Intralesional Therapies for Metastatic Melanoma

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Since my 2012 report in The Melanoma Letter on promising intralesional therapies for metastatic melanoma,1 researchers have achieved important milestones in the field. Foremost were the October 2015 U.S. Food and Drug Administration’s approval and January 2016 European approval of talimogene laherparepvec (T-VEC, brand name Imlygic®, formerly OncoVEX GM-CSF), an oncolytic immunotherapy derived from HSV (herpes simplex virus)-1. T-VEC received approval in the U.S. for melanoma patients with inoperable tumors, and in Europe for melanoma patients with certain inoperable tumors.

Researchers have also been accumulating significant clinical efficacy findings with other intralesional strategies and gathering evidence yielding insights into mechanisms behind their systemic effects.

**Allovectin-7**

Not all the news is good. Our initial report in The Melanoma Letter noted that in a phase 2 trial, one of the experimental intralesional therapies, Allovectin-7 (velimogene aliplasmid), a plasmid/lipid complex, had produced an objective response rate of 12 percent and stable disease in 25 percent of patients, without grade 3 or higher toxicities. Its phase 3 trial versus the chemotherapy combination dacarbazine (DTIC)/temozolomide (TMZ) in 390 patients with recurrent stage III or IV melanoma was ongoing.

In more recent phase 3 trial reporting, the overall response rate at/or >24 weeks, the primary endpoint, was only 4.6 percent for velimogene aliplasmid and 12.3 percent for DTIC/TMZ (P=.01). Duration of response among velimogene aliplasmid responders was marginally...

**From the Editors**

In the past five years, therapies targeting the MAPK signaling pathway and a succession of new immunotherapies have dramatically changed the landscape of treatment for advanced melanoma. The checkpoint blockade immunotherapies, which work by impeding immune regulators such as CTLA-4, PD-1 and PD-L1 so that more T cells can be released to fight the disease, have perhaps justly captured the lion’s share of the attention, producing long-term remissions in many patients and recently gaining FDA approvals across several types of cancer.

Unfortunately, as is the case with the targeted therapies, the disease eventually advances or recurs in the majority of patients on checkpoint blockade therapy, while others have limited partial responses and some do not respond at all. Yet others have such serious adverse reactions to the medicines that the melanoma therapy must be stopped and other treatment instituted to correct potentially life-threatening conditions.

Thus, we still need therapies to use in lieu of, or in conjunction with, these revolutionary systemic therapies.

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Intralesional Therapies, from page 1

longer ($P$.066), but overall survival, a median 18.8 months, was shorter [95% CI 16.6, 21.3] than the 24.1 months [17.1, 27.9] ($P$.491) with DTIC/TMZ. The results led the authors to conclude that for the selected population, velipogene aliplasmid was not an effective treatment, and researchers discontinued its development program.

The Gains with T-VEC

We had also reported on the ongoing phase 3 OPTiM trial of T-VEC (designed to secrete the cytokine GM-CSF, granulocyte macrophage-colony stimulating factor) versus subcutaneous GM-CSF alone in stage IIIB/IV melanoma patients. OPTiM included 436 patients (median age 63 years, 57 percent male), with 295 receiving T-VEC and 141 receiving GM-CSF alone. Durable response rate (complete or partial response lasting continuously for at least six months by independent review) and overall survival were the primary endpoints.

The research moved ahead successfully after that. The primary OPTiM results, presented at the American Society of Clinical Oncology (ASCO) annual meetings in 2013 and 2014, and published in the Journal of Clinical Oncology in 2015, included a durable response rate (DRR) with T-VEC of 16.3 percent (48/205) (95% CI: 12.1%, 20.5%) vs only 2.1 percent with GM-CSF (3/141, $P$.0001) (95% CI: 0%, 4.5%). The overall response rate (ORR) with T-VEC was 26.4 percent (95% CI: 21.4%, 31.5%), with 10.8 percent complete responses (CR). For GM-CSF the ORR was only 5.7 percent (95% CI: 2%, 10%) with <1 percent CR.

Median overall survival (OS) with T-VEC, 4.4 months longer than with GM-CSF alone, was 23.3 months (95% CI, 19.5 to 29.6 months), vs 18.9 months with GM-CSF alone (95% CI, 16.0 to 23.7 months). The finding achieved near-statistical significance ($P$.051) with a hazard ratio of 0.79 (95% CI, 0.62 to 1.00).

An exploratory analysis of relative effects of the treatment yielded some noteworthy differences across patient subgroups. In patients with stage IIIB or IIC melanoma, durable response rate differences between the T-VEC and GM-CSF arms were more pronounced (33 percent vs 0 percent), as they were with stage IVM1a disease (16 percent vs 2 percent). The differences were not as striking for patients with stage IVM1b (3 percent vs 4 percent) or stage IVM1c disease (7 percent vs 3 percent).

Among treatment-naïve patients, this pattern was also clearly evident, with DRRs of 24 percent for T-VEC and 0 percent for GM-CSF patients. However, the differences were less pronounced in the second-line setting and beyond: 10 percent with T-VEC vs 4 percent with GM-CSF. Similarly, the OS difference between T-VEC and GM-CSF was greater in stages IIIB, IIC or IVM1a (HR, 0.57; 95% CI, 0.40 to 0.80). The authors speculated that these disparities may reflect the differences between locoregional and visceral disease: With earlier-stage, locoregional disease, both lytic and systemic immune effects are operant, but with visceral disease only systemic immune effects come into play, and to date, T-VEC has not proven to have significant systemic effects. Tumor reductions of ≥50 percent with T-VEC were observed in only 15 percent of un injected measurable visceral lesions.

Fatigue (T-VEC 49 percent, GM-CSF 36 percent), chills (T-VEC 49 percent, GM-CSF 9 percent) and pyrexia (T-VEC 43 percent, GM-CSF 9 percent) were the most common adverse events (AEs). Discontinuations for AEs were uncommon, with 4 percent of T-VEC patients and 2 percent of GM-CSF patients discontinued. The only grade 3 or 4 AE occurring with T-VEC (in >2 percent of T-VEC–treated patients) was cellulitis (2.1 percent).

The authors emphasized that OPTiM, to their knowledge, “is the first randomized controlled phase 3 study evaluating an oncolytic immunotherapy to demonstrate a therapeutic benefit in melanoma.”
An OPTiM study extension of randomized treatment including 30 patients (27 receiving T-VEC; 3 receiving GM-CSF), reported at the 2014 European Society for Medical Oncology (ESMO) meeting, revealed continuing improvement among patients receiving T-VEC but not those on just GM-CSF. Best overall responses improved in seven patients in the T-VEC group, with five patients who had partial responses in the main trial achieving complete responses, and two patients with stable disease in the one treatment cycle, the results (based on modified RECIST criteria) were 32.2 percent of patients with an objective response and 10.7 percent of patients with a complete response. The CR rate for 85 evaluated lesions was 44.7 percent, with partial responses (PRs) in 8.2 percent of lesions and SD in 30.6 percent. In 22 patients with evaluable untreated distant lesions, regression was reported in 13 (59.1 percent). There were no serious adverse events. Injection site pain (69 percent of patients) and inflammation (20.7 percent of patients) were all grade 1 and 2, except for one report of grade 3 pain. An expansion protocol is planned.

CAVATAK™ (CVA21)

In some cancer tumors (melanoma, non-small cell lung, bladder, breast and prostate tumors included), surface intercellular adhesion molecule-1 (ICAM-1) is upregulated. Coxsackievirus A21 (CVA21) is a naturally occurring “common cold” ICAM-1-targeted RNA virus. CVA21-lysed tumor cells have been shown to induce a secondary systemic host-generated antitumor immune response in animal models.

Rates of immune-related progression-free survival (irPFS) were favorable for CAVATAK in CALM (CAVATAK in Late-Stage Melanoma), a phase 2 trial in patients with stage IIIC and IV melanoma. Andtbacka, et al reported responses in both injected and uninjected lesions. CALM included 57 stage IIIC and stage IV patients (42.1 percent stage III, 57.9 percent stage IV), 36 of them male, all with at least one injectable dermal, cutaneous, subcutaneous or lymph node lesion. The proportion of patients at six months with a complete response, partial response or stable disease (irPFS) (by irRECIST 1.1 criteria) was the primary endpoint, and overall response rate (complete response + partial response) was the secondary endpoint.

While investigators had initially hoped that at least 10 patients would achieve irPFS, at final analysis the total was 22 of the 57 enrolled patients (38.6 percent). Continued on page 4

With ongoing T-VEC treatment, complete resolution [in injected lesions] was achieved in a quarter of the patients and at least stable disease in 86 percent. To date, T-VEC has not proven to have significant systemic effects.

main trial also achieving complete responses. With ongoing T-VEC treatment, complete resolution was achieved in a quarter of the patients, at least stable disease in 86 percent and a new durable response in one patient.

Electroporation of Plasmid Interleukin-12 (IL-12)

In electroporation, scientists apply an electrical field to cells to increase their permeability so that certain agents or coding DNA can be introduced into them therapeutically. In melanoma treatment, physicians can use an electrode to open tumor cell pores to allow a higher influx of the cytokine interleukin-12 (IL-12) for a longer time span than would occur with simple administration of IL-12 as a systemic therapy. This administration route also helps by comparatively reducing systemic IL-12 concentrations necessary for therapy. The IL-12 promotes antitumor activity by augmenting adaptive and innate immune responses, among other mechanisms. Specifically, it enhances the immune capacity of NK (natural killer) cells and T cells, upregulating interferon (IFNγ) as well as antigen presenting and processing.

Electrochemotherapy is widely available in Europe.

In a phase 1 dose-escalation safety study of intratumoral electroporation of plasmid IL-12, presented at the 2014 Melanoma Bridge Meeting by Daud, et al, median long-term OS among 24 melanoma patients was 24.2 months. Among the nine patients whose treatment led to stable disease (SD) or better, OS was 46.4 months. Systemic responses to the local plasmid IL-12 therapy, as evidenced by SD or objective regression of noninjected lesions, were observed in 53 percent of patients (10/19) with metastatic disease. Without any concurrent or subsequent systemic therapy, regression of all distant lesions was complete in 11 percent of patients (2/19). Grade 1 and 2 procedure-related transient pain, the most frequent adverse events, occurred in 54 percent and 46 percent of patients, respectively.

The study, launched in 2007, was the first to assess gene therapy delivered locally in humans via electroporation with the aim of using DNA plasmid to induce systemic antitumor immunity. Plasmid IL-12-induced disease stabilization correlated with improved survival, the authors said. The results suggest the potential for both monotherapy and combination applications.

A phase 2 study of IL-12 electroporation among 28 patients with advanced melanoma offered promising results. The schedule called for IL-12 injections on days 1, 5 and 8 for a maximum of four cycles at 12-week intervals, with a primary endpoint of best overall response rate within 24 weeks of first treatment. In those receiving at least one treatment cycle, the results (based on modified RECIST criteria) were 32.2 percent of patients with an objective response and 10.7 percent of patients with a complete response. The CR rate for 85 evaluated lesions was 44.7 percent, with partial responses (PRs) in 8.2 percent of lesions and SD in 30.6 percent. In 22 patients with evaluable untreated distant lesions, regression was reported in 13 (59.1 percent). There were no serious adverse events. Injection site pain (69 percent of patients) and inflammation (20.7 percent of patients) were all grade 1 and 2, except for one report of grade 3 pain. An expansion protocol is planned.

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The overall response rate was 28.1 percent (16/57 [8 CR + 8 PR]). Other noteworthy endpoints included a durable response rate of 21.1 percent, median time to response of 3.4 months (95% CI: 1.5, 4.2), median overall survival of 26 months (95% CI: 16.7, NR) and one-year survival of 75.4 percent (43/57).

There were no grade 3 or grade 4 treatment-related adverse events. Overall, multidose intralesional therapy with CVA21 was well tolerated.

The investigators observed responses in injected lesions, un.injected nonvisceral lesions and distant uninjected visceral lesions. To learn if observed tumor responses in un injected lesions were immune-related or a consequence of CVA21 virus entering the tumor and stimulating a response, CALM investigators determined that virtually all patients had developed neutralizing antibodies to CVA21 by around day 22 after the fifth CAVATAK injection. Initially, 85 percent or more did not have neutralizing antibodies. The objective responses, despite the presence of the antibodies, suggests that the responses were likely immune-related.

Andtbacka, et al\(^6\) concluded that use of CVA21 in combination treatment with CTLA-4 or PD-1 checkpoint inhibitors such as ipilimumab or pembrolizumab, or with targeted small molecules such as BRAF and MEK kinase inhibitors, might result in enhanced antitumor activity. Clinical evaluation of CVA21 administered both intralesionally and intravenously in combination with ipilimumab in patients with unresectable melanoma is ongoing.

**PV-10 (Rose Bengal)**

Our original overview of intralesional therapies detailed interim findings of a phase 2 80-patient trial of PV-10 in stage III and stage IV melanoma, showing a 24 percent complete response rate in both target and bystander lesions, with loco-regional disease control in 71 percent of target lesions and 55 percent of bystander lesions. Regression of bystander lesions strongly correlated with response in target lesions. The objective response rate (complete plus partial response) was 49 percent in target lesions and 33 percent in designated bystander lesions. Analysis of the first 40 patients with complete responses showed PFS to be longer (11.1 months) than in those with stable disease or progressive disease (2.8 and 2.7 months, respectively).

In subsequent reporting of the final results in 2012, the objective response rate had climbed to 58 percent in target lesions and to 40 percent in bystander lesions. Locoregional disease control had increased to 80 percent for target lesions and 60 percent for bystander lesions. The close correlation between response in injected lesions and response in untreated “bystanders” persisted. Also, stasis or regression in distant visceral lesions was noted in several subjects.

Our stratification of target lesion findings according to disease stage\(^7\) revealed consistently robust responses to PV-10 in stage III melanoma subjects. It showed also that response duration was significantly longer in stage III patients than in stage IV patients, a mean of 9.6 months in stage III compared to 3.1 months in stage IV (\(P<.001\)). Greater baseline tumor burden in stage IV patients adversely affected response, as did progression of non-study lesions that precluded repeat treatment.

Guided by these observations, we restricted inclusion into the now ongoing phase 3 trial of PV-10 to subjects with stage IIIIB-IIIC disease. In our phase 2 subgroup analysis of the original 28 patients in whom all lesions were injected with PV-10 (ASCO 2014), we had seen enhanced benefits. The complete response rate was 50 percent (CI 31-70 percent) and the overall response rate was 71 percent (CI 51-87 percent). A group of 26 patients added to the phase 2 analysis, among whom all had one or two monitored, un injected bystander lesions, had a complete response rate of 64 percent (232/363) in injected lesions and a 36 percent complete response rate (10 of 28) in uninjected bystander lesions.

While we were conducting our preliminary phase 3 clinical trials, we undertook additional investigations into how local ablation may be activating systemic responses. Since responses in untreated lesions have occurred only...
When responses have occurred in injected lesions, and since these bystander lesion responses are typically delayed relative to the responses in the injected lesions, it suggests an immune-mediated process. A hypothetical mechanism for systemic immune activation for all the intralesional therapies that induce tumor lysis is that tumor lysis exposes antigenic tumor fragments to antigen-presenting cells, leading to specific T cell responses. Insights from these studies may suggest means to further enhance responses.

A Pilon-Thomas, et al murine study sought to determine if the lysis of distant tumor cells was caused by systemic distribution of PV-10 or by induction of a T cell response that spread systemically. (See Figure 1.)

When the researchers treated induced tumors with PV-10 or placebo, tumor size shrank in the PV-10-treated tumors by two-thirds (to 100 mm² from about 300 mm², \( P<.001 \)) and bystander lesion size by about 38 percent (to 220 mm² from about 300 mm², \( P<.05 \)). Survival and production of IFN-\( \gamma \), a cytokine critical for innate and adaptive immunity (including tumor control) and for activating macrophages, were significantly higher with PV-10 treatment.

A murine adoptive transfer experiment by Pilon-Thomas, et al further demonstrated that T cells purified from the spleens of B16 tumor-bearing mice treated with intralesional PV-10 were activated against B16 melanoma tumors in other mice.8 Other studies showed that direct injection of PV-10 into tumors is necessary to produce a systemic effect. Pilon-Thomas concluded that the studies confirmed PV-10 chemoablation’s direct effects on injected lesions as well as systemic effects leading to regression of uninjected subcutaneous and distant lesions.

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### Combination Therapy

During the developmental testing phases for intralesional melanoma therapies, researchers have commonly espoused the view that their ultimate use would be in combination with the emerging systemic immunotherapy agents (e.g., anti-CTLA-4, anti-PD-1, anti-PD-L1). It is indeed very plausible that by evoking the release of tumor-derived antigens, intralesional therapies could enhance the efficacy of the T cell responses triggered by the systemic immunotherapies. Keeping in mind the intralesional therapies’ low and non-overlapping side effects, such combination therapies might well prove more effective than either agent alone.

### From the Editors, continued from page 1

Among the alternatives, surgery and radiation therapy remain the staples, and in the right clinical settings, they can be extremely effective, especially for palliation. A less commonly considered approach is intralesional therapy, which is emerging as an increasingly viable and encouraging option. In this issue of *The Melanoma Letter*, Sanjiv S. Agarwala, MD, provides an incisive review of the strategies developed to date in intralesional therapy for melanoma, including the recently FDA-approved T-VEC and several promising experimental strategies.

As noted by Dr. Agarwala, the FDA’s 2015 approval of T-VEC (taliomogene laherparepvec, or Imlygic®) was the first significant salvo fired in the field of intralesional therapy. In patients with inoperable melanoma tumors, direct intratumoral injections of T-VEC, a genetically modified herpes virus, have had notable success in eliminating or shrinking the injected tumors, and in some patients have also eliminated or shrunk uninjected nearby (“bystander”) lesions. This has spurred hope of developing intralesional strategies with broader systemic effects. Dr. Agarwala explores the most exciting of these experimental strategies, including electroporated interleukin-12, CAVATAK (CVA21) and PV-10 (rose bengal). His detailed review of the response rates for both injected and uninjected lesions seen in completed studies and his breakdown of studies to come offer an excellent overview of the promise and remaining challenges in this field.

The advent of increasingly effective but imperfect individual melanoma therapies has paved the way for even more promising combination therapies. In the near future, despite their apparently limited systemic effects as monotherapies, the intralesional therapies may have an extremely important role to play in both potentiating and complementing the systemic therapies.

*Allan C. Halpern, MD • Editor-in-Chief
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**Preclinical Combination Research**

Murine studies with a melanoma model of intrallesional PV-10 combined with a systemic anti-CTLA-4 analog (9H10) showed significantly reduced lung metastases compared with the systemic 9H10 alone. Separately, flank tumor size increased with 9H10 alone, but became no longer measurable with the combination. A further study showed longer overall survival with the combination versus 9H10 alone.

**Clinical Combination Research**

The promising animal research has helped lead to human trials. In phase 1b testing of T-VEC combined with ipilimumab in 19 treatment-naïve stage IIIB-IV melanoma patients, Puzanov, et al showed an objective response rate of 50 percent with durable responses in 44 percent, complete responses in 22 percent and a 72 percent disease control rate. The 70-patient phase 2 portion of the trial is ongoing.

A phase 1b/2 clinical trial of PV-10 in combination with pembrolizumab, an approved anti-PD-1 therapy, is ongoing among patients with stage IV metastatic melanoma, with completion of the 1b portion expected this year. In the subsequent phase 2 study, participants will be randomized 1:1 to the combination of PV-10 and pembrolizumab or to pembrolizumab alone (i.e., PV-10 + standard of care vs. standard of care).

At the same time, a phase 3 international multicenter, open-label, randomized controlled trial of single-agent intrallesional PV-10 monotherapy is ongoing with systemic chemotherapy as the comparator. Patients are BRAF V600 wild-type and have locally advanced cutaneous melanoma. Treatment with ipilimumab or another immune checkpoint inhibitor has failed in these patients or they are not candidates for such treatment. Subjects in the PV-10 arm receive intrallesional PV-10 to all of their melanoma lesions, while patients in the comparator arm receive the investigator’s choice of dacarbazine or temozolomide. Progression-free survival is the primary outcome.

**Discussion**

The recent approval of T-VEC as an intrallesional therapy for advanced melanoma is a significant milestone. We need checkpoint inhibitors. Potentially, they may be paired with targeted therapies as well. Initial findings from early-phase clinical trials of intrallesional therapies combined with systemic immunotherapies suggest that response rates to these combinations improve beyond those historically achieved with the individual components alone. Yet we have to wait a while longer to see if survival benefits accrue and if recurrence rates go down. If they do, that will support the notion that early use of intrallesional therapies may strengthen systemic immune responses.

**References**


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FROM THE SKIN CANCER FOUNDATION

Updated Melanoma Information on SkinCancer.org

We’ve updated the content and the format of the melanoma section on our website (SkinCancer.org/melanoma). In addition to refining details based on the latest scientific findings, we audited the section on advanced melanoma treatment, adding frontline therapies and removing those that are outdated.

New Patient Education Material

Our Guide to Skin Cancers and Precancers has been completely revised and redesigned in 2016. This 22-page brochure has a more user-friendly format with color-coded sections to help you easily find the condition you’re looking for, including: actinic keratoses, atypical moles, basal cell carcinoma, squamous cell carcinoma and melanoma. Using easy-to-understand language and helpful photos, it provides up-to-date information for your patients on who’s at risk, warning signs, what to look for and the full array of new and established treatment options. It also directs readers to more detailed and regularly updated information on SkinCancer.org.

Please note: If you’re a physician member of The Skin Cancer Foundation, you are eligible for a limited number of complimentary patient brochures. For information about this and other membership benefits, please contact Adrienne Cea at acea@skincancer.org or 212-725-5176.

Introducing the Sun & Skin News Blog

We’re connecting with the public in a fresh and exciting way as we launch our new Sun & Skin News blog. This gives us a vehicle to explore and dig deeper into topics related to skin cancer prevention, early detection and treatment and engage with readers in a more interactive way. We’ll cover a mix of health and lifestyle issues, provide our point of view on trending skin cancer topics and interview patients as well as leaders in the field. Blog contributors will include Foundation staff, our physician members and industry partners. We hope you’ll visit blog.skincancer.org regularly.
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The Skin Cancer Foundation is now accepting applications for support of pilot research projects related to all types of skin cancer. Researchers are invited to submit applications for one-year projects to be conducted at Dermatology Departments of academic institutions within the United States.

Research must be conducted by dermatology residents, fellows, or junior investigators (5-10 years post first academic appointment) from institutions within the United States. Projects should address, at the basic science and clinical level, improved methods of prevention, detection and treatment of skin cancers.

4 GRANTS OF $25,000 WILL BE AWARDED

The research grant application must be received no later than October 14, 2016. Submissions will be reviewed by the Foundation's Research Grants Committee and applicants will be notified by December 15, 2016. Award presentations will take place at the Foundation's Research Grant Awards Reception on Friday, March 3, 2017, in Orlando, FL. Grantees must be present at the reception to accept their awards in person.

DEADLINE: FRIDAY, OCTOBER 14, 2016

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