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# Current Landscape of Immuno-Oncology in Advanced Melanoma

## Epidemiology of Advanced Melanoma

Melanoma is the most lethal type of skin cancer.<sup>1</sup> In 2017, approximately 87,110 new cases of melanoma will be diagnosed and approximately 9730 deaths will occur due to the disease.<sup>2</sup> Compared with individuals younger than 50 years, individuals 50 years and older consistently experience higher rates of melanoma. Incidence in this age group increased up to 3% each year from 2003 to 2014.<sup>2</sup> Melanoma is more likely to spread than other skin cancers and, if caught after metastasis, is difficult to treat.<sup>1,2</sup> The 5-year survival rate for patients with metastatic melanoma is 18%.<sup>2</sup>

## Economic Burden of Advanced Melanoma

The financial burden of treating metastatic melanoma weighs heavily on patients and the healthcare system, and with each progressive stage of melanoma, treatment costs increase.<sup>1,3</sup> Recently, a retrospective, longitudinal, open-cohort study in patients with metastatic melanoma (N = 834) measured the total all-cause per-patient-per-month (PPPM) direct healthcare costs and utilization for traditional and newer therapies.<sup>1</sup> Study treatments included ipilimumab (n = 265), vemurafenib (n = 234), interleukin-2 (IL-2; n = 104), dacarbazine monotherapy (n = 24), dacarbazine combination therapy (n = 22), paclitaxel monotherapy (n = 44), paclitaxel combination therapy (n = 130), and temozolomide (n = 11).<sup>1</sup> Average PPPM costs for the ipilimumab cohort were the highest at \$35,472, followed by IL-2 (\$34,850) and vemurafenib (\$17,793). Temozolomide was the least costly (\$10,879).<sup>1</sup>

Newer therapies in this study were more expensive. Ipilimumab and vemurafenib, approved in 2011, were the primary therapies for 60% of patients, and although the adjusted PPPM total costs were \$18,337 higher with ipilimumab, this was mainly due to the expense of its administration in the outpatient setting. There were no significant differences observed in resource utilization (hospitalizations and emergency department visits) between ipilimumab and vemurafenib.<sup>1</sup>

Considerable toxicity associated with current treatments for metastatic melanoma may lead to higher healthcare resource utilization and related expenditures. A study reviewing the cost of managing grade 3 or 4 treatment-related adverse events (AEs) reported with FDA-approved or National Comprehensive Cancer Network–recommended monotherapies in patients with metastatic melanoma (N = 2998) found that serious AEs led to costly inpatient and outpatient procedures. The agents reviewed were dabrafenib, dacarbazine, IL-2, ipilimumab, temozolomide, trametinib, vemurafenib, and talimogene laherparepvec (T-VEC).<sup>4</sup> Investigators performed a literature search to determine the most common grade 3 or 4 AEs with each drug, then interviewed oncologists specializing in melanoma to assess their treatment approaches for these AEs.<sup>4</sup>

In the outpatient setting, the most expensive treatment-related AEs were neutropenia, headache, peripheral neuropathy, cutaneous squamous cell carcinoma, and dyspnea. Treatment for neutropenia was the most »

expensive, at \$2088 per incident, and dyspnea was the least expensive, at \$277.<sup>4</sup> In the inpatient setting, the most expensive treatment-related AEs were acute myocardial infarction (MI), sepsis, acidosis, acute kidney failure, pneumonitis, neuropathy, thrombocytopenia, and oliguria/anuria. Hospitalization for acute MI was the most expensive, at an average of \$47,069 per event. The lowest average inpatient costs were seen with nausea, at \$14,043 per event.<sup>4</sup>

Although this study was conducted before the FDA approval of pembrolizumab and nivolumab, the investigators determined that the list of toxicities would not change if these agents were included and that the estimated costs would remain the same.<sup>4</sup> In addition, costs for outpatient treatment were based on Medicare reimbursements, which are typically lower than payments from commercial health insurance plans, potentially underestimating the financial burden of managing these AEs.<sup>4</sup>

In another retrospective cohort study in patients with metastatic melanoma (N = 2621), incremental costs, defined as the differences in 30-day costs, linked to specific treatment-related AEs were also considerably high.<sup>5</sup> This study evaluated patients receiving vemurafenib (n = 119), ipilimumab (n = 152), dacarbazine (n = 254), temozolomide (n = 847), high-dose IL-2 (n = 227), paclitaxel (n = 153), and interferon- $\alpha$  (n = 869).<sup>5</sup> AEs were identified using each therapy's package insert and consultation with a clinical expert and were grouped into 8 categories: cardiovascular, central nervous system and psychiatric, gastrointestinal (GI), hematologic and lymphatic, metabolic and nutritional, pain, skin and subcutaneous tissue, and other.<sup>5</sup> Healthcare costs comprised the total amount paid to all providers for inpatient and outpatient services minus the cost of study drugs and other cancer therapies.<sup>5</sup> Compared with patients who did not experience these AEs, adjusted costs were highest for "metabolic and nutritional disorders" (\$7800 vs \$16,936, respectively) and "hematologic and lymphatic disorders" (\$7715 vs \$16,165, respectively).<sup>5</sup> To decrease the financial burden of new and existing treatments for metastatic melanoma, the prevention of these AEs may be important.<sup>4,5</sup>

### Quality of Life

Regardless of stage, melanoma has significant impact on quality of life (QoL), and efficacy of therapy is an important factor in establishing healthcare priorities.<sup>6</sup> Patients typically experience the lowest QoL upon receiving a diagnosis of melanoma, reporting higher levels of physical and emotional stress, lower levels of energy, and more pain, which affect social interactions. About one-third of patients with melanoma report significant levels of distress.<sup>7</sup> Owing to the poor prognosis of metastatic melanoma, there is a lack of cost-benefit ratio information when comparing available

treatment regimens.<sup>8</sup> While new agents improve survival, they are also associated with new toxicities.<sup>7</sup> Increasingly, studies are including health-related QoL assessments as part of their design.<sup>7</sup>

A pilot study was conducted in which patients with melanoma (N = 163) were asked to estimate the impact of the disease at stages other than their own.<sup>6</sup> Investigators assessed the face validity of melanoma utilities (ie, trade-off of money, time, or risk of death to not have the disease), which decreased significantly with each subsequent stage.<sup>6</sup> Patients with stage I melanoma reported higher QoL and overestimated the impact of a later-stage diagnosis, while patients with stage II and IV disease reported lower QoL and underestimated the impact of a stage I diagnosis.

Early diagnosis and treatment of melanoma, and remission status, result in better QoL. After 2 years of follow-up, patients who have undergone treatment for stage 0 to II melanoma have a health-related QoL similar to the general population.<sup>3,9</sup> Patients with advanced melanoma whose disease is in remission report similar health-related QoL.<sup>9</sup>

### Mutational Burden

The majority of patients with metastatic melanoma develop mutations in their disease that complicate treatment. Approximately 50% have *BRAF*-mutated disease. Other common mutations include the *NRAS* subtype (28%), *NFI* subtype (14%), and *KIT* subtype (3%).<sup>10-12</sup> The presence of a *BRAF*V600 mutation is key in guiding treatment decisions. The V600E mutation accounts for 74% to 86% of all *BRAF* mutations, while V600K mutations can occur in 10% to 30% of cases. The latter are mostly found in patients older than 65 years or in those with confirmation of prolonged UV exposure. Adequate data obtained with the *BRAF* inhibitors vemurafenib and dabrafenib warranted inclusion of the V600K mutation subpopulation in the regulatory approvals of both of these agents.<sup>13</sup> FDA-approved targeted therapies for mutated melanomas currently exist only for those with *BRAF* mutations.<sup>13</sup>

*NRAS*-mutated melanomas are more commonly diagnosed in older patients and on sun-damaged skin and are typically located on the extremities. These mutations rarely co-occur with *BRAF* mutations.<sup>14</sup> Several mechanisms of *NRAS*-targeted treatment have been tested in preclinical studies with little effect. Targeting the mitogen-activated ERK kinase (MEK) 1/2 pathway is the most developed approach, with second- and third-generation MEK inhibitors in phase 2 and 3 clinical trials.<sup>14</sup>

*NFI* is another important mutation in melanoma and is found more often in older patients and patients with chronic sun exposure. These mutations result in increased RAS/mitogen-activated protein kinase (MAPK) pathway signaling, and preclinical evidence supports treatment with agents that target this pathway (eg, MEK inhibitors).<sup>15</sup>

*KIT* mutations occur in only 3% of melanomas, most commonly in acral and mucosal melanomas.<sup>12</sup> *KIT* is a receptor tyrosine kinase that plays a role in melanocyte growth and can be mutated or amplified.<sup>12</sup> It is difficult to assess because common markers in mutated *KIT* are easily missed when testing for hotspot mutations. Thorough testing involves complete sequencing of relevant exons, which creates challenges in identifying which patients should be screened.<sup>12</sup> Case reports and phase 2 studies in patients with *KIT*-mutated melanoma have described responses to tyrosine kinase inhibitors, such as imatinib, sunitinib, and nilotinib.<sup>12</sup>

### Targeted Therapies

Although dacarbazine was approved for metastatic melanoma in 1975, innovations in therapy over the next 30 years were limited to chemotherapies and IL-2.<sup>1</sup> Recently, however, several new therapies have been approved, capitalizing on decades of research into the genomics of cancer and new understandings of the immune response.<sup>13</sup>

#### *BRAF* Inhibition

The treatment paradigm for melanoma with *BRAF* mutations has evolved.<sup>13</sup> Single-agent, small-molecule *BRAF* inhibition has been enhanced by combination therapy with a MEK inhibitor.<sup>13</sup>

Vemurafenib, a first-in-class selective inhibitor of V600-mutant *BRAF*, was studied in a multinational randomized phase 3 trial in treatment-naïve patients with unresectable stage III or IV melanoma with *BRAF*V600E mutations. Patients received either vemurafenib (n = 337) or dacarbazine (n = 338).<sup>16</sup> Vemurafenib demonstrated an overall response rate of 48% compared with 5% for dacarbazine and progression-free survival (PFS) of 5.3 versus 1.6 months, respectively (hazard ratio [HR], 0.26; 95% CI, 0.20-0.33;  $P < .001$ ). The most common AEs with vemurafenib were cutaneous events, joint pain, and fatigue, and for dacarbazine, fatigue, nausea, vomiting, and neutropenia. AEs leading to dose interruption or adjustment occurred in 38% of patients receiving vemurafenib and 16% of patients receiving dacarbazine.<sup>13,16</sup>

Dabrafenib, another selective *BRAF* inhibitor, was studied in an open-label, multicenter, phase 3 trial in patients with unresectable stage III or IV melanoma who had not received antitumor therapy other than IL-2 (N = 250). Patients were randomized 3:1 to receive dabrafenib (n = 187) or dacarbazine (n = 63). Results were reviewed by a masked independent review committee.<sup>17</sup> Dabrafenib showed significant improvement over dacarbazine with an objective response rate (ORR) of 50% (95% CI, 42.4%-57.1%) versus 6% (95% CI, 1.8%-15.5%), respectively, and a median PFS of 5.1 versus 2.7 months, respectively (HR, 0.30; 95% CI, 0.18-0.51;  $P < .0001$ ). AEs with dabrafenib occurring in at least 5% of patients were cutaneous AEs, fever, fatigue, headache, and

joint pain. AEs with dacarbazine in at least 5% of patients were nausea, vomiting, fatigue, and neutropenia. Grade 3 and 4 events were not common in either group.<sup>17</sup>

As *BRAF* signaling is dependent on activation of MEK, the success of *BRAF* inhibitors spurred development of MEK inhibitors. The first FDA-approved MEK inhibitor was trametinib,<sup>13</sup> which was evaluated in an international, prospective, open-label phase 3 trial in patients with unresectable stage III or IV melanoma with V600E or V500K *BRAF* mutations (N = 322). Patients were randomized 2:1 to receive either trametinib (n = 214) or chemotherapy (dacarbazine or paclitaxel; n = 108).<sup>18</sup> Trametinib demonstrated an ORR of 22% (95% CI, 17%-28%) versus 8% (95% CI, 4%-15%) with chemotherapy ( $P < .01$ ). The median PFS with trametinib versus chemotherapy was 4.8 versus 1.5 months, respectively (HR, 0.45; 95% CI, 0.33-0.63;  $P < .001$ ).<sup>13</sup> The most common AEs with trametinib were rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. In patients receiving chemotherapy, common AEs included fatigue, nausea, constipation, vomiting, and alopecia. AEs led to dose reductions in 27% of patients receiving trametinib and 10% of patients receiving chemotherapy.<sup>18</sup>

#### Combination *BRAF* Plus MEK Inhibition

Concurrent with the development of vemurafenib and trametinib, investigators researching the MAPK pathway observed downstream activation in *BRAF* signaling. Consequently, additional studies in combined *BRAF* inhibition plus MEK inhibition were conducted.<sup>13,19</sup>

In an international double-blind phase 3 trial, *BRAF* inhibition plus MEK inhibition was evaluated in patients with unresectable stage IIIC or IV melanoma with *BRAF* Val600Glu or Val600Lys mutations (N = 423) who had no previous systemic treatment for metastatic disease. Patients were randomized 1:1 to receive either dabrafenib plus trametinib (n = 211) or dabrafenib plus placebo (n = 212).<sup>20</sup> The ORR with combination therapy was 69% (95% CI, 62%-75%) versus 53% (95% CI, 46%-69%) for dabrafenib alone ( $P = .0014$ ). The median PFS with dabrafenib plus trametinib was 11.0 months (95% CI, 8.0-13.9) versus 8.8 months (95% CI, 5.9-9.3) with dabrafenib alone (HR 0.67; 95% CI, 0.53-0.84;  $P = .0004$ ), and median overall survival (OS) was 25.1 months (95% CI, 19.2-not reported) versus 18.7 months (95% CI, 15.2-23.7), respectively (HR, 0.71; 95% CI, 0.55-0.92;  $P = .0107$ ). The most common treatment-related AEs observed with combination therapy were fever, chills, fatigue, rash, and nausea; in patients receiving dabrafenib alone, hyperkeratosis, fatigue, alopecia, fever, hand-foot syndrome, and joint pain. Fewer patients receiving dabrafenib plus trametinib experienced cutaneous AEs compared with dabrafenib alone, while more patients receiving dabrafenib experienced fever compared with patients receiving combination therapy. »

Discontinuation due to AEs occurred in 11% of patients receiving combination therapy versus 14% of patients receiving dabrafenib alone.<sup>20</sup>

BRAF plus MEK inhibition was evaluated against BRAF inhibition alone in an international open-label phase 3 trial. Patients with unresectable stage IIIC or IV melanoma with *BRAF* V600E or V600K mutations (N = 704) were randomized 1:1 to receive dabrafenib plus trametinib (n = 352) or vemurafenib monotherapy (n = 352).<sup>21</sup> The ORR with dabrafenib plus trametinib was 64% (95% CI, 59%-69%) versus 51% (95% CI, 46%-57%) with vemurafenib ( $P < .001$ ). The median PFS was 11.4 versus 7.3 months, respectively (HR, 0.56; 95% CI, 0.46-0.69;  $P < .001$ ), and the OS at 12 months was 72% (95% CI, 67%-77%) versus 65% (95% CI, 59%-70%), respectively. In patients receiving dabrafenib plus trametinib, the most common AEs were fever, nausea, vomiting, diarrhea, chills, headache, and fatigue. In patients receiving vemurafenib, the most common AEs were joint pain, rash, alopecia, diarrhea, nausea, and fatigue. Fever occurred more frequently in patients receiving combination therapy compared with vemurafenib (53% vs 21%, respectively) and was the most common reason for dose interruption and reduction (33% and 14%, respectively). In patients receiving vemurafenib, rash was the most common reason for dose interruption or reduction (14% and 11%, respectively).<sup>21</sup>

Cobimetinib, another FDA-approved MEK inhibitor, was studied in an international phase 3 trial in treatment-naïve patients with unresectable, locally advanced, stage IIIC or IV melanoma with *BRAF* V600 mutations (N = 495). Patients were randomized 1:1 to receive vemurafenib plus cobimetinib (n = 247) or vemurafenib plus placebo (n = 248).<sup>22</sup> The ORR was significantly higher with vemurafenib plus cobimetinib at 70% (95% CI, 63.5%-75.3%) versus 50% (95% CI, 43.6%-56.4%) with vemurafenib alone ( $P < .0001$ ). The median OS for patients receiving combination therapy was 22.3 months (95% CI, 20.3-not estimable) versus 17.4 months (95% CI, 15.0-19.8) with vemurafenib alone (HR, 0.70; 95% CI, 0.55-0.90;  $P = .005$ ), and the 1-year OS was 74.5% (95% CI, 68.9%-80.2%) versus 63.8% (95% CI, 57.6%-70.0%), respectively.<sup>22</sup> Serious AEs occurred in 36% of patients receiving vemurafenib plus cobimetinib and 28% of patients receiving vemurafenib alone. Pyrexia and dehydration were the most common serious AEs reported with combination therapy. MEK-inhibitor-specific AEs reported in the combination therapy group and vemurafenib-only group included serious retinopathy (any grade, 27% vs 4%, respectively), decreased left ventricular ejection fraction (grade  $\geq 2$ , 11% vs 5%), and increased creatine phosphokinase (grade  $\geq 3$ , 12% vs  $< 1\%$ ). Discontinuations due to AEs occurred in 14% of patients receiving vemurafenib plus cobimetinib and 11% of patients receiving vemurafenib alone.<sup>22</sup>

Results from these pivotal clinical trials have established combination therapy with a BRAF inhibitor plus a MEK inhibitor as the standard of care in targeted treatment for *BRAF*-mutant melanoma.<sup>13</sup>

### Immunotherapy

Recent breakthroughs in targeted therapies (eg, BRAF inhibitors and MEK inhibitors) have improved outcomes over chemotherapy in patients with advanced melanoma; however, treatment challenges remain for patients who relapse or do not respond to these agents. Immunotherapies are effective in advanced melanoma regardless of mutation status, aiming to interrupt processes in the tumor microenvironment that allow tumors to grow uncontrolled. Standard treatments that generally target the immune system (cytokines, interferon- $\alpha$  and IL-2) are accompanied by significant toxicities.<sup>13,23-26</sup> With the development of monoclonal antibodies (mAbs), which bind to only 1 substance,<sup>27</sup> immunotherapy has transitioned from broad-based treatment to specific antibody-mediated blockade of cytotoxic T-lymphocyte-antigen-4 (CTLA-4) and shows promise in combination with programmed cell death protein 1 (PD-1) inhibitors in mediating immune checkpoints.<sup>13</sup>

### CTLA-4 Inhibitors

CTLA-4, expressed on activated T cells, tends to stop the antitumor response. Ipilimumab is the first anti-CTLA-4 antibody approved for patients with melanoma.<sup>26</sup> The efficacy of ipilimumab was evaluated in 2 phase 3 trials using 2 dosages. In a multinational double-blind study of 403 patients with stage III or IV melanoma who had been on a previous therapy, patients were randomized 3:1:1 to either ipilimumab 3 mg/kg plus a cancer vaccine (glycoprotein 100 [gp100]; n = 403), ipilimumab 3 mg/kg alone (n = 137), or gp100 alone (n = 136).<sup>28</sup> The highest median OS of 10.1 months was observed in patients receiving ipilimumab alone (95% CI, 8.0-13.8) compared with 10.0 months for patients receiving ipilimumab plus gp100 (95% CI, 8.5-11.5) and 6.4 months with gp100 alone (95% CI, 5.5-8.7). The HR for death with ipilimumab alone versus gp100 alone was 0.66 ( $P < .003$ ). At 12 months, the OS was also highest with ipilimumab alone, at 45.6%, compared with 43.6% for ipilimumab plus gp100 and 25.3% for gp100 alone.<sup>28</sup>

Common AEs in this study were immune related and usually affected the skin and GI tract. Grade 3 or 4 AEs occurred in 10% to 15% of patients who received ipilimumab and in 3% of patients who received gp100 alone. The most common AE of any grade with ipilimumab was diarrhea. In patients surviving through the 2-year follow-up, residual effects included injection site reaction, vitiligo, and diarrhea or colitis; ongoing events included grade 1 or 2 rash, pruritus, diarrhea, anorexia, and fatigue, and grade 3 leukocytosis.

There were 14 deaths related to the study drug, half of which were associated with immune-related AEs (irAEs).<sup>28</sup>

Ipilimumab was also studied in combination with dacarbazine in patients with stage III or IV melanoma. In this multinational double-blind study, 502 patients were randomized 1:1 to receive ipilimumab plus dacarbazine (n = 250) or dacarbazine alone (n = 252).<sup>29</sup> The median OS with ipilimumab plus dacarbazine was 11.2 months (95% CI, 9.4-13.6) compared with 9.1 months (95% CI, 7.8-10.5) for patients receiving dacarbazine alone. Estimated 1-year survival rates for ipilimumab plus dacarbazine and dacarbazine alone were 47.3% and 36.3%, respectively; at 2 years, 28.5% and 17.9%; and at 3 years, 20.8% and 12.2%, respectively (HR, 0.72;  $P < .001$ ). The most common AEs were immune related. AEs occurring more frequently with ipilimumab plus dacarbazine than with dacarbazine alone included increased alanine aminotransferase (33.2% vs 5.2%, respectively), increased aspartate aminotransferase (29.1% vs 5.6%), diarrhea (36.4% vs 24.7), pruritus (29.6% vs 8.8%), and rash (24.7% vs 6.8%). There were no deaths related to ipilimumab plus dacarbazine treatment.<sup>29</sup>

Adjuvant treatment with ipilimumab was evaluated in a multinational double-blind phase 3 trial in high-risk patients with stage IIIA, IIIB, or IIIC melanoma with no in-transit metastasis (N = 951) and following complete regional lymph node dissection. Patients were randomized 1:1 to receive ipilimumab (n = 475) or placebo (n = 476).<sup>30</sup> Recurrence-free survival (RFS) with ipilimumab was significantly longer compared with placebo (HR, 0.75; 95% CI, 0.64-0.90). In patients receiving ipilimumab, the median RFS was 26.1 months (95% CI, 19.3-39.3) versus 17.1 months (95% CI, 13.4-21.6) with placebo; the 3-year RFS rate was 46.5% (95% CI, 41.5%-51.3%) versus 34.8% (95% CI, 30.1%-39.5%), respectively ( $P = .0013$ ). In the ipilimumab group, 54% of patients experienced grade 3 or 4 AEs compared with 25% in the placebo group. irAEs were reported more often in patients receiving ipilimumab versus placebo and most commonly (grade 3 or 4) were related to the GI, hepatic, or endocrine system. Discontinuation due to AEs occurred in 52% of patients receiving ipilimumab versus 4% for placebo.<sup>30</sup>

Healthcare providers should be informed about the diagnosis and management of ipilimumab-specific AEs, especially those that have been observed across clinical studies with the agent. Proper management requires a multidisciplinary approach. In a pooled analysis of patients receiving 10 mg/kg ipilimumab every 3 weeks for 4 cycles (N = 325), treatment-related AEs were seen in 84.6% of patients and irAEs were seen in 72.3% of patients.<sup>31</sup> After an average of 3.6 weeks, 47% to 68% of patients experienced maculopapular rash with intense itch. For grade 3 immune-related skin reactions, withholding a dose of ipilimumab and administering oral corticosteroids is

recommended; permanent discontinuation is recommended for life-threatening toxicity. Diarrhea was reported in 44% of patients and can be associated with symptoms of colitis (which can further lead to bowel obstruction and perforation). In patients with grade 3 or 4 diarrhea (18%), ipilimumab should be discontinued and intravenous steroids, electrolytes, and hydration should be administered. Immune-related hepatotoxicity was reported in 3% to 9% of patients. Ipilimumab should be discontinued in patients with grade 3 or 4 hepatotoxicity.<sup>31</sup> One percent to 6% of patients treated with ipilimumab experienced hypophysitis, which must be differentiated from the occurrence of new brain metastases. To monitor for hypophysitis, thyroid function tests and clinical chemistry profiles should be assessed in all patients before the start of treatment and before each dose.<sup>31</sup> Less than 1% of patients experienced episcleritis and uveitis, commonly co-occurring with diarrhea or colitis. In patients with grade 3 or 4 episcleritis or uveitis, ipilimumab should be discontinued. Immune-related pancreatitis occurred in less than 1.5% of patients. In patients whose pancreatic enzymes increase to grade 3 or 4 toxicity, ipilimumab should be discontinued. Less than 1% of patients experienced transient sensory or motor peripheral neuropathies. For mild neuropathies, a dose of ipilimumab can be withheld; for grade 3 or 4 neuropathy, treatment should be discontinued. Lymphadenopathy and sarcoid-like syndrome have been described in anecdotal reports.<sup>31</sup>

### PD-1 Inhibitors

PD-1 receptor activation is another immune checkpoint that can interfere with the antitumor response. Melanoma tumors suppress cytotoxic T-cell activity by expressing PD-1 ligand (PD-L1). Researchers have identified anti-PD-1 antibodies that block PD-L1 from activating PD-1 receptors, potentially reversing T-cell suppression and inducing durable responses in patients with advanced melanoma.<sup>26,32</sup>

Nivolumab, a fully human, immunoglobulin G4 (IgG4) anti-PD-1 mAb, was evaluated in an international, double-blind, phase 3 study in treatment-naïve patients with unresectable stage III or IV melanoma without a *BRAF* mutation (N = 418). Patients were randomized 1:1 to receive either nivolumab (n = 210) or dacarbazine (n = 208), plus matched placebo.<sup>32</sup> At 1 year, the OS with nivolumab was 72.9% (95% CI, 65.5%-78.9%) compared with 42.1% (95% CI, 33.0%-50.9%) with dacarbazine and at a significant benefit over the latter (HR, 0.42; 99.79% CI, 0.25-0.73;  $P < .001$ ). The median PFS was 5.1 months (95% CI, 3.5-10.8) versus 2.2 months (95% CI, 2.1-2.4), respectively. Nivolumab demonstrated an ORR of 40.0% (95% CI, 33.3%-47.0%) compared with 13.9% (95% CI, 9.5%-19.4%) with dacarbazine (OR, 4.06;  $P < .001$ ). The incidence rate of treatment-related AEs was similar between groups (74.3% and 75.6%, respectively), although grade 3 to 4 AEs »

were less frequent in patients receiving nivolumab (11.7% vs 17.6%, respectively). The most common treatment-related AEs with nivolumab were fatigue, pruritus, and nausea, and with dacarbazine, GI and hematologic events. This study showed a consistent benefit in OS versus dacarbazine chemotherapy.<sup>32</sup>

Nivolumab was evaluated against chemotherapy in another open-label phase 3 trial in patients with unresectable phase III or IV melanoma. Patients were randomized 2:1 to receive nivolumab (n = 405) or investigator's choice of chemotherapy (ICC) (dacarbazine or carboplatin plus paclitaxel; n = 268). For patients receiving nivolumab, the median OS was 15.7 months (95% CI, 12.9-19.9) compared with 14.4 months (95% CI, 11.7-18.2) for ICC (HR, 0.95; 95.54% CI, 0.73-1.24). In the nivolumab group, 1-year survival was 58.9% (95% CI, 52.8%-64.5%) versus 55.1% (95% CI, 46.1-63.3) with ICC, and 2-year survival was 38.7% (95% CI, 32.8%-44.5%) and 33.9% (95% CI, 25.8%-42.1%), respectively. Grade 3 or 4 AEs occurred in 14% of patients receiving nivolumab versus 34% of patients receiving ICC. The most common treatment-related AE was fatigue (32% and 39%, respectively), and those that were possibly immune related occurred in the skin, GI, and hepatic systems. Treatment-related AEs leading to discontinuation occurred in 5% of patients receiving nivolumab and 11% of those receiving ICC.<sup>33</sup>

Pembrolizumab is a humanized, IgG4-κ anti-PD-1 mAb that blocks PD-1 from interacting with PD-L1 and PD-L2.<sup>34</sup> The antitumor activity and safety of pembrolizumab were evaluated using data pooled from an international, open-label, multiple-cohort, phase 1 clinical trial in patients with advanced melanoma (N = 655). Patients in these cohorts were randomized and nonrandomized, ipilimumab-naïve and ipilimumab-experienced, and therapy naïve. In the primary pooled analysis, 581 patients meeting Response Criteria In Solid Tumors (RECIST) criteria were evaluated. Pembrolizumab demonstrated an ORR of 33% (95% CI, 30%-37%), with a complete response (CR) rate of 8% (95% CI, 6%-11%) and a disease control rate (DCR) of 51% (95% CI, 47%-55%). In a subgroup analysis of patients who were ipilimumab naïve (n = 277), the ORR was 39% (95% CI, 33%-45%; n = 107) compared with 29% (95% CI, 24%-34%; n = 87) in patients who previously received ipilimumab (n = 304). In patients who received no previous therapy (n = 133), the ORR was 45% (95% CI, 36%-54%; n = 60), the CR rate was 14% (95% CI, 8%-21%; n = 18), and the DCR was 61% (95% CI, 52%-69%; n = 81).

Investigators observed no dose- or regimen-related toxicities with pembrolizumab, which was shown to be generally well tolerated. Grade 3 or 4 treatment-related toxicities occurred in 14% of patients, the most common of which was fatigue, at 1.8%; all others occurred in less

than 1% of patients. The most common serious treatment-related AEs were colitis, pyrexia, and pneumonitis. Discontinuations due to treatment-related AEs occurred in 4% of patients, and no treatment-related deaths were reported.<sup>35</sup>

In a separate pooled analysis of the same multiple-cohort phase 1 trial in patients with advanced melanoma (N = 655), the antitumor activity of pembrolizumab relative to PD-L1 expression was evaluated. Again, patients in these cohorts were randomized and nonrandomized, ipilimumab-naïve and ipilimumab-experienced, and therapy naïve. Of these patients, 451 were evaluable for PD-L1 expression using the melanoma (MEL) scale of 0-5 (0 is negative and 2-5 are positive for PD-L1). Tumor response was also evaluated by RECIST criteria. Of the 405 patients evaluable for both PD-L1 and tumor response, the ORR was 33% (95% CI, 28%-37%). Patients with higher MEL scores had significantly better ORRs: 57% in those with MEL 4 versus 8% for those with MEL 0, showing that PD-L1 expression is positively correlated with improved tumor response. Higher PD-L1 MEL scores were also associated with increased PFS (HR, 0.76; 95% CI, 0.71-0.82;  $P < .001$ ) and OS (HR, 0.76; 95% CI, 0.69-0.83;  $P < .001$ ).<sup>36</sup>

#### **Combination PD-1/PD-L1 Inhibition Plus CTLA-4 Inhibition**

PD-1 inhibitors and CTLA-4 inhibitors target distinct mechanisms in T-cell activation. Nivolumab and pembrolizumab demonstrated significant clinical efficacy against PD-L1, and ipilimumab was shown to improve outcomes when targeting CTLA-4; therefore, researchers evaluated the potential impact of treatment with these agents in combination.<sup>24</sup>

In an international, open-label, phase 3 trial (N = 834), patients with unresectable stage III or IV melanoma with or without *BRAF* mutations who had not had more than 1 systemic therapy for advanced disease were randomized 1:1:1 to receive pembrolizumab every 2 weeks (n = 279), pembrolizumab every 3 weeks (n = 277), or ipilimumab (n = 278).<sup>24</sup> OS rates for both pembrolizumab groups were superior to the ipilimumab group, and the study was stopped early to allow patients receiving ipilimumab to receive pembrolizumab, if desired. Estimated survival at 1 year was 74.1% for patients receiving pembrolizumab every 2 weeks (HR vs ipilimumab, 0.63; 95% CI, 0.47-0.83;  $P < .0005$ ), 68.4% with pembrolizumab every 3 weeks (HR vs ipilimumab, 0.69; 95% CI, 0.52-0.90;  $P = .0036$ ), and 58.2% with ipilimumab. Pembrolizumab demonstrated significantly improved response rates over ipilimumab (11%) both with pembrolizumab every 2 weeks (33.7%;  $P < .001$ ) and every 3 weeks (32.9%;  $P < .001$ ). More patients receiving ipilimumab (9.4%) discontinued the study due to AEs compared with pembrolizumab every 2 weeks (4.0%) and pembrolizumab every 3 weeks (6.9%). Grade 3 to 5 treatment-related AEs

occurred in 13.3% of patients receiving pembrolizumab every 2 weeks, 10.1% receiving pembrolizumab every 3 weeks, and 19.0% receiving ipilimumab. The most common treatment-related AEs (any grade) observed with pembrolizumab and ipilimumab were fatigue, diarrhea, rash, and pruritus. In this study, both regimens of pembrolizumab improved OS compared with ipilimumab.<sup>24</sup>

Adjuvant treatment with nivolumab was compared with ipilimumab in an international, double-blind, phase 3 trial in patients with resected stage IIIB, IIIC, or IV melanoma with or without *BRAF* mutations (N = 906). Patients were randomized 1:1 to receive nivolumab (n = 453) or ipilimumab (n = 453).<sup>37</sup> As of the prespecified interim analysis, the median RFS had not been reached. At 1 year, the RFS in patients receiving nivolumab was 70.5% (95% CI, 66.1%-74.5%) versus 60.8% (95% CI, 56.0%-65.2%) for ipilimumab. At 18 months, these rates were 66.4% (95% CI, 61.8%-70.6%) and 52.7% (95% CI, 47.8%-57.4%), respectively. Nivolumab resulted in significantly longer RFS versus ipilimumab, with recurrence or death reported in 34.0% and 45.5% of patients, respectively (HR, 0.65; 97.56% CI, 0.51-0.83;  $P < .001$ ).<sup>37</sup>

In early clinical trials, researchers observed a correlation between pretreatment levels of tumor-expressed PD-L1 and treatment response and that PD-L1 expression varies by tumor type. Taube et al found that PD-L1 is expressed by both tumor cells and tumor infiltrating cells (TILs) in melanoma. TIL expression of PD-1 was significantly associated with tumor expression of PD-L1, thus more likely to respond to anti-PD-1 therapy.<sup>38</sup> In the subgroup analysis of RFS according to PD-L1 expression, HRs favored patients in the nivolumab group whose PD-L1 expression was 5% or greater. In this subgroup, the 1-year RFS was 81.9% (95% CI, 74.7%-87.2%) versus 73.8% (95% CI, 65.9%-80.1%) with ipilimumab. In patients whose PD-L1 expression was  $\leq 5\%$ , the 1-year RFS with nivolumab was 64.3% (95% CI, 58.3%-69.7%) versus 53.7% (95% CI, 47.6%-59.4%) with ipilimumab.<sup>37</sup> Treatment-related AEs were observed in 14.4% of patients receiving nivolumab and 45.9% receiving ipilimumab; grade 3 or 4 AEs resulting in study discontinuation were reported in 4.6% and 30.9% of patients, respectively. In this prespecified analysis, adjuvant nivolumab resulted in significant improvement in RFS compared with ipilimumab.<sup>37</sup>

Combination nivolumab plus ipilimumab was evaluated against monotherapy with each agent in an international, randomized, double-blind, phase 3 trial in treatment-naïve patients with unresectable stage III or IV melanoma with or without *BRAF* mutations (N = 945). Patients were randomized 1:1:1 to receive nivolumab (n = 316), nivolumab plus ipilimumab (n = 314), or ipilimumab (n = 315). Patients receiving nivolumab or ipilimumab received matched placebo.<sup>39</sup> The median PFS with nivolumab

plus ipilimumab was 11.5 months (95% CI, 8.9-16.7) compared with 6.9 months (95% CI, 4.3-9.5) with nivolumab alone and 2.9 months (95% CI, 2.8-3.4) with ipilimumab alone. Both patients in the nivolumab-plus-ipilimumab group and the nivolumab group experienced significantly longer PFS versus those receiving ipilimumab alone (nivolumab plus ipilimumab: HR, 0.42; 99.5% CI, 0.31-0.57; nivolumab: HR, 0.57; 99.5% CI, 0.43-0.76;  $P < .001$  for both). The ORR for nivolumab plus ipilimumab was 57.6% (95% CI, 52.0%-63.2%) compared with 43.7% (95% CI, 38.1%-49.3%) with nivolumab alone and 19.0% (95% CI, 14.9%-23.8%) with ipilimumab alone.<sup>39</sup>

In the same study, in patients whose tumor was PD-L1 positive, the median PFS was 14.0 months (95% CI, 9.7-not reached) with nivolumab plus ipilimumab, 14.0 months (95% CI, 9.1-not reached) with nivolumab alone, and 3.9 months (95% CI, 2.8-4.2) with ipilimumab alone. In patients who were negative for tumor PD-L1, the median PFS was 11.2 months (95% CI, 8.0-not reached), 5.3 months (95% CI, 2.8-7.1), and 2.8 months (95% CI, 2.8-3.1), respectively.<sup>39</sup> A higher incidence of grade 3 or 4 treatment-related AEs were observed in patients receiving nivolumab plus ipilimumab (55.0%) compared with nivolumab alone (16.3%) and ipilimumab alone (27.3%).

The most common AEs in patients receiving nivolumab plus ipilimumab were diarrhea, pruritus, and fatigue. The percentage of patients who discontinued the study drug due to AEs (any grade) were 36.4% for nivolumab plus ipilimumab, 14.8% for ipilimumab alone, and 7.7% for nivolumab alone.<sup>39</sup>

Recently, data were presented from a post hoc analysis of 3 phase 3 clinical studies evaluating combination therapy with nivolumab plus ipilimumab (N = 409) versus each agent alone (nivolumab, N = 526; ipilimumab, N = 362). In this pooled analysis, the ORR was 58.9% in patients receiving combination therapy versus 43.9% with nivolumab alone and 18% with ipilimumab alone; CRs were observed in 18%, 16%, and 4% of patients, respectively. Of patients in the combination therapy cohort experiencing a CR, 77% are no longer receiving treatment, and 2-year PFS and OS are 86% and 92%, respectively. Of patients in the combination therapy cohort, 60% of patients who had a CR experienced grade 3 to 4 treatment-related AEs and 31% of those patients discontinued. In the same combination therapy cohort, 65% of patients who achieved a partial response and 60% of patients who had stable disease experienced grade 3 to 4 treatment-related AEs, with 36% and 35% of patients discontinuing treatment respectively. No treatment-related deaths were reported.<sup>40</sup>

### **IDO Inhibitors**

New agents in development for advanced melanoma target indoleamine-2,3-dioxygenase (IDO), an intracellular »

enzyme that is induced by an immune response. IDO initiates tryptophan degradation along the kynurenine metabolic pathway and aids tumor progression by supporting an immunosuppressive tumor microenvironment. Tumor cells use the IDO pathway to build tolerance to tumor antigens, and antigen-presenting cells expressing IDO can directly suppress a T-cell response, allowing tumor cells to escape detection by the immune system. Inhibiting IDO can restore the proliferation of various immune cells, including dendritic cells (DCs), natural killer (NK) cells, and T cells, as well as boost interferon (IFN) production, and reduce the numbers of tumor-associated regulatory T cells.<sup>41-43</sup>

Epacadostat is a hydroxyamidine small-molecule IDO<sub>1</sub> inhibitor currently being evaluated in early clinical trials. A phase 1/2 study is exploring the safety, tolerability, and efficacy of epacadostat in combination with pembrolizumab in patients with melanoma and other solid tumors (estimated N = 508).<sup>41,44</sup> Updated phase 1 results were recently presented. Responses were observed in all groups receiving epacadostat at a dose of 50 mg or higher twice a day. The median PFS was not reached at the time of this report; however, responses were observed in patients previously treated for advanced melanoma and other cancers. A maximum tolerated dose was not established. Most common treatment-related AEs ( $\geq 15\%$ , any grade) were fatigue, joint pain, rash, diarrhea, pruritus, and nausea. Grade 3 treatment-related AEs occurred in 18% of patients, and there were no treatment-related deaths. This study is expected to be completed in February 2020. Based on the interim results of this study, investigators recommended a phase 2 dose of 100 mg twice daily, and a phase 3 study in treatment-naïve patients with advanced melanoma was initiated (NCT02752074).<sup>45</sup>

### TNF Receptor Family Antibodies

Members of the tumor necrosis factor (TNF)/TNF receptor (TNFR) family are responsible for many components of an effective immune response, including cellular activation, proliferation, and effector function, and cell survival and memory. More than 40 TNF/TNFR members have been identified thus far. Three TNFR members, OX40, CD27, and 4-1BB, have been shown to activate numerous signaling cascades and regulate the expression and survival of CD4+ and CD8+ cells, among other immune-stimulating mechanisms.<sup>46-48</sup>

Varlilumab is a fully human, IgG1 $\kappa$  anti-CD27 mAb that was shown to be well tolerated and clinically active in a phase 1, open-label, dose-escalation and expansion study (N = 25). The study was open to patients with metastatic melanoma and other cancers whose disease had progressed and who had no remaining approved therapy options. Varlilumab demonstrated a transient increase in

IP-10 (a key cytokine that is upregulated by CD27 co-stimulation in CD8+ cells) and an increase in effector T cells, circulating T cells with an active phenotype, and fewer naïve T cells. Treatment-related AEs were fatigue, rash, nausea, and diarrhea, and were generally grade 1 to 2. There was 1 case each of grade 3 hyponatremia, decreased appetite, and decreased lymphocyte count.<sup>49</sup>

Utomilumab is a fully human IgG2 agonist of 4-1BB currently being evaluated in combination with pembrolizumab. An open-label, multicenter, phase 1b dose-escalation study was conducted in patients with advanced cancers, including melanoma, who had progressed on therapy or for whom no standard therapy was available (N = 23). All patients received utomilumab and pembrolizumab and were assessed for safety and tumor response. The ORR was 26% (95% CI, 10.2%-48.4%); 5 of the 6 patients who responded to treatment maintained a response for longer than 6 months. The best overall response of stable disease was achieved by 43.5% of patients across tumor types. No dose-limiting toxicities were observed and AEs were generally mild. The most common treatment-related AEs were fatigue, rash, pruritus, fever, decreased appetite, dry mouth, dry skin, and nausea. There was 1 instance each of grade 3 adrenal insufficiency and hypokalemia.<sup>50</sup>

An OX40 agonist, PF04518600, is being studied in early clinical trials for various cancers, including melanoma. An open-label, dose-escalation, phase 1/2 study in patients with locally advanced or metastatic cancer will evaluate the safety and tolerability of PF04518600 alone or in combination with utomilumab (estimated N = 210). This study is expected to be completed by December 2020.<sup>47,51</sup>

### Advancements in Immuno-Oncology Oncolytic Viral Therapies

An encouraging new field within immuno-oncology (IO) is that of virus-based therapies to induce systemic tumor-specific immunity. Although gene therapy uses viruses to simply carry and deliver information, in oncolytic viral therapy, the virus itself is active against the tumor. Viruses used in IO are genetically engineered to be noninfectious and are typically DNA based. T-VEC is a double-mutated herpes simplex virus-1 with gene deletions that render it unable to replicate in normal cells, but allow it to enter cancer cells due to their impaired regulatory functions. Also, T-VEC is augmented with the human granulocyte-macrophage colony-stimulating factor (*GM-CSF*) gene, intended to help induce antitumor immunity.<sup>52</sup>

T-VEC, a first-in-class intralesional oncolytic viral therapy, was administered in combination with ipilimumab in an open-label phase 1b/2 study in patients with unresectable stage IIIB-IVM1c melanoma, with no systemic therapy except adjuvant therapy in the preceding 6 months (N = 19).



The ORR was 50% (95% CI, 26.0%-74.0%). All but 1 patient who achieved CRs (22%) had a response lasting 6 months or longer. No dose-limiting toxicities were reported and no new emerging toxicities were observed. Grade 3 or higher treatment-related AEs were reported in 26.3% of patients; nausea was the only grade 3 or higher event reported in more than 1 patient.<sup>53</sup>

T-VEC is also being evaluated in combination with pembrolizumab in a multicenter, double-masked, phase Ib/3 study in patients with unresectable stage IIIB or IVM1c melanoma with no previous systemic treatment. In phase Ib, all patients received T-VEC plus pembrolizumab (N = 21). The confirmed ORR was 48%, with 14% of patients achieving a CR. The median time to response was 17 weeks. During treatment with T-VEC, circulating CD8+ cells were elevated, but decreased after pembrolizumab was initiated. Most common AEs were fatigue, fever, and chills. All patients experienced treatment-related AEs, with 33% experiencing grade 3 or 4 AEs.<sup>54</sup> In phase 3 (estimated N = 660), patients will be randomized to receive T-VEC plus pembrolizumab or pembrolizumab and placebo. This study is expected to be completed by September 2022.<sup>55</sup>

### DC Vaccines

Upon infection or inflammation, DCs collect and present antigens to naïve T cells, activating them against an antigen-specific target. DC vaccines aim to take advantage of this key role in the immune response. In the past, researchers matured undifferentiated DC cells from a progenitor line in vitro, yielding limited clinical responses. However, recent advances show that by using naturally occurring DCs, a measurable clinical effect can be achieved. Therefore, DC vaccines currently in development are created by loading tumor-specific peptides into patients' own harvested DCs for individualized therapy.<sup>56,57</sup>

In a first-in-human feasibility study evaluating the ability of plasmacytoid DCs (pDCs) to initiate an antitumor response, 16 patients with metastatic melanoma received autologous activated pDCs loaded with tumor-associated peptides. To evaluate the clinical outcomes, investigators identified matched historical controls who received standard dacarbazine chemotherapy. The number of patients in the study did not allow investigators to draw conclusions of clinical significance; however, compared with the historical control group, the median OS showed notable improvement over the matched controls: 22.0 months (95% CI, 1.8-42.2) versus 7.6 months (95% CI, 5.8-9.4;  $P = .001$ ), respectively. Vaccines were well tolerated and no severe toxicities were observed.<sup>56</sup>

In another safety and feasibility study, patients with metastatic melanoma were administered tumor antigen-loaded autologous CD1c+ myeloid DCs (mDCs) isolated from peripheral blood and cultured overnight. After the

first cycle of therapy, 5 patients showed at least stable response; these patients received a second cycle of therapy, of whom 2 experienced disease progression and the remaining 3 received a third cycle of therapy. Of these 5 remaining patients, 2 also showed an objective response that was correlated with the presence of functional T cells. One patient converted to a CR, and at the time of study publication (2016) was in remission after 35 months. The median OS for patients with functional T cells was 29.0 months compared with 10.9 months in patients who did not have functional T cells (HR, 0.43; 95% CI, 0.12-1.54;  $P = 0.103$ ). The median OS for all patients was 13.3 months. Vaccines were well tolerated and no serious toxicities were observed.<sup>57</sup>

Other elements within the immune system are being explored for possible applications in cancer. One such component is LAG-3, a cell-surface molecule expressed on activated T cells, NK cells, and B cells.<sup>58</sup> LAG-3 is interesting because several approaches to manipulating its role in the immune process appear to have clinical use. In preclinical studies, blocking LAG-3 with a LAG-3 antibody resulted in more persistent proliferation of T cells in vitro, potentially increasing antitumor activity, whereas upregulating LAG-3 with LAG-3-Ig increased the expression of co-stimulatory molecules and interleukin-12 in DCs.<sup>58</sup> Both of these approaches are being evaluated in early clinical trials: LAG-3-Ig (IMP321, Immutep, France) and LAG-3 mAb (NCT01968109, Bristol-Myers Squibb, United States).<sup>59</sup>

### Conclusions

The incidence of advanced melanoma is steadily increasing and comes at considerable economic cost and emotional burden. However, in the recent past, the number of useful treatment options and burgeoning fields of research for these patients have increased considerably. Accordingly, patients should be informed of ongoing clinical trials that may alter their individual treatment journeys. ♦

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