# MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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## The Current Role of Intralesional Therapy in Advanced Melanoma

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**H&O** Which patients with melanoma are potential candidates for intralesional therapy?

**RA** To undergo intralesional therapy, patients must have injectable lesions, which may be dermal, subcutaneous, or nodal. Eligible patients include those with stage III disease who have in-transit disease or lymph node metastases that we can inject, and those with stage IV disease who have metastatic spread through the lungs, liver, and other organs and who also have an injectable lesion. It is possible to inject visceral metastases under image guidance, although the experience with this technique is still quite limited.

The patients who respond best to intralesional therapy are those who have earlier disease. For instance, in the OPTiM study (Oncovex Pivotal Trial in Melanoma), which served as the basis for the approval of talimogene laherparepvec, commonly known as T-VEC (Imlygic, Amgen), we found that the response rate in patients who had earlier disease—stage IIIB, IIIC, or IVM1a—was 38.2% higher with T-VEC than with granulocyte-macrophage colony–stimulating factor (GM-CSF; 40.5% vs 2.3%), and median overall survival was nearly doubled (41.1 vs 21.5 months). In contrast, little difference was found between the T-VEC and GM-CSF arms in response rate (9.1% vs 10.9%) or median overall survival (15.9 vs 13.4 months) among those with stage IVM1b or IVM1c disease. As a result, we now try to enroll patients with more advanced disease in a clinical trial in which they can receive intralesional therapy in combination with other agents, such as programmed death 1 (PD-1) inhibitors.

**H&O** Are any agents besides T-VEC currently being used as intralesional therapy?

**RA** We almost always use T-VEC, which is the only agent approved for this use. We occasionally used Bacillus Calmette-Guérin or interleukin 2 before T-VEC was available, but neither of these agents was indicated for this use. Of course, numerous other intralesional agents are in development.

**H&O** What are the most important clinical studies since OPTiM to look at T-VEC?

**RA** We looked at T-VEC plus the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) in the Amgen 264 study, which appeared in the *Journal of Clinical Oncology* in 2018 with Chesney as the first author. In phase 1b of the trial, we established the safety of talimogene plus ipilimumab. In phase 2 of the trial, we randomly assigned 198 patients with stage IIIB or IV melanoma to receive either ipilimumab alone or ipilimumab plus T-VEC. We found that although grade 3 toxicity was slightly increased with the combination, nearly all of the grade 3 toxicity could be attributed to the ipilimumab. Unlike what we have seen with other combination immunotherapies, such as the combination of CTLA-4 inhibitors plus PD-1 inhibitors (which produces a substantial increase in toxicity), the added toxicity with the combination of ipilimumab plus T-VEC was truly minimal. We also found that adding T-VEC to ipilimumab more than doubled the objective

response rate, from 18% to 39%. Although Amgen does not appear to be seeking approval for this combination, the study showed that it is a viable option.

Another study examining T-VEC plus a checkpoint inhibitor is MASTERKEY-265, also known as KEYNOTE-034 (Pembrolizumab With or Without Talimogene Laherparepvec or Talimogene Laherparepvec Placebo in Unresected Melanoma). This study is looking at talimogene plus pembrolizumab (Keytruda, Merck). For the phase 1b portion of the study, which appeared in *Cell* in 2017 with Ribas as the first author, we treated 21 patients who had advanced melanoma with T-VEC alone followed by T-VEC in combination with pembrolizumab. The objective response rate was 62%. Although this was a small study, the results were dramatic because the rate of response to pembrolizumab alone is between 35% and 40%, and the rate of response to T-VEC alone is approximately 26%. It is always exciting to see a potentially additive effect in terms of the response rate. The combination was well tolerated, with no dose-limiting toxicities. Fatigue, fevers, and chills were the most common adverse events.

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Another exciting finding of this study, based on the examination of tumor biopsy specimens, was that T-VEC had clearly activated the immune system. This supports the idea that T-VEC causes agents such as pembrolizumab to work more effectively—we saw responses even among patients who were not expected to respond to pembrolizumab.

In the phase 3 portion of MASTERKEY-265, we randomly assigned 660 patients to receive pembrolizumab plus either a placebo injection or T-VEC as first-line melanoma therapy. The study was completed almost a year ago, and we expect to see preliminary results presented in the next year.

Another study examining T-VEC is Amgen 324, which looked at shedding of the virus. At the 2017 American Society of Gene & Cell Therapy Annual Meeting, I presented results of this study showing that T-VEC is present in the blood and urine of patients after injection but is no longer seen at approximately 30 days after we stop the injections. We also found no evidence that T-VEC can infect the health care providers who administer it, or the family members of patients who receive it.

All of the studies I have discussed so far have looked at T-VEC in patients with unresectable disease. However, in the phase 2 Amgen 266 study (Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Melanoma), we are examining the use of T-VEC in patients before surgery. In this open-label study, patients with completely resectable stage IIIB, IIIC, or IVM1a melanoma are being randomly assigned to receive either neoadjuvant T-VEC followed by surgery, or surgery alone. So far, the complete pathologic response rate to T-VEC is 21%, which is far better than what we would expect. We look forward to presenting results from this study soon.

**H&O** What other agents are being studied for use as intralesional therapy in melanoma?

**RA** A slew of intralesional agents are being tested for use in melanoma—probably more than a hundred different agents in preclinical, phase 1, phase 2, or phase 3 trials, either as monotherapy or in combination. For example, the phase 2 CALM study (CAVATAK in Late Stage Melanoma) is looking at the use of coxsackievirus type A21 (CVA21) as monotherapy. In addition, the phase 1b MITCI study (Intratumoral CAVATAK and Ipilimumab in Patients With Advanced Melanoma) is looking at the combination of CVA21 plus ipilimumab in patients whose disease has failed to respond to or stopped responding to PD-1 inhibition. CVA21 is also being studied in combination with pembrolizumab as frontline therapy in melanoma; in one study, the response rate with the combination was greater than 60%. Data from these 3 studies have been presented at meetings but have not yet been published.

A randomized phase 3 study showed that velimogene aliplasmid (Allovectin-7) did not work, so that agent is not moving forward in development. PV-10, also known as rose bengal, is being studied as monotherapy in patients with early disease and in combination with pembrolizumab in patients with more advanced disease.

In addition, a number of Toll-like receptor 9 (TLR-9) agonists are being studied in combination with both ipilimumab and pembrolizumab, specifically in patients whose disease is not responding to treatment with PD-1 inhibitors. This group is becoming one of

the largest growing patient populations in metastatic melanoma, so we are eager to find new approaches to treatment. Rates of response to combination treatment with an intralesional agent plus ipilimumab have been greater than 30%, whereas the typical rates of response to ipilimumab as second-line therapy are between 10% and 16%.

**H&O** What is the mechanism by which intralesional therapy may be able to ablate tumors locally and also produce a systemic bystander effect?

**RA** The answer depends on the agent. PV-10, for instance, causes rapid necrosis that leads to activation of the innate and adaptive immune system. Other agents, such as viruses, replicate inside the tumor, causing lysis of the tumor cells and exposure of the tumor-associated antigen to the immune system. The antigens are taken up by the dendritic cells, which then activate the adaptive immune system. Locally, we see a lytic effect of viral replication inside the tumor cells. On a systemic level, we see activation of the immune system at both local and distant sites. The responses vary a bit depending on the agent used, but that is the general idea. T-VEC works similarly to other viruses, but it also produces GM-CSF, which appears to further activate the immune system at the injection site.

**H&O** What other treatments have the potential to increase the effectiveness of intralesional therapy?

**RA** We are looking at electroporation, in which small needles are inserted into a tumor and a current is applied to open the cell membranes before a therapeutic agent is injected. For example, the PISCES/KEYNOTE-695 study (Tavo and Pembrolizumab in Patients With Stage III/IV Melanoma Progressing on Pembrolizumab or Nivolumab Treatment) is investigating the use of electroporation with intralesional tavokinogene telseplasmid plus pembrolizumab in patients who have metastatic disease that is not responding to PD-1 inhibitors. Electroporation has the potential to be used with a variety of intralesional therapies.

**H&O** What would you say the next steps in research should be?

**RA** The next steps in research should be to look for the mechanisms by which these therapies alter the immune system inside tumors, and to determine which patients are most likely to respond to these therapies at the injected site and noninjected sites. We also need to figure out how to optimize the responses to the therapies.

Intralesional therapies are extremely well tolerated, with very few side effects. Even so, we want to know in advance who is most likely to respond to them. We also need to learn about using the agents in earlier disease, specifically in the neoadjuvant setting. Finally, we need to study the use of intralesional agents in other malignancies that include injectable lesions; studies have already begun in head and neck cancer and in Merkel cell carcinoma.

***Disclosure***

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

***Note:*** *Dr Andtbacka was affiliated with the University of Utah Huntsman Cancer Institute in Salt Lake City, Utah, at the time of this interview.*

## Suggested Readings


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