

# MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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## The Role of Talimogene Laherparepvec (T-VEC) in the Age of Checkpoint Inhibitors



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### **H&O** How does virus-based oncolytic immunotherapy work?

**RA** A number of oncolytic viral immunotherapies are being developed for use in melanoma and other cancers. The only one approved by the US Food and Drug Administration (FDA) is talimogene laherparepvec, which is commonly known as T-VEC (Imlygic, Amgen). T-VEC is a double-stranded DNA, JS1 herpes simplex virus 1 (HSV-1) that has been genetically modified in several ways. First, infected cell protein (ICP)34.5 has been deleted, which prevents HSV infection of nontumor cells and provides tumor-selective replication. Second, ICP47 has been deleted, which enables antigen presentation. Third, the US11 protein has been inserted earlier in the genome, which increases viral replication and tumor cell lysis. Finally, granulocyte-macrophage colony-stimulating factor (GM-CSF) has been inserted, which enhances the antitumor immune response by recruiting dendritic cells to the tumor site and stimulating them.

When T-VEC is injected directly into metastatic melanoma—whether that be a dermal tumor, a subcutaneous tumor, or metastasis to a lymph node—the virus is preferentially taken up by the tumor. It then undergoes replication in the tumor cells, which leads to cell lysis that exposes tumor-associated antigens to the immune system. This causes the immune system to become activated, with further activation caused by the production of GM-CSF in the tumor.

Something that is becoming increasingly clear as we have done more research is that the immune system is activated not only locally, but also at distant sites via dendritic cells and CD8-positive T cells.

We believe that most of the other oncolytic viral therapies work pretty much the same way as T-VEC, although the specific virus and the precise way it enters the cell varies. For example, a commonly used virus in these types of therapies is Cocksackievirus A21, which uses the intercellular adhesion molecule 1 (ICAM-1) protein on the surface of the tumor cell in order to gain access to the cell. Melanoma and many other cancers express large amounts of ICAM-1 on the cell surface. This means that Cocksackievirus A21 can be administered intravenously in addition to intralesionally, and it will seek out and infect just those cells that express ICAM-1.

### **H&O** Could you talk about the trials you have conducted that have established the value of T-VEC in melanoma?

**RA** The OPTiM (Oncovex [GM-CSF] Pivotal Trial in Melanoma) trial, which we published in the *Journal of Clinical Oncology* in 2015, was the trial that led to approval of T-VEC later that year. OPTiM was a phase 3, multicenter, randomized clinical trial that was conducted in 4 countries: the United States, the United Kingdom, Canada, and South Africa. We randomly assigned 436 patients with unresectable stage IIIB, IIIC, or IV melanoma 2:1 to receive either intratumoral T-VEC (295 patients) or subcutaneous GM-CSF (141 patients). We used GM-CSF as the comparator because the trial was designed back in 2007 and 2008, when we had no therapies that were proven to work well for melanoma. Data showed that GM-CSF might be effective for melanoma in both the adjuvant and metastatic settings, so the FDA suggested that we use this as the control treatment.

The primary endpoint of this trial was durable response rate, which had never been used as a primary endpoint but was very important to the trial. Durable response was defined as a response that lasted for at least 6 months as assessed by modified World Health Organization criteria. The results from OPTiM showed that the durable response rate was significantly better in patients treated with T-VEC than in those treated with GM-CSF: 16.3% vs 2.1% ( $P < .001$ ). The objective response rate, which was a secondary endpoint, also was significantly higher with T-VEC than with GM-CSF: 26.4% vs 5.7% ( $P < .001$ ).

Another secondary endpoint was overall survival. Although the trial was not necessarily powered to detect a difference in overall survival, the third of 3 preplanned analyses—when patients had been followed for at least 3 years—showed an improved median overall survival with T-VEC compared with GM-CSF: 23.3 months vs 18.9 months (hazard ratio, 0.79; 95% CI, 0.62–1.00;  $P = .049$ ). I believe that this difference of 4.4 months is clinically significant. We presented these results at the 2014 annual meeting of the Society for Immunotherapy of Cancer.

We also did an exploratory analysis in which we attempted to determine whether specific subsets of patients responded better to treatment with T-VEC. We found that the patients with earlier disease—stage IIIB, IIIC, or IVM1a—had a near doubling in median overall survival with T-VEC compared with GM-CSF (41.1 vs 21.5 months). In contrast, there was little difference in median overall survival between the T-VEC and GM-CSF arms (15.9 vs 13.4 months) among those with stage IVM1b or IVM1c disease. T-VEC is approved in the United States for the entire intent-to-treat population, whereas in Europe it is approved for patients with stage IIIB, IIIC, or IVM1a melanoma.

Why did the patients with stage IIIB, IIIC, or IVM1a melanoma react so much better to T-VEC than to GM-CSF? We did not find any difference in subsequent treatment between the T-VEC arm and the GM-CSF arm. Because patients with stage IIIB or IIIC melanoma have not yet developed visceral or lung metastases, we theorized that T-VEC might be reducing the risk of these metastases. Indeed, a retrospective exploratory analysis that we presented at the 2015 annual meeting of the Society of Surgical Oncology found a 59% greater reduction in the development of visceral and bone metastases in patients who received T-VEC compared with GM-CSF, so this is a potential explanation.

Given that the patients in the OPTiM trial had unresectable melanoma, this brings up the possibility of using T-VEC earlier in an attempt to reduce the risk of recurrence or development of visceral metastases. We are currently conducting a clinical trial in patients with

resectable IIIB, IIIC, or IVM1a disease to address that very question. We are randomly assigning patients 1:1 to either have surgery alone, as is the current standard of care, or be treated with T-VEC for 3 months and then have surgery. The primary endpoint of this trial is recurrence-free survival (NCT02211131).

Another fact we learned from the OPTiM trial is that patients who responded to T-VEC tended to have a very durable response. A total of 65% of patients had a response lasting for at least 12 months. As shown in an analysis that we presented at the most recent meeting of the Society of Surgical Oncology, the complete response rate also was high, at 17%, for T-VEC. Of the patients with a complete response, the disease had not progressed after 3 years in 72%. The durability of response in patients with either a complete or partial response is very encouraging.

### H&O What adverse events occur with T-VEC?

**RA** T-VEC was extremely well tolerated in OPTiM, with very few grade 3 or 4 toxicities. The most common grade 3 or greater toxicity was cellulitis at the injection site, which was seen in 2.1% of patients.

My clinical experience with T-VEC is that patients do really well on it. When we initiate therapy, they may have some shakes and chills that are similar to what can occur after getting a flu shot. The shakes and chills usually stop after the first 4 or 5 injections of T-VEC. Patients also may have a bit of discomfort at the injection site, but the discomfort is truly minimal. Treatment usually has minimal impact on the patient's daily life.

### H&O What made you decide to use T-VEC in combination with a checkpoint inhibitor?

**RA** We saw that we had a good response rate—64%—in the lesions that we injected, and the majority of these responses were complete responses. By contrast, the response rate in regional lesions that were not injected was 34%, and in visceral lesions at distant sites it was 15%.

That low response in patients with visceral disease led us to ask how we might do better, and that is where combination studies come in. We recently published a paper with Igor Puzanov as the first author on T-VEC in combination with the checkpoint inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb). This was a phase 1b trial, so we were mostly looking at safety.

Of course, combining agents always raises concerns about toxicity and side effects. For example, we know that combining ipilimumab and nivolumab (Opdivo, Bristol-Myers Squibb) leads to an increase in grade 3 and 4 toxicities, which are seen in 55% of patients. What we found in this phase 1b trial is that a combination of



**Figure.** Response to talimogene laherparepvec injections in a patient with metastatic melanoma.

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T-VEC and ipilimumab did not cause any substantial increase in toxicity compared to what we would see with ipilimumab alone, which was very encouraging.

This small trial also found a response rate of 50% with the combination, which is better than what we have seen with ipilimumab or T-VEC alone. We are encouraged by the possibility that we might be able to obtain a better response without an increase in toxicity. We recently completed a phase 2 trial in which patients were randomly assigned to ipilimumab alone or ipilimumab plus T-VEC; we expect to present these results later this year (NCT01740297).

We have also studied a combination of T-VEC and pembrolizumab (Keytruda, Merck). We reported on the results of this trial at last year's Society for Melanoma Research and European Society for Medical Oncology annual meetings, and presented a poster with updated data at the most recent annual meeting of the American Society of Clinical Oncology (ASCO). What we found is that combining T-VEC with pembrolizumab did not increase the toxicity for the patients. The response rate among this very small number of patients was 57%, but of course this was not a randomized trial.

We are currently conducting a phase 3 trial in which patients with unresectable stage IIIB, IIIC, or IV melanoma are randomly assigned to pembrolizumab plus T-VEC or pembrolizumab plus a placebo injection. This is a large trial of 660 patients that is being conducted in multiple centers around the world (NCT02263508).

**H&O** When should T-VEC and similar oncolytic immunotherapies be used in melanoma?

**RA** I think that T-VEC is a very robust agent (see Figure) when used as monotherapy for patients with earlier

disease, especially those with unresectable stage IIIB, IIIC, or IVM1a melanoma. The response rate to T-VEC for patients with just stage IIIB or IIIC disease is 52%, which is a very robust response. The majority of those patients are complete responders, which is very encouraging.

T-VEC can also work very well in patients who have melanoma in hard-to-treat areas, such as the head and neck. Subset analyses of the OPTiM trial showed that T-VEC was very effective in patients with head and neck melanoma; we presented these results at the 2014 annual meeting of the Society for Melanoma Research.

T-VEC also is very suitable for patients who have a lot of comorbidities and would not be candidates for many of the other immunotherapies. As for patients with visceral disease, combination therapy with T-VEC plus a checkpoint inhibitor and enrollment in one of the clinical trials is the best option.

**H&O** Is T-VEC being studied for use in patients with resectable melanoma?

**RA** I am the international primary investigator for a trial that is looking at the use of T-VEC as neoadjuvant treatment for patients with resectable melanoma. In this trial, patients with resectable stage IIIB, IIIC, and IVM1a disease are randomly assigned to surgery upfront or to T-VEC for 3 months and then surgery. The primary endpoint is recurrence-free survival (NCT02211131).

**H&O** Could you talk more about your work with Coxsackievirus A21?

**RA** We conducted the phase 2 CALM (CAVATAK in Late Stage Melanoma) trial, which I presented as a poster at the 2015 ASCO annual meeting. In this trial, we found that a

preparation of Coxsackievirus A21 called CAVATAK has the ability to change the tumor microenvironment.

Some patients do not respond to checkpoint inhibitors, and if we perform a biopsy before treatment we can see that their tumors have few or no tumor-infiltrating lymphocytes. We have been able to show that just 3 injections of Coxsackievirus A21 can produce a robust increase in tumor-infiltrating lymphocytes, particularly CD8-positive T cells. By changing the tumor microenvironment—basically turning a “cold” tumor into a “hot” one—can we get a better response from the checkpoint inhibitor? We are currently examining this question in ongoing clinical trials.

The role of these oncolytic viral immunotherapies is truly multifold. Not only do they treat the tumor, they also change the immune system to make other agents, including checkpoint inhibitors, work better.

### H&O Have you studied the use of additional types of viruses?

**RA** I presented preliminary results of a trial at the most recent ASCO annual meeting that we conducted using a different type of herpes simplex type 1 virus, called HF10. This was a phase 2 trial of patients with unresectable stage IIIB, IIIC, or IV melanoma; half of the patients had been pretreated and had progressed on prior therapy.

A total of 46 patients received HF10 plus ipilimumab. As with similar studies, we showed that adding intratumoral HF10 to ipilimumab did not significantly increase toxicity. The interim response rate was 49%, which is much higher than what we would expect to see with ipilimumab alone in these pretreated patients. Also, the fact that half of these patients had been pretreated stands in contrast with the combination studies using T-VEC with ipilimumab or pembrolizumab, in which all the patients were treatment-naïve.

### H&O What other considerations come up when deciding whether a patient is a candidate for T-VEC?

**RA** We always want to find the best treatment for each patient with melanoma, which means the treatment with the least amount of side effects, the greatest response, and the greatest durable response for that patient. We

also want to avoid burning any bridges down the line, because the first treatment does not work for many of these patients. If we continue to show that combining T-VEC with checkpoint inhibitors does not increase toxicity, this will be an important advantage of T-VEC because many therapies increase toxicity when combined with a checkpoint inhibitor.

### Disclosures

*Dr Andtbacka has received honoraria from Amgen, Takara, and Provectus.*

### Suggested Readings

Andtbacka R, Kaufman H, Collichio F, et al. Durable complete responses (CRs) in patients (pts) with stage IIIB-IV melanoma treated with talimogene laherparepvec (T-VEC) in OPTiM [SSO abstract 68]. *Ann Surg Oncol*. 2016;20(1)(suppl).

Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015;33(25):2780-2788.

Andtbacka RHI, Agarwala SS, Ollila DW, et al. Cutaneous head and neck melanoma (CHNM) in OPTiM, a randomized phase 3 trial of talimogene laherparepvec (T-VEC) vs GM-CSF for the treatment (tx) of unresected stage IIIB/C and IV melanoma. Poster presented at: 11th International Congress of the Society for Melanoma Research; November 13-16, 2014; Zurich, Switzerland.

Andtbacka RHI, Collichio FA, Amatruda T, et al. Final planned overall survival (OS) from OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC) versus GM-CSF for the treatment of unresected stage IIIB/C/IV melanoma (NCT00769704). Poster presented at: Annual Meeting of the Society for Immunotherapy of Cancer; November 6-9; National Harbor, Maryland. Abstract P263.

Andtbacka RHI, Curti BD, Kaufman H, et al. Dynamics of tumor response in advanced melanoma patients treated with Coxsackievirus A21 [ASCO abstract 9553]. *J Clin Oncol*. 2016;34(15)(suppl).

Andtbacka RHI, Kaufman HL, Collichio F, et al. Lower risk of visceral/bone metastasis (VM) in patients (pts) with stage IIIB/C/IVM1a melanoma treated with talimogene laherparepvec (T-VEC) vs GM-CSF in OPTiM (NCT00769704) [SSO abstract 52]. *Ann Surg Oncol*. 2015;22(suppl 1):S23.

Andtbacka RHI, Ross ML, Agarwala SS, et al. Preliminary results from phase II study of combination treatment with HF10, a replication-competent HSV-1 oncolytic virus, and ipilimumab in patients with stage IIIB, IIIC, or IV unresectable or metastatic melanoma [ASCO abstract 9543]. *J Clin Oncol*. 2016;34(15)(suppl).

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Ribas A, Puzanov I, Gajewski T, et al. A multicenter, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresected, stage IIIB-IV melanoma [ASCO abstract TPS9081]. *J Clin Oncol*. 2015;33(15)(suppl).

Senzer NN, Kaufman HL, Amatruda T, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor–encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. *J Clin Oncol*. 2009;27:5763-5771.