Melanoma represents the most dangerous form of skin cancer. According to recent data, the 5-year relative survival rate for Americans with distant melanoma is only 17%. The National Cancer Institute estimated that in 2015 there were 73,870 new cases of skin melanoma and more than 9900 patients died from this disease. In the United States, the total estimated national expenditures for the treatment of melanoma reached $2.8 billion in 2015.

The management of patients with advanced stages of melanoma has traditionally been very challenging. Today, however, the introduction of novel agents has changed the treatment landscape significantly. The armamentarium of systemic treatments for patients with advanced stages of melanoma has expanded to include BRAF inhibitors (eg, vemurafenib, dabrafenib, and trametinib), as well as immune checkpoint inhibitors.

Immunotherapy agents have always played a role in the management of melanoma. Historically, interleukin-2 and interferon were considered standard treatments for early and advanced stages of the disease. As scientific knowledge has evolved, however, it has become evident that naturally occurring immune checkpoints and other regulatory pathways thwart the body's attempts to remove cancer cells.

Commercially available therapies that can affect these pathways include monoclonal antibodies targeting either cytotoxic T-lymphocyte antigen-4, such as ipilimumab, or PD (programmed-cell death)-1, such as pembrolizumab or nivolumab. By blocking these pathways, checkpoint inhibitors strengthen the ability of tumor-infiltrating T-lymphocytes (T-cells) to detect cancer cells for the danger that they represent and remove them. Clinical trials of checkpoint inhibitors in patients with melanoma have demonstrated impressive objective response rates, and, in some cases, extended survival, despite advanced stages of disease and significant tumor burden.

Recognizing that melanoma and other cancer cells have the ability to avoid immune detection using a wide variety of strategies, a new array of treatments is being developed with the goal of enhancing T-cell, dendritic cell, and other immune-mediator functioning. Several novel immunotherapy agents are being studied in melanoma to determine whether they can eliminate melanoma cells and establish active, ongoing, and long-term immune surveillance against new cancer cells.

First-in-Class Oncolytic Viral Therapy for Melanoma

On October 27, 2015, the US Food and Drug Administration (FDA) approved talimogene laherparepvec (Imlygic; Amgen) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma that has recurred after initial surgery. Talimogene laherparepvec (T-VEC) is the first genetically modified oncolytic viral therapy approved for direct injection into melanoma lesions.

The FDA approval was based on the pivotal study of T-VEC, OPTiM, a multicenter, phase 3, clinical trial that enrolled patients with metastatic melanoma that could not be surgically removed. The primary end point was the durable response rate, which was defined as the percentage of patients who achieved a complete or a partial response for a minimum of 6 months. Patients who received T-VEC in this study were significantly more likely to experience a durable response compared with patients who received the comparator therapy, granulocyte-macrophage colony-stimulating factor (GM-CSF). T-VEC has not been shown to affect overall survival, or to have a clinical benefit on disease that has spread to the brain, bone, liver, lungs, or other internal organs.

According to Karen Midthun, MD, Director of the FDA’s Center for Biologics Evaluation and Research, “Melanoma is a serious disease that can advance and spread to other parts of the body, where it becomes difficult to treat. This approval provides patients and health care providers with a novel treatment for melanoma.”

Mechanism of Action

The exact mechanism of action of T-VEC is unknown. This agent is a genetically modified herpes simplex virus (HSV) type 1 that replicates within tumors and produces GM-CSF, an immune stimulatory protein. T-VEC causes lysis of tumors, followed by the release of tumor-derived antigens. Together with virally
derived GM-CSF, T-VEC may promote an antitumor immune response.\textsuperscript{14}

**Dosing and Administration**

T-VEC is administered by direct injection into cutaneous, subcutaneous, and/or nodal melanoma lesions that are visible, palpable, or detectable by ultrasound guidance.\textsuperscript{14} T-VEC is provided in single-use vials of 1 mL each in 2 different dose strengths\textsuperscript{14}:

- $10^6$ (1 million) plaque-forming units (PFU) per mL; this vial has a light green cap and is used for the initial dose only
- $10^8$ (100 million) PFU per mL; this vial has a royal blue cap and is used for all subsequent doses.

The recommended starting dose of T-VEC is $10^6$ (1 million) PFU per mL up to a maximum of 4 mL. Subsequent doses are $10^8$ (100 million) PFU per mL up to a maximum of 4 mL.\textsuperscript{14}

During the initial treatment, the largest lesions should be injected first, followed by smaller lesions; new lesions and large lesions should be prioritized 3 weeks after the initial treatment. Every 2 weeks thereafter, T-VEC should be administered at a dose of $10^6$ (100 million) PFU per mL to new lesions and large lesions. During each treatment with T-VEC, the total injection volume should not exceed 4 mL for all injected lesions combined. As such, at each treatment visit and during the full course of treatment, injection of all lesions with T-VEC may not be possible.\textsuperscript{14}

T-VEC is stored frozen (−90°C to −70°C) and then thawed at room temperature before dosing.\textsuperscript{14} Approximately 30 minutes is required for the drug to liquefy.\textsuperscript{14,15}

**Pivotal Clinical Trial: OPTiM**

The approval of T-VEC in metastatic melanoma was based on the results of OPTiM, a phase 3, multicenter, open-label, randomized clinical trial that enrolled 436 patients with unresectable stage IIIB, IIIC, and IV melanoma.\textsuperscript{12-14} T-VEC was injected into cutaneous, subcutaneous, or nodal melanoma lesions only. Previous systemic treatment for melanoma was allowed. Patients with active cerebral metastases, bony metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic antitherapeutic agent were excluded from the study.\textsuperscript{14}

The majority (98%) of patients enrolled in the OPTiM trial were white and 70% had an ECOG performance status of 0 at baseline.\textsuperscript{14} Overall, 70% of patients had stage IV disease (27% M1a; 21% M1b; 22% M1c), and 30% had stage III disease.\textsuperscript{14} In addition, 53% of patients had received therapy for melanoma either in addition to or as an alternative to surgery, adjuvant therapy, or radiation.\textsuperscript{14} More than half (58%) of the patients were seropositive for HSV-1 wild-type at baseline.\textsuperscript{14}

Of the 436 patients enrolled in OPTiM, 295 were randomized to receive T-VEC, and 141 received GM-CSF.\textsuperscript{14} T-VEC was administered by intramuscular injection at an initial concentration of $10^6$ (1 million) PFU per mL on day 1, followed by a concentration of $10^8$ (100 million) PFU per mL on day 21 and every 2 weeks thereafter, with doses of up to 4 mL per visit.\textsuperscript{14} GM-CSF was administered subcutaneously in 28-day cycles—125 μg/m² daily for 14 days, followed by 14 days with no GM-CSF administration.\textsuperscript{14}

The patients received treatment for at least 6 months or until no injectable lesions were present. After 6 months of treatment, patients continued therapy until clinically relevant disease progression up to 12 months. All patients were followed for at least 36 months.\textsuperscript{14}

The major efficacy measure was the durable response rate, with tumor responses determined according to the World Health Organization response criteria that were modified to allow patients who developed new lesions or whose disease progressed to continue treatment and to be evaluated later for tumor response.

The durable response rate was 16.3% in the T-VEC compared with 2.1% in the GM-CSF arm (Table).\textsuperscript{3,14} The median time to response to T-VEC was 4.1 months.\textsuperscript{14} Although a trend in overall survival was noted in favor of T-VEC versus GM-CSF (median overall survival, 22.9 months vs 19 months, respectively), it did not reach significance ($P = .116$).\textsuperscript{14}

<table>
<thead>
<tr>
<th>End point</th>
<th>Talamogene laherparepvec (N = 295)</th>
<th>GM-CSF (N = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable response rate, %</td>
<td>16.3 (95% CI, 12.1-20.5)</td>
<td>2.1 (95% CI, 0-4.5)</td>
</tr>
<tr>
<td>Unadjusted relative risk, %</td>
<td>7.6 (95% CI, 2.4-24.1)</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Median time to response, mo</td>
<td>4.1 (range, 1.2-16.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Median overall survival, mo</td>
<td>22.9</td>
<td>19.0</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GM-CSF, granulocyte-macrophage colony-stimulating factor; N/A, not available.

Adverse Events
A total of 292 patients with unresectable advanced-stage melanoma received at least 1 dose of T-VEC in the OPTiM study. In this cohort, the median duration of exposure to T-VEC was 5.3 months. Overall, 26 patients were exposed to T-VEC for at least 1 year.

The majority of adverse reactions associated with T-VEC were mild or moderate and typically resolved within 72 hours. The most common grade ≥3 adverse reaction was cellulitis.

Adverse reactions (all grades) in the OPTiM study that occurred in ≥20% of patients receiving T-VEC included fatigue (50%), chills (49%), pyrexia (43%), nausea (36%), influenza-like illness (31%), injection-site pain (28%), and vomiting (21%).

Other adverse reactions associated with T-VEC in the OPTiM study included glomerulonephritis, vitiligo, cellulitis, and oral herpes.

Contraindications
Because T-VEC is a live, attenuated HSV, it can cause life-threatening disseminated herpetic infection in patients who are immunocompromised. T-VEC is contraindicated in immunocompromised patients, as well as in pregnant women.

Drug Interactions
Studies regarding drug interactions have not been conducted with T-VEC. Because T-VEC is sensitive to acyclovir, the use of acyclovir or other antiviral viral agents may interfere with T-VEC’s effectiveness.

Warnings and Precautions
Accidental exposure. Exposure to T-VEC can lead to the transmission of T-VEC and herpetic infection. Accidental needle sticks and splashback of T-VEC to the eyes have been reported by healthcare providers during T-VEC preparation and administration. Consequently, the following are recommended:

- Healthcare providers, close patient contacts (eg, household members, caregivers, sex or bed partners), pregnant women, and newborns should avoid direct contact with lesions that have been injected with T-VEC, dressings, or body fluids of treated patients
- Healthcare providers who are immunocompromised or pregnant should not prepare or administer T-VEC
- Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings; they should also observe safety precautions for the disposal of used dressings, gloves, and cleaning materials
- Patients should avoid touching or scratching injection sites or their occlusive dressings; this could lead to the inadvertent transfer of T-VEC to other areas of the body.

In the event of accidental exposure to T-VEC, clean the affected area thoroughly. If the symptoms of herpetic infection develop, the patient must receive appropriate treatment.

Herpetic infection. In clinical studies, herpetic infections, including cold sores and herpetic keratitis, were reported with T-VEC. Patients who develop suspicious herpetic-like lesions should follow standard hygienic practices to prevent viral transmission. Because T-VEC is sensitive to acyclovir, acyclovir and other antiviral agents can interfere with T-VEC’s effectiveness. Before recommending antiviral agents to manage herpetic infection, the risks and benefits of T-VEC treatment should be considered.

Injection-site complications. Necrosis or tissue ulceration can occur at the site of T-VEC injection. Cellulitis, systemic bacterial infection, and impaired healing have been reported in clinical studies. T-VEC can affect healing in patients with underlying risk factors. The risks and benefits of T-VEC should be considered before continuing treatment if persistent infection or delayed healing at the injection site occurs.

Immune-mediated events. Immune-mediated events (eg, glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, vitiligo) were reported in clinical trials of T-VEC. The risks and benefits of T-VEC should be considered before starting treatment in patients with autoimmune disease, or before continuing treatment in patients who have immune-mediated events.

Plasmacytoma at injection site. Plasmacytoma was reported after the administration of T-VEC to a patient with smoldering multiple myeloma. The risks and benefits of T-VEC should be considered in patients with multiple myeloma or in patients experiencing plasmacytoma during treatment.

Use in Specific Populations
Pregnancy. There are no studies of T-VEC in pregnant women. However, if a pregnant woman is infected with wild-type HSV-1, the virus can cross the placental barrier, and can be transmitted to the baby during birth. If a patient becomes pregnant while taking T-VEC, she should be apprised of the potential hazard to the fetus and to the neonate.

Lactation. There is no information regarding the presence of T-VEC in human milk, or its effects on the breast-fed infant or on milk production. Patients should discontinue nursing or discontinue T-VEC while breast-feeding.

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Females and males of reproductive potential. There are no data regarding the effect of T-VEC on fertility.14

Pediatric use. The safety and effectiveness of T-VEC have not been established in children.14

Geriatric use. No differences in the safety or efficacy were observed between patients aged ≥65 years and younger patients who received T-VEC.4

Renal or hepatic impairment. There are no data regarding the effect of renal or hepatic impairment on the pharmacokinetics of T-VEC.14

Conclusion

Breakthroughs in immunotherapy have changed the management of advanced melanoma. T-VEC is the first oncolytic virus therapy that has received FDA approval for patients with unresectable melanoma lesions. Compared with GM-CSF, intralesionial injections of T-VEC significantly improved the rate of durable responses to treatment. T-VEC has not been shown to significantly improve overall survival or to affect visceral metastases.

The clinical activity of T-VEC, alone and in combination with other immuno-oncology agents, such as nivolumab or pembrolizumab, is being evaluated in patients with melanoma, as well as in other malignancies, including head and neck cancer and hepatocellular carcinoma.16

References