E. E., & Lowe, D. K. (2011). Ipilimumab: A novel treatment for metastatic melanoma. *Annals of Pharmacology, 45*(4), 510–519. doi:10.1345/aph.1P651.

Davis, K. L., Kotapati, S., Mitra, D., & Iloeje, U. (2008). Death rates, survival time, and disease progression in high risk, and metastatic melanoma: Evidence from the SEER-Medicare linked database [Abstract 17544]. *Journal of Clinical Oncology, 26* (15S).

Di Giacomo, A. M., Ascierto, P. A., Fonsatte, E., Pittiglio, E., Queirolo, P., Pilla, L.,...Maio, M. (2011). A phase II study combining ipilimumab and fotemustine in patients with metastatic melanoma: The NIBIT-M1 trial [Abstract TPS230]. *Journal of Clinical Oncology, 29* (suppl).

Downey, S. G., Klapper, J. A., Smith, F. O., Yang, J. C., Sherry, R. M., Royal, R. E.,...Rosenberg, S. A. (2007). Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clinical Cancer Research, 13*(22), 6681–6688. doi:10.1158/1078-0432.CCR-07-0187.

Genentech, Inc. (2011). Zelboraf package insert. Retrieved from www.zelboraf.com.

Hersch, E. M., O'Day, S. J., Powderly, J., Khan, K. D., Pavlick, A. C., Cranmer, L. D.,...Weber, J. S. (2011). A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Investigational New Drugs, 29*(3), 489–498. doi:10.1007/s10637-009-9376-8.

Hodi, F. S., Friedlander, P. A., Atkins, M. B., McDermott, D. F., Lawrence, D. P., Ibrahim, N.,...Van Den Abbeele, A. D.

(2011). A phase I trial of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma [Abstract 8511]. *Journal of Clinical Oncology, 29*(suppl).

Hodi, F. S., O'Day, S. J., McDermott, D. F., Weber, R. W., Sosman, J. A., Haanen, J. B.,...Urba, W. J. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. *New England Journal of Medicine, 363*(8), 711–723. doi:10.1056/NEJMoa1003466.

International Agency for Research on Cancer Working Group on Artificial Ultraviolet (UV) Light and Skin Cancer (2007). The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *International Journal of Cancer 120*(5), 1116–1122. doi:10.1002/ijc22453.

Maker, A. V., Phan, G. Q., Attia, P., Yang, J. C., Sherry, R. M., Topalian, S. L.,...Rosenberg, S. A. (2005). Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: A phase I/II study. *Annals of Surgical Oncology, 12*(12), 1005–1016. doi:10.1245/ASO.2005.03.536.

Maker, A. V., Yang, J. C., Sherry, R. M., Topalian, S. L., Kammula, U. S., Royal, R. E.,...Rosenberg, S. A. (2006). Intrapatient dose escalation of anti-CTLA-4 antibody in patients with metastatic melanoma. *Journal of Immunotherapy, 29*(4), 455–463.

National Comprehensive Cancer Network. (2011). Drugs & Biologics Compendium: Ipilimumab. Retrieved from nccn.org.

O'Day, S. J., Maio, M., Chiarion-Sileni, V., Gajewski, T. F., Pehamberger, H., Bondarenko, I. N.,...Wolchok, J. D. (2010). Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: A multicenter single-arm phase II study. *Annals of Oncology 21*(8), 1712–1717. doi:10.1093/annonc/mdq013.

Patel, S. P., Bedikian, A. Y., Papadopoulos, N. E., Hwu, W., Kim, K. B., Homsi, J.,...Hwu, P. (2011). Ipilimumab plus temozolomide in metastatic melanoma [Abstract 8579]. *Journal of Clinical Oncology, 29*(suppl).

Phan, G. Q., Yang, J. C., Sherry, R. M., Hwu, P., Topalian, S. L., Schwartzentruber, D. J.,...Rosenberg, S. A. (2003). Cancer regression and autoimmunity induced by cytotoxic t lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proceedings of the National Academy of Sciences, 100*(14), 8372–8377. doi:10.1073/pnas.1533209100.

Robert, C., Thomas, L., Bondarenko, I., O'Day, S., Weber, J., Garbe, C.,...Wolchok, J. D. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *New England Journal of Medicine* (Epub ahead of print). doi:10.1056/NEJMoa1104621

Sanderson, K., Scotland, R., Lee, P., Liu, D., Groshen, S., Snively, J.,...Weber, J. (2005). Autoimmunity in a phase I trial of a fully human anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody with multiple melanoma peptides and montanide ISA 51 for patients with resected stages III and IV melanoma. *Journal of Clinical Oncology, 23*(4), 741–750. doi:101200/JCO.2005.01.128.

Serrone, L., Zeuli, M., Sega, F. M., & Cognetti, F. (2000). Dacarbazine-based chemotherapy for metastatic melanoma: Thirty-year experience overview. *Journal of Experimental Clinical Cancer Research, 19*(1), 21–34.

Smalley, K. S. M., & Sondak, V. K. (2011). Melanoma—An unlikely poster child for personalized cancer therapy. *New England Journal of Medicine 363*(9), 876–878.

Solit, D. B., & Rosen, N. (2011). Resistance to BRAF inhibition in melanoma. *New England Journal of Medicine, 364*(8), 772–774.

Thumar, J. R., & Kluger, H. M. (2010). Ipilimumab: A promising immunotherapy for melanoma. *Oncology, 24*(14), 1280–1288.

Weber, J. S., O'Day, S., Urba, W., Powderly, J., Nichol, G., Yellin, M.,...Hersh, E. (2008). Phase I/II study of ipilimumab for patients with metastatic melanoma. *Journal of Clinical Oncology, 26*(36), 5950–5956. doi:10.1200/JCO.2008.16.1927.

Weber, J. (2009). Ipilimumab: Controversies in its development, utility and autoimmune adverse events. *Cancer Immunology Immunotherapy, 58*(5), 823–830. doi:10.1007/s00262-008-0653-8.

Wolchok, J. D., Neyns, B., Linette, G., Negrier, S., Lutzky, J., Thomas, L.,...Lebbe, C. (2010). Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomized, double-blind, multicenter, phase 2, dose-ranging study. *Lancet Oncology, 11*(2), 155–164. doi:10.1016/S1470-2045(09)70334-1.

Woo, D. K., & Eide, J. J. (2010). Tanning beds, skin cancer, and vitamin D: An examination of the scientific evidence and public health implications. *Dermatologic Therapy, 23*(1), 61–71.