Immune Modulation in Melanoma and Advanced Cancer Therapy: Anti–Cytotoxic T Lymphocyte-Associated Antigen 4 Monoclonal Antibodies

Two fully human monoclonal antibodies (mAbs) that target cytotoxic T lymphocyte-associated antigen 4 (CTLA4), tremelimumab and ipilimumab, are in clinical development for the treatment of advanced cancers. The investigational agents enhance T-cell activation and are hypothesized to generate antitumor immunity. Clinical data have shown that treatment with an anti-CTLA4 mAb is tolerable in most patients. In addition, enhanced antitumor activity was observed in some patients. As expected with an agent that enhances the immune response, immune-related adverse events are observed frequently in treated patients. The immune-related adverse events are not observed with standard chemotherapy agents, so many nurses may be unfamiliar with their management. Early recognition and management of immune-related adverse events by oncology nurses is an essential component of effective treatment with an anti-CTLA4 mAb. As immunomodulatory agents such as anti-CTLA4 mAbs are introduced in oncology treatment, nurses will need a greater understanding of the complexities associated with the therapies. Knowledge of immune system functions and how altering the functions may affect the development of side effects will enhance safety and quality of care for patients receiving anti-CTLA4 mAbs.

Incidence of cutaneous melanoma rose at a rate of about 3% per year from 1981–2000; however, incidence has been stable since 2000 (American Cancer Society, 2009). In 2009, 68,720 new cases of melanoma are expected, and an estimated 8,650 patients will die from the disease (American Cancer Society). Risk factors for melanoma include family history of melanoma, presence and number of melanocytic moles on the body, sensitivity to sunburns, excessive exposure to natural sunlight or artificial ultraviolet light, and the immune status of individuals.

Prognosis for patients with melanoma depends largely on the stage of the disease, which most often is based on the American Joint Committee on Cancer staging system (National Cancer Institute, 2008). Although most cases of early-stage melanoma are curable with surgery, patients with inoperable and distant metastatic melanoma have an extremely poor survival rate (National Cancer Institute); the five-year survival rate is 6%, with a median survival time of 6–7.5 months (Bajetta et al., 2002). To date, dacarbazine is the only U.S. Food and Drug Administration (FDA)-approved chemotherapeutic agent to treat advanced melanoma; response rates range from 10%–20%, with a median response duration of four to six months (Bajetta et al.; Tarhini & Agarwala, 2006). In a randomized phase III trial of temozolomide versus dacarbazine, temozolomide demonstrated equivalent efficacy (Middleton et al., 2000). Cytokine-based therapies with
interferon-α (IFN-α) or interleukin-2 (IL-2) have antitumor activity; however, the treatments are tolerated poorly (Kirkwood, Tarhini, et al., 2008).

With increased understanding of the mechanisms of immune regulation, immunotherapy now is recognized as a potentially viable method for the treatment of many cancers, including advanced melanoma. Many targeted, investigational immunotherapeutic agents are in clinical development for patients with advanced cancer, including two monoclonal antibodies (mAbs) specific for cytotoxic T lymphocyte-associated antigen 4 (CTLA4) (Camacho, 2008; Langer, Clay, & Morse, 2007). The goal of anti-CTLA4 mAbs treatment is to activate antitumor immune responses by breaking peripheral tolerance of T cells and prolonging T-cell activation. As expected with this mechanism of action, toxicities associated with the treatment often are immune-related and are distinct from adverse events associated with standard chemotherapy. Therefore, the management of immune-related adverse events, which includes monitoring and recognizing early symptoms, is critical to the success of anti-CTLA4 mAb therapy. This article highlights the overall rationale for the use of anti-CTLA4 mAbs to treat advanced melanoma, results from early-phase clinical trials, and the importance of recognizing and managing toxicities that may be observed.

**New Immunomodulatory Approach**

**Mechanism of Action**

Adaptive immunity is a critical component of the immune system, and T lymphocytes play a crucial role in recognizing and killing tumor cells. T lymphocytes are activated on recognition of an antigen in the form of a peptide-major histocompatibility complex through T-cell receptors. On activation, effector T cells are capable of attacking target cells, including tumor cells. The T-cell receptor–peptide-major histocompatibility complex interaction is extremely specific, and the specificity may be harnessed by immunotherapy for the treatment of patients with advanced cancer. The specificity potentially provides a major advantage for immunotherapy because tumor-specific immune effector cells can target tumors selectively.

Understanding the underlying mechanisms regulating the activation of T cells is essential to the development of new immunotherapeutic strategies. Preclinical studies have shown that CD28 and CTLA4, molecules on T cells that provide costimulatory signals, are important regulators of T-cell activation (Lenschow, Walunas, & Bluestone, 1996; Schwartz, 1992). In addition to the T-cell receptor–peptide-major histocompatibility complex interaction, engagement of constitutively expressed CD28 on T cells to B7 ligands expressed on antigen-presenting cells is required for optimal T-cell activation (see Figure 1). Unlike its close homologue, CD28, CTLA4 is detectable readily on T cells only after activation; its major function is to inhibit T-cell activation, in effect turning the immune system “off” after the response is complete (Kearney et al., 1995; Krummel & Allison, 1995; Walunas et al., 1994). In addition, CTLA4 has a higher binding affinity to the B7 ligands than CD28; therefore, CTLA4 competitively inhibits the CD28-B7 interaction (Linsley et al., 1991). When T-cell receptor–peptide-major histocompatibility complex and CD28-B7 interactions occur, T cells are activated and begin to proliferate, and CTLA4 can reduce the risk for relapse and improve overall survival in patients with melanoma; however, the treatment has a relatively small absolute survival benefit of about 3% (confidence interval: 1%, 5%) at five years (Wheatley et al., 2007). In addition, IFN-α2b treatment is associated with significant toxicities, such as flu-like symptoms and neuropsychiatric, hematologic, and hepatic toxicities (Kirkwood et al., 2002); the adverse events generally limit the number of patients who complete treatment. The FDA approved high-dose IV bolus IL-2 (600,000–720,000 units/kg) in 1998 for the treatment of adult patients with metastatic melanoma (Atkins, 2006). High-dose bolus IL-2 therapy is associated with durable objective responses in about 16% of patients with metastatic melanoma (Atkins). However, IL-2 therapy is poorly tolerated because of treatment-related capillary leak syndrome, which leads to hypotension, renal insufficiency, and hypoxia. Therefore, IL-2 therapy has been administered mainly to patients with good performance status and is available in a limited number of centers with experienced personnel (Tarhini & Agarwala, 2006).

Neither IFN-α2b nor IL-2 is associated with antitumor activity in most patients with metastatic melanoma, and the treatments are highly toxic. A new approach to specifically modulate the immune response is through the use of anti-CTLA4 mAbs, which enhance T-cell activation and break peripheral T-cell tolerance.

**Immunomodulatory Drugs and Melanoma**

**Immunity and Melanoma**

Rationale for the use of immunotherapy to treat melanoma is based on several lines of evidence. Although rare, cases of spontaneous regression have been reported in patients with advanced melanoma, which suggests the involvement of adaptive immunity (Wang et al., 1998). Adaptive immunity also is supported by the identification of several melanoma-associated antigens (Coulie et al., 1994; Kawakami et al., 1994) and the isolation of tumor-infiltrating T lymphocytes that recognize these antigens (Topalian, Solomon, & Rosenberg, 1989). In addition, a follow-up study on the treatment of patients with metastatic melanoma with high-dose bolus IL-2 revealed that 43 of 270 patients had objective responses and achieved median duration of response of 8.9 months and median survival of 12 months (Atkins, Kunkel, Sznol, & Rosenberg, 2000). An update through 2004 showed that 12 of 43 (28%) responding patients had remained tumor-progression free (more than 13.3 years), and disease progression was not observed in patients who had responded for more than 30 months (Atkins, 2006). Results suggest that immune effector cells in patients with metastatic melanoma have recognized malignant cells and that the patients have established T cells that confer immunologic memory. Collectively, the findings support the idea that the immune system is capable of combating melanoma.

**Immunomodulatory Agents in Use**

To date, approved immunotherapies for melanoma include two exogenous cytokines: IFN-α2b and IL-2. The first adjuvant immunotherapeutic agent to be approved by the FDA for the treatment of patients at high risk for recurrent melanoma was IFN-α2b in 1993 (Kirkwood et al., 1996). Recent meta-analysis concluded that...
Antigen-presenting cell

Peptide-MHC complex

CD28

Activated T cell

Anti-CTLA4 mAb

Peptide-MHC complex

CD28

Downregulated T cell

Activated T cell

Note. The left illustration shows that recognition of peptide–major histocompatibility complexes (MHCs) through T-cell receptors (TCRs) and the engagement of CD28 on T cells to B7 on antigen-presenting cells leads to T-cell activation. The center illustration shows that, once activated, CTLA4 becomes detectable on the surface of activated T cells, competes for B7 ligands on antigen-presenting cells, and inhibits further T-cell activation. The right illustration shows that using anti-CTLA4 monoclonal antibodies (mAbs) to block CTLA4 from binding to B7 can lead to prolonged T-cell activation and enhanced T-cell proliferation and production of cytokines (e.g., interleukin-2, interferon-α). In addition, blockade of CTLA4 breaks peripheral T-cell tolerance.

Figure 1. Downregulation of T-Cell Activation Through Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA4) and Prolonged T-Cell Activation Through CTLA4 Blockade

molecules become detectable on the surface of the T cells. Subsequently, CTLA4 acts to limit the sensitivity of T cells to activation and proliferation. In essence, CTLA-4 prevents additional T-cell stimulation, halting the immune response. CTLA4 also is involved in the maintenance of T-cell peripheral tolerance, thus preventing autoreactive T lymphocytes from being activated (Chambers, Cado, Truong, & Allison, 1997; Tivol et al., 1995). In support of this notion, CTLA4-deficient mice exhibit spontaneous activation of T cells, uncontrolled T-cell proliferation, and massive lymphoproliferative disease (Tivol et al.; Waterhouse et al., 1995).

The balance of T-cell activation through T-cell receptors, CD28, and CTLA4 provides a regulatory mechanism to limit T-lymphocyte activation and proliferation. Preclinical studies have demonstrated that blockade of the CTLA4-B7 interaction or loss of CTLA4 leads to enhanced proliferation and production of cytokines by T cells; cytokines are believed to be critical to the immune response and play an important role in recruiting other immune cells to enhance the immune response (Krummel & Allison, 1995; Tivol et al., 1995; Walunas et al., 1994). In addition, systemic administration of anti-CTLA4 mAbs has resulted in elimination of established tumors in animal models of cancer (Leach, Krummel, & Allison, 1996). The findings, combined with the identification of melanoma-specific antigens and melanoma-specific T lymphocytes, provided a sound rationale for investigating anti-CTLA4 mAbs for the treatment of metastatic melanoma. The central hypothesis of anti-CTLA4 mAb-mediated therapy is that modulation of the regulatory mechanism of T-cell activation and peripheral T-cell tolerance can generate antitumor immunity.

Clinical Trials

Two fully human anti-CTLA4 mAbs, tremelimumab (formerly CP-675,206) and ipilimumab (formerly MDX-010), have been developed by Pfizer, Inc. and Medarex, Inc./Bristol-Myers Squibb Co., respectively (Camacho, 2008; Hodi et al., 2003; Langer et al., 2007; Ribas et al., 2005; Ribas et al., 2007). Tremelimumab and ipilimumab are immunoglobulin G molecules that recognize human CTLA4 with a high affinity (less than 1 nM) (Korman, Yellin, & Keler, 2005). Tremelimumab is an immunoglobulin G2 mAb with a serum half-life of 22.1 days (Ribas et al.), whereas ipilimumab is an immunoglobulin G1 mAb with a 12.5-day serum half-life (Langer et al.). The mAbs have been studied mainly in patients with metastatic melanoma (Phan et al., 2003; Ribas et al., 2005); however, the anti-CTLA4 mAbs also are being studied in phase I, II, and III trials in patients with other types of advanced cancer, such as lymphoma, leukemia, urothelial carcinoma, and breast, non-small cell lung, pancreatic, colon, prostate, ovarian, and renal cell cancers (Margolin, 2008). To date, neither agent has received FDA approval for the treatment of cancer.

Antitumor activity of tremelimumab and ipilimumab has been evaluated in clinical trials (see Tables 1 and 2). In most trials to date, tremelimumab has been administered IV as a single agent, whereas most studies of ipilimumab have been in combination with other agents (e.g., peptide vaccines, IL-2, or dacarbazine) (Attia et al., 2005; Fischkoff et al., 2005; Maker et al., 2005). In addition, ranges of doses have been tested for both mAbs, and optimal dosing regimens are still under investigation. Collectively, objective responses are observed in about 10% of patients with metastatic melanoma treated with tremelimumab or ipilimumab (Attia et al.; Fischkoff et al.; Hamid et al., 2007; Kirkwood, Lorigan, et al., 2008; Ribas et al., 2008). In addition, most objective responses are durable, ranging from 7.5 months to five years or more (Ribas et al., 2008; Weber et al., 2007). Ongoing subanalyses of data from patients with melanoma treated with tremelimumab aim to identify patients who are most likely to receive benefit from treatment.

Safety

As expected from a therapy designed to manipulate the regulatory mechanisms of T-cell activation and peripheral T-cell tolerance, the most common adverse events associated with anti-CTLA4 mAb therapy are assumed to be immune-related adverse events (see Table 3). Organs commonly affected by anti-CTLA4 mAbs...
are the gastrointestinal tract and skin, and common dose-limiting toxicities include diarrhea and colitis, dermatitis and rash, and pruritus (Camacho, 2008; Gomez-Navarro et al., 2006). Although developed by most patients, the treatment-related adverse events generally are mild to moderate (grade 1 and 2) and self-limiting (Antonia et al., 2007; Camacho; Wallis et al., 2008). Rarer nondose-limiting toxicities include patchy losses of skin pigmentation (commonly known as vitiligo), thyroid-function abnormalities, uveitis, gastritis, and elevated serum amylase and lipase concentrations (Camacho).

Of note in immunotherapy, a relationship may exist between antitumor activity and manifestations of autoimmunity. For example, the appearance of clinical autoimmune manifestations or serum autoantibodies was associated with significantly better overall survival (p < 0.001) in patients with advanced melanoma treated with high-dose IFN-α2b (Gogas et al., 2006). In addition, an association may exist between antitumor activity and autoimmune manifestations in patients with advanced melanoma treated with anti-CTLA4 mAbs (Camacho, 2008; Pavlov, Bulanhagui, Wallis, & Gomez-Navarro, 2007; Tarhini et al., 2008). Although patients with treatment-induced autoimmune reactions do not always develop antitumor immune responses, most patients with objective antitumor immune responses have an immune-related adverse event. As patients with clinical benefit remain on study longer and have increased drug exposure versus patients without clinical benefit, an analysis of patients treated with tremelimumab was performed to assess a possible relationship between development of immune-related adverse events and survival and survival.

### Table 1. Single-Agent Studies of Tremelimumab in Patients With Metastatic Melanoma

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PHASE</th>
<th>DOSE (MG/KG)</th>
<th>N</th>
<th>OBJECTIVE RESPONSE (CR + PR) n</th>
<th>GRADE 3 OR 4 ADVERSE EVENTS n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3671001 (Gomez-Navarro et al., 2006; Ribas et al., 2005)</td>
<td>I</td>
<td>0.01–15</td>
<td>34</td>
<td>4 (11%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>A3671002 (Antonia et al., 2007; Camacho et al., 2009; Gomez-Navarro et al., 2006; Ribas et al., 2007)</td>
<td>I</td>
<td>3, 6, or 10</td>
<td>29</td>
<td>2 (7%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>10 Q1M</td>
<td>44</td>
<td>4 (9%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>15 Q3M</td>
<td>46</td>
<td>4 (9%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>A3671008 (Kirkwood, Lorigan, et al., 2008)</td>
<td>II</td>
<td>15 Q3M</td>
<td>251</td>
<td>16 (6%)</td>
<td>51 (20%)</td>
</tr>
<tr>
<td>A3671009 (Ribas et al., 2008)</td>
<td>III</td>
<td>15 Q3M</td>
<td>328</td>
<td>30 (9%)</td>
<td>105 (32%)</td>
</tr>
</tbody>
</table>

a Percentage based on response-evaluable patients.
b Includes redosed patients.
c Percentage based on randomized patients.
CR—complete response; PR—partial response; Q1M—once every month; Q3M—once every three months

### Table 2. Clinical Trials With Ipilimumab in Patients With Metastatic Melanoma

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PHASE</th>
<th>REGIMEN</th>
<th>N</th>
<th>OBJECTIVE RESPONSE (CR + PR) n</th>
<th>GRADE 3 OR 4 ADVERSE EVENTS n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (Hamid et al., 2007; Tchekmedyian et al., 2002)</td>
<td>I</td>
<td>3 mg/kg</td>
<td>17</td>
<td>2 (12%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Study 2 (Attia et al., 2005; Hamid et al., 2007)</td>
<td>I and II</td>
<td>3 mg/kg plus gp100 Q3W 3 mg/kg plus gp100, then 1 mg/kg plus gp100 Q3W</td>
<td>56</td>
<td>7 (13%)</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Study 3 (Fischkoff et al., 2005; Hamid et al., 2007)</td>
<td>II</td>
<td>3 mg/kg Q1M 3 mg/kg Q1M plus dacarbazine</td>
<td>72</td>
<td>2 (3%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Study 4 (Hamid et al., 2007; Maker et al., 2005)</td>
<td>I and II</td>
<td>0.1–3 mg/kg Q3W plus interleukin-2</td>
<td>36</td>
<td>8 (22%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Study 5 (Weber et al., 2008)</td>
<td>II</td>
<td>10 mg/kg Q3W times four and placebo plus maintenance 10 mg/kg Q3W times four and budesonide plus maintenance</td>
<td>115</td>
<td>9 (8%)</td>
<td>22 (19%)</td>
</tr>
<tr>
<td>Study 6 (Hamid et al., 2007; Urba et al., 2008; Weber et al., 2007)</td>
<td>I and II</td>
<td>2.8–5 mg/kg on days 1, 57, and 85 7.5–20 mg/kg 10 mg/kg on days 1, 22, 43, and 64</td>
<td>88</td>
<td>1 (1%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

a These trials only reported immune-related adverse events.
CR—complete response; NR—not reported; PR—partial response; Q1M—once every month; Q3W—once every three weeks
avoid bias introduced by time on study. The analysis indicated a nonsignificant trend toward improved survival in patients with immune-related adverse events by day 45 versus those without immune-related adverse events by day 45 (12.2 months versus 7.7 months; \( p = 0.14 \)) (Pavlov et al.). Also of note, some patients with objective responses do not have immune-related adverse events; therefore, treatment should not be discontinued in the absence of an immune-related adverse event. Additional studies of larger patient databases are required to validate the observations.

**Nursing Management**

As scientific knowledge advances, immunomodulatory agents such as anti-CTLA4 mAbs may be incorporated into many cancer therapeutic strategies. Nursing management related to the care of patients receiving the agents involves patient education and recognition and evaluation of immune-related adverse events that can be attributed to the agents and interventions to manage them.

**Patient Education**

Patient education priorities in oncology have highlighted the role of nurses in helping patients understand the differences between newer, novel agents and traditional chemotherapy (Oncology Nursing Society, 2006). Anti-CTLA4 mAbs represent a unique class of agents, and the complexities associated with this type of immunomodulation must be explained at an appropriate level to individual patients. The following specific areas should be included in the educational plan:

- Difference between “immune-stimulating” strategy versus over-the-counter immune supplements frequently sought by patients with cancer
- Potential conditions that would exclude the use of an immune-stimulating therapy, such as a history of autoimmune or inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease)
- Potential adverse events and management strategies
- Who to contact and how when treatment-related adverse events emerge
- Potential delay in response to treatment before the onset of measurable antitumor activity; a response to treatment may not be seen for several months and patients may have radiographic evidence of progressive disease before seeing a response to treatment (Lens, Ferrucci, & Testori, 2008).

**Recognition and Management of Immune-Related Adverse Events**

The most commonly observed immune-related adverse events (all grades) with treatment with anti-CTLA4 mAbs include diarrhea, rash, fatigue, pruritus, and nausea (see Tables 3 and 4). Of note, time to occurrence can vary widely among patients, and median time to onset of diarrhea typically is three to four weeks (Antonia et al., 2007). Therefore, nurses should ensure that monitoring of patients is ongoing and that patients are provided with 24-hour contact information in case existing adverse events worsen or new adverse events develop unexpectedly.

To date, no evidence-based studies exist that could help guide the management of each toxicity associated with anti-CTLA4 mAb therapy. Supportive management for fatigue, rash, pruritus, and nausea include standard measures. Patients should be reminded to keep well hydrated and apply fragrance-free and alcohol-free lotions to skin to avoid increased dryness and irritation (Esper, Gale, & Muehlbauer, 2007). Antipruritic medications may need to be prescribed for those patients experiencing excessive itching.

Diarrhea is the most frequently experienced side effect in patients receiving anti-CTLA4 mAb therapy and must be monitored carefully. In addition, diarrhea and its complications (e.g., dehydration) are the most common adverse events requiring hospitalization. Initially, antidiarrheal preparations should be used liberally and started with the first episode of diarrhea. Dosages are titrated to individual patients’ needs. Over-the-counter loperamide (Imodium®, McNeil-PPC, Inc.) typically is used for initial therapy, but diarrhea management may require diphenoxylate (Lomotil®, Pfizer, Inc.). Healthcare providers also should provide patients with instructions in dietary strategies to combat diarrhea, such as the implementation of a BRAT (bananas, rice, applesauce, and

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>ANY GRADE</th>
<th>GRADE 3 OR HIGHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea*</td>
<td>315</td>
<td>40.1</td>
</tr>
<tr>
<td>Rash*</td>
<td>184</td>
<td>23.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>177</td>
<td>22.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>172</td>
<td>21.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>163</td>
<td>20.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>102</td>
<td>13</td>
</tr>
<tr>
<td>Anorexia</td>
<td>77</td>
<td>9.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>53</td>
<td>6.7</td>
</tr>
<tr>
<td>Headache</td>
<td>52</td>
<td>6.6</td>
</tr>
</tbody>
</table>

\( N = 786 \)

* Diarrhea or enterocolitis occurs with a high relative frequency; symptoms may include watery to bloody severe diarrhea, severe abdominal pain, and severe nausea and vomiting.

* Dermatitis occurs relatively frequently; symptoms may include generalized maculopapular rash with or without pruritus.

**Note.** Other rare adverse events (e.g., uveitis, hypophysitis) have been reported in trials of anti-CTLA4 monoclonal antibodies. Uveitis is uncommon; symptoms may include decreased visual acuity, painful tearing, and photophobia. Hypophysitis also is uncommon; symptoms may include severe fatigue, memory loss, personality changes, headaches, and loss of libido. **Note.** Data include patients with melanoma (90%), refractory colorectal cancer (6%), advanced non-small cell lung cancer (3%), and other advanced cancers (1%). **Note.** From “Safety of Tremelimumab (CP-675,206) in Patients (pts) With Advanced Cancer,” by N. Wallis, C. Bulanhagu, P.C. Dorazio, D.I. Healey, M.A. Marshall, J.Q. Liang, et al., 2008, May. Poster session presented at the 44th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL. Used with permission.
toast) diet. However, patients may progress rapidly to enterocolitis, which requires more aggressive and intensive management. Extent of severity may ultimately require hospitalization for patients to maintain their hydration status and treat diarrhea. The examination of diarrhea that is beyond grade 2 or prolonged should include a stool evaluation (including assessment for *Clostridium difficile*) and possible endoscopy to check risk for bowel perforation. Surgical management may be required in rare cases. Steroids also have been recommended for severe or prolonged diarrhea and colitis, but the efficacy of steroids has not been established and their effects on response duration are unclear (Downey et al., 2007; Weber, 2007). For example, in a randomized, placebo-controlled, phase II trial of ipilimumab plus prophylactic budesonide in 115 patients with metastatic melanoma, rates of grade 2 diarrhea were not reduced with budesonide (Weber et al., 2008). Infliximab (5 mg/kg) has been used in patients with refractory diarrhea receiving ipilimumab (Beck et al., 2006). However, infliximab is immunosuppressive and generally reserved for patients at risk for bowel perforation (primarily those who have steroid refractory enterocolitis). Prompt recognition and management of immune-related adverse events is essential.

Endocrine adverse events also have been observed in patients treated with anti-CTLA4 mAbs, but the incidence generally is less than 5% (Wallis et al., 2008). The adverse events include hypophysitis, thyroiditis, and panhypopituitarism primarily affect the thymus, pituitary, or adrenal glands. Although most endocrine adverse events resolve or respond to appropriate therapy, some patients may require hormone replacement. Regular monitoring of thyroid-stimulating hormone levels should be performed, and endocrine workups may be considered for patients with excessive fatigue.

A small subset of patients (n = 7; ~0.5%) treated with tremelimumab have been diagnosed with immune thrombocytopenia. The cases usually are severe and can develop rapidly. Unlike thrombocytopenia associated with chemotherapy, treatment of immune-mediated thrombocytopenia should include steroids as well as platelet transfusions. Nurses should instruct patients to contact the clinic immediately if any of the following symptoms are observed: unexpected bruising, small purple or red spots under the skin (petechia), bleeding from the nose or gums, heavier menstrual periods than usual, black or bloody bowel movements or reddish or pinkish urine, hematemesis, bad headaches, dizziness, pain in the joints or muscles, and increased weakness.

### Conclusions

Anti-CTLA4 mAbs are novel immunotherapeutic agents being evaluated in clinical trials for advanced cancer that are designed to manipulate the activation and peripheral tolerance of T cells. Tremelimumab and ipilimumab are two fully human mAbs specific for human CTLA4 that can break peripheral T-cell tolerance and prolong T-cell activation by blocking the CTLA4-B7 interaction. Early phase clinical trials have shown antitumor activity in some patients with advanced cancer. In addition, CTLA4 blockade is tolerated in most patients and generally manageable, and treatment-related toxicities often are consistent with the expected mechanism of action. When knowledgeable in the mechanism of action of such agents, oncology nurses can provide prompt management of events, such as rash and diarrhea, thus enabling patients to remain on therapy.

To date, a phase III study of first-line, single-agent tremelimumab versus chemotherapy in patients with metastatic melanoma was discontinued for futility in overall survival. However, studies continue in this disease population with tremelimumab and ipilimumab in combination with chemotherapy or immunotherapy. The agents also are being evaluated in other advanced cancers, including colorectal, prostate, breast, and non-small cell lung cancers (Margolin, 2008). The continued clinical investigation of immune-modulating agents such as anti-CTLA4 mAbs represents a new era in oncology. Scientific advances likely will continue to use the power of the immune system in fighting cancer, and oncology nurses will play a key role in monitoring and educating patients receiving these agents now and in the years to come.

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**Table 4. Number of Patients With Melanoma With Treatment-Related Grade 3 or 4 Adverse Events Associated With Ipilimumab**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>GASTROINTESTINAL (COLITIS OR DIARRHEA)</th>
<th>SKIN (DERMATITIS, PRURITUS, OR RASH)</th>
<th>EYE (UVEITIS)</th>
<th>ENTIRE BODY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Attia et al., 2005b</td>
<td>56</td>
<td>8</td>
<td>14</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Fischkoff et al., 2005</td>
<td>72</td>
<td>7</td>
<td>14</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Maker et al., 2005a</td>
<td>36</td>
<td>4</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weber et al., 2008b</td>
<td>115</td>
<td>27</td>
<td>23</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

* NR—not reported

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* Patients may have had multiple adverse events; Fischkoff et al. (2005) did not report any adverse events.
* Trials only reported immune-related adverse events.

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References


Gomez-Navarro, J., Sharma, A., Bozon, V., Bulanaghi, C., Pavlov, D., Eck, S., et al. (2006, June). Dose and schedule selection for the anti-CTLA4 monoclonal antibody (mAb) CP-675,206 in patients (pts) with metastatic melanoma. Poster session presented at the 42nd Annual Meeting of the American Society of Clinical Oncology, Atlanta, GA.


