Injectables in Head and Neck Cutaneous Melanoma Treatment

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KEYWORDS

• Otolaryngology • Cutaneous melanoma • Injectable • Talimogene laherparepvec • Oncolytic virus

KEY POINTS

- Local injectables for cutaneous melanoma offer the benefit of local and possibly systemic antitumor effects with minimal adverse effects compared with other systemic therapies.
- Local injectables are particularly beneficial for unresectable melanomas, an occurrence often seen in otolaryngology.
- Talimogene laherparepvec, an attenuated type 1 herpes simplex virus, is the most clinically relevant local injectable for unresectable melanoma.
- In patients with unresectable stage IIIB to IV melanoma, talimogene laherparepvec showed a durable response rate of 19% and suggested overall survival advantages in phase III studies. Subanalyses showed strengthened durable response rates for lower-stage melanoma and treatment naivety. These findings were maintained in patients who had cutaneous head and neck melanoma.
- There are numerous ongoing trials for intratumoral injectables in melanoma, including talimogene laherparepvec combined with systemic immunotherapies, other oncolytic viruses, and a variety of nonviral agents.

INTRODUCTION: MELANOMA IN OTOLARYNGOLOGY

Up to 15% to 20% of cutaneous melanomas occur in the head and neck region, possibly because of increased sun exposure and melanocyte concentration in this region.[1–3] Several factors distinguish cutaneous head and neck melanomas from those occurring on other body parts. First, head and neck melanomas have lower survival and higher recurrence rates compared with other primary cutaneous melanomas.[1,3,4] There is a rich, complex, and superficial lymphatic system of the head and neck that is thought to play a role in facilitating metastases.[4] Importantly, surgical resection of

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head and neck melanomas are often limited because of functional and cosmetic concerns. Although there have been many advances in melanoma therapy, management of head and neck melanoma has remained challenging.[5] Intratumoral injectables may aid in the management of head and neck melanomas where resection is difficult or impossible.

A Historical Perspective

The goal of intratumoral immunotherapies is to stimulate local and systemic immune responses through direct tumor injection. Theoretically, lysis of local tumor cells and release of tumor-derived antigens could evoke a systemic immune response, much like a vaccination. William Bradley Coley is often recognized as the father of cancer immunotherapy, because, in the 1890s, he refined previous reports of erysipelas-induced tumor regression by using heat-killed *Streptococcus pyogenes* and *Serratia marcescens* as a direct inoculum to manage recurrent sarcoma.[6] His contemporary, George Dock, reported the first viral-induced tumor regression in a patient with leukemia in 1904.[7]

In 1975, a metastatic melanoma case report described a remarkable response to direct tumor injection with bacillus Calmette-Guérin bacterium, an attenuated *Mycobacterium bovis* strain.[8] However, use of this technique in melanoma has been limited by serious adverse events (AEs) such as disseminated intravascular coagulation and death from hypersensitivity reactions.[9] Rose Bengal, an inflammatory dye, has been studied since the 1980s and is currently under investigation for melanoma, as described at the end of this article.[9] Other nonviral injectables, such as toll-like receptor agonists and immunomodulating cytokines (ie, interleukin-2 [IL-2]), have received continued attention since the 1990s.[9,10]

A large variety of viral species, predominately adenovirus, herpesvirus, vaccinia virus, and reovirus, have been studied for use as oncolytic viruses.[11] In 2005, the Chinese Food and Drug Administration provided the world's first approval of an oncolytic virus, H101 variant of adenovirus, for refractory nasopharyngeal carcinoma in combination with chemotherapy.[12] In 2015, talimogene laherparepvec (T-VEC), a modified herpes simplex virus, became the first, and currently the only, United States Food and Drug Administration (FDA)–approved oncolytic virus for use in melanoma.[13]

Talimogene Laherparepvec Background and Mechanism of Action

T-VEC is an FDA-approved oncolytic virus with the labeled indication for treating unresectable cutaneous, subcutaneous, and nodal melanoma lesions.[13] T-VEC is a second-generation, live attenuated, type 1 herpes simplex virus (HSV-1). First-generation oncolytic HSVs were developed through deletion of the *neurovirulence factor infected cell protein 34.5* (*ICP 34.5*) gene. *ICP34.5* gene deletion attenuates HSV pathogenicity toward healthy cells while enhancing tumor-cell specificity.[14] In addition to maintaining deletion of the *ICP34.5* gene, T-VEC has further modifications summarized in **Table 1**.[15] Selective and rapid oncolysis causes release of tumor antigens and granulocyte-macrophage colony-stimulating factor (GM-CSF), thereby stimulating a local and sometimes systemic immune response against tumor cells (**Fig. 1**).[16,17]

Talimogene Laherparepvec Monotherapy: Clinical Trials

The phase III Oncovex$^{GM\text{-}CSF}$ Pivotal Trial in Melanoma (OPTiM) study is the largest randomized controlled trial studying oncolytic viruses for unresectable melanoma. In this multicenter study, patients with unresectable stage IIIB to IV melanoma were randomized in a 2:1 ratio to receive intralesional T-VEC versus subcutaneous GM-CSF. T-VEC was administered with an initial 10^6 plaque forming units (pfu)/mL dose, to

Table 1
Herpes simplex virus pathophysiology and talimogene laherparepvec modifications

Gene	Pathophysiologic Function	Modification
ICP34.5	Infection of neurons and other healthy cells	ICP34.5 deletion: tumor-selective virulence
ICP47	Inhibits HSV antigen presentation	ICP47 deletion: disinhibits antigen presentation and increases antigenicity of infected tumor cells
US11	Permits HSV-1 replication	US11 increased expression: increased viral replication and thus increased oncolytic potency
GM-CSF	Enhances dendritic cell recruitment (thereby increasing antigen presentation and T-cell activation)	GM-CSF gene insertion: release of GM-CSF on oncolysis thus strengthening local, and likely systemic, antitumor immune response

seroconvert HSV-seronegative patients. Three weeks later, 10^8 pfu/mL was then dosed once every 2 weeks thereafter. Injected volume per lesion varied from 0.1 mL to 4.0 mL based on the size of each lesion. Maximum total volume per treatment session was 4.0 mL. The GM-CSF regimen was 125 mg/m^2 subcutaneously once daily for 14 days in 28-day cycles. The primary end point was durable response rate (DRR), defined as the rate of complete response (CR) plus partial response (PR) lasting greater than or equal to 6 months and beginning within the first 12 months of therapy.[18]

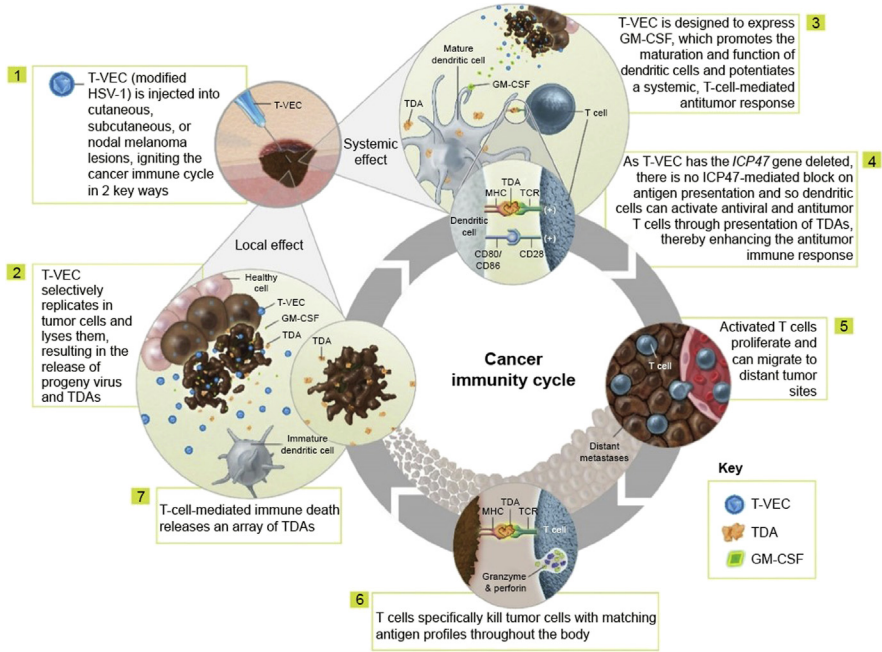

Fig. 1. Mechanism of action of T-VEC. MHC, major histocompatibility complex; TCR, T-cell receptor; TDA, tumor-derived antigen. (Used with permission of Amgen Inc.)

The OPTiM study included 436 patients in the intention-to-treat analysis, of which 57% of the patients had stage IIIB, IIIC, or IVM1a melanoma (considered lower stages in this trial). At time of final analysis, 3 years after the last patient was randomized, median duration of treatment was 23.1 weeks (range, 0.1–176.7 weeks) for T-VEC and 10 weeks (range, 0.6–120 weeks) for GM-CSF. Median follow-up time from randomization to analysis was 49 months. Regarding the primary end point, T-VEC had a favorable DRR compared with GM-CSF (**Table 2**). Exploratory analyses revealed improved T-VEC outcomes for lower melanoma stages compared with those with stage IVM1b or IVM1c disease. The following DRRs were calculated: stage IIIB/IIIC (T-VEC 33% vs GM-CSF 0%, $P<.0001$), IVM1a (24% vs 0%, $P = .0003$), IVM1b (6.3% vs 3.8%, $P = 1.0$), and IVM1c (9% vs 3.4%, $P = .67$). The primary OPTiM analysis also revealed patients had improved DRRs with T-VEC in treatment-naive disease (24% vs 0% with GM-CSF) compared with those receiving T-VEC as salvage therapy (10% vs 4% with GM-CSF).[18,19]

Systemic immune effects of local T-VEC injection were shown by responses seen in uninjected lesions, as described in **Table 3**. In addition, 5% of T-VEC patients developed vitiligo compared with 0.8% (n = 1) of GM-CSF patients, suggesting an immune response elicited against melanocyte proteins.[18]

Among responding patients, median time to response and median duration of response are summarized in **Table 2**. The final analysis of OPTiM further showed the durable response to T-VEC. Of the 17% of T-VEC–treated patients who obtained a CR, median duration of CR was not reached over a median follow-up period of 4 years.[19]

The final analysis of the OPTiM study in 2019 revealed no difference in median overall survival (OS) for T-VEC versus GM-CSF; however, in T-VEC–treated patients with CRs, the median OS was not reached, with an estimate of 90% living at 5 years[19]

A subanalysis was conducted on the OPTiM study patients who had cutaneous head and neck melanoma.[20] The T-VEC group consisted of 61 patients versus 26 patients in the GM-CSF group. T-VEC efficacy was maintained in the cutaneous head and neck melanoma subgroup because DRRs for T-VEC and GM-CSF were 36.1% versus 3.8% ($P = .001$), respectively. Notably, 29.5% of head and neck patients

Table 2
Oncovex^{GM-CSF} pivotal trial in melanoma study: response rates and timing

	T-VEC n = 295	GM-CSF n = 141	Statistical Analysis
DRR (%)	19.0	1.4	Odds ratio (95% CI): 16.6 (4.0–69.2) $P<.0001$
ORR, % (95% CI)	31.5 (26.3–37.2)	6.4 (3.0–11.8)	$P<.0001$
CR, %	16.9	0.7	—
PR (%)	14.6	5.7	—
Median Time to Response, mo (Range)[a]	4.1 (1.2–16.7)	3.7 (1.9–9.1)	—
Median Duration of Response, mo (Range)[b]	Not reached	2.8 mo	—

Abbreviation: ORR, overall response rate.

[a] Values obtained from OPTiM 2015 primary analysis. In the 2019 final analysis, median time to CR in T-VEC–treated patients was 8.6 months (range, 2.1–42.3 months).

[b] Values obtained from OPTiM 2015 primary analysis. In the 2019 final analysis, duration of response was not reached over a median 4-year follow-up period for patients treated with T-VEC and who achieved a CR.

Table 3
2015 Oncovex^{GM-CSF} pivotal trial in melanoma study primary analysis: comparison of talimogene laherparepvec–treated general study population versus talimogene laherparepvec–treated patients with cutaneous head and neck melanoma

Parameter Measured	T-VEC OPTiM General Population n = 295	T-VEC OPTiM Head and Neck n = 61
Disease Stage		
IIIB (%)	8	15
IIIC (%)	22	28
IVM1a (%)	25	18
IVM1b (%)	22	25
IVM1c (%)	23	15
IIIB + IIIC (%)	30	43
DRR, % (95% CI)	16.3 (12.1–20.5)	36.1 (24.2–49.4)
ORR, % (95% CI)	26.4 (21.4–31.5)	47.5 (34.6–60.7)
CR (%)	10.8	29.5
PR (%)	15.6	18
Injected Lesions Response	64% of injected lesions decreased ≥50% in size	Responses were identified in 63.8% of injected lesions
Uninjected Lesions Response	34% of nonvisceral and 15% of visceral lesions decreased ≥50% in size	Responses were identified in 7.9% of uninjected lesions and 10.8% of visceral lesions

Abbreviations: CR, complete response; DRR, durable response rate; ORR, overall response rate; PR, partial response; T-VEC, talimogene laherparepvec.

had a CR with T-VEC compared with 0% with GM-CSF. T-VEC also produced an effect on uninjected lesions, as summarized in **Table 3**. Median OS for GM-CSF was 25.2 months but was not reached for the T-VEC group; additionally, a multivariate sensitivity analysis to adjust for baseline characteristics calculated that T-VEC had an improved OS (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.20–0.72; $P = .003$). Compared with the original OPTiM study T-VEC group, the T-VEC–treated patients with cutaneous head and neck melanoma had a higher DRR, overall response rate (ORR), CR, and PR (see **Table 3**). Importantly, these more favorable response rates were seen in the context of a higher proportion of stage IIIB and IIIC patients in the T-VEC–treated head and neck melanoma group (43%) compared with the T-VEC–treated original study population (30%).[18,20]

In summary, the phase III OPTiM study showed that T-VEC treatment leads to improved DRR and suggested OS advantages compared with GM-CSF. Improved DRR and OS in T-VEC–treated patients were most notable for stages IIIB to IVM1a and treatment-naive patients. Local T-VEC injections also showed clinically meaningfully effects on uninjected tumors. The beneficial effects of T-VEC were maintained in the head and neck population.

Talimogene Laherparepvec Combination Therapy: Clinical Trials

Immune checkpoint inhibitors, including ipilimumab, a cytotoxic T lymphocyte–associated antigen-4 (CLTA-4) inhibitor, and pembrolizumab, an anti–programmed

death-1 (PD-1) receptor antibody, have led to improved survival responses with tolerable side effect profiles in patients with melanoma.[21] Data are maturing regarding T-VEC therapy combined with immune checkpoint inhibitors such as ipilimumab and pembrolizumab (discussed later).[10,22,23] Overall, T-VEC plus checkpoint inhibitors show promise; however, further studies and longer follow-up times are required to further elucidate the utility of T-VEC combination therapy.

Talimogene Laherparepvec Adverse Events

The OPTiM study found T-VEC to be well tolerated. The most common AEs were fatigue (50.3%), chills (48.6%), pyrexia (42.8%), nausea (35.6%), and influenzalike symptoms (30.5%). Within the T-VEC group, 11.3% of patients experienced grade 3 or grade 4 AEs versus 4.7% in the GM-CSF group. Immune-related AEs occurred in 8.1% of the T-VEC–treated patients, of which 4 events were grade 3 and there were no grade 4 immune-related AEs. Vitiligo, the presence of which suggests systemic immune response to melanocytes, was the most common immune-related AE seen in 6.2% of the T-VEC patients.[18] Overall, the incidence of grade 3 or grade 4 AEs was similar to reports for PD-1 inhibitors and lower than for CTLA-4, and T-VEC lacked the common AEs seen in immune checkpoint inhibitors, such as autoimmune thyroiditis, adrenalitis, hypophysitis, and hepatitis.[21,24,25]

Implications of Herpes Simplex Virus Oncolytic Virus and Talimogene Laherparepvec Administration

Using HSV as the oncolytic virus has several implications. First, during the phase I study of T-VEC, the initial dose of 10^8 pfu/mL had to be reduced to 10^6 pfu/mL for all HSV-seronegative patients because of pronounced AEs.[26] This dosing strategy, 10^6 pfu/mL for the first dosing session, was adopted for the subsequent phase III OPTiM study and is now the recommended strategy for all patients (**Tables 4** and **5**).[13] Baseline serology to assess HSV serostatus is not a requirement for starting

Table 4
Talimogene laherparepvec dosing schedule

Treatment Visit	Treatment Interval	Concentration (PFU/mL)	Prioritization of Lesions to be Injected
Initial	—	10^6	Inject largest lesions first. Prioritize injection of remaining lesions based on lesion size until maximum injection volume is reached or until all injectable lesions have been treated
Second	3 wk after initial treatment	10^8	Inject any new lesions (lesions that have developed since initial treatment) first Prioritize injection of remaining lesions based on lesion size until maximum injection volume is reached or until all injectable lesions have been treated
All subsequent treatments	2 wk after previous treatment	10^8	Inject any new lesions (lesions that have developed since previous treatment) first Prioritize injection of remaining lesions based on lesion size until maximum injection volume is reached or until all injectable lesions have been treated

Adapted from Imlygic® (talimogene laherparepvec) package insert. Used with permission of Amgen Inc.

Table 5
Recommended dosing ratio: injection volume to lesions size

Lesion Size (Longest Dimension) (cm)	Injection Volume[a] (mL)
>5	Up to 4
>2.5–5	Up to 2
>1.5–2.5 cm	Up to 1
>0.5–1.5 cm	Up to 0.5
≤0.5	Up to 0.1

[a] Maximum injection volume per treatment visit (eg, all lesions combined) is 4 mL.
Adapted from Imlygic® (talimogene laherparepvec) package insert. Used with permission of Amgen Inc.

T-VEC. There has been no statistically significant association between HSV serostatus and efficacy outcomes.[19,22]

The phase III OPTiM study had 16 subjects (5.5%) in the T-VEC group who developed HSV-related AEs (15 subjects developed oral herpes and 1 subject, with a past history of herpetic keratitis, had recurrence of herpetic keratitis).[18,27] Polymerase chain reaction testing was not performed to determine wild-type status, so the herpetic reactions may have been activation of dormant native HSV. T-VEC is contraindicated in immunocompromised patients because it is a live, attenuated HSV, which could lead to a life-threatening infection. Avoidance of T-VEC should also be considered on a case-by-case basis during pregnancy because of theoretic fetal risks.[28] Viral shedding risk is low and close contacts are at low risk of contracting HSV; however, patients should still be educated on viral shedding and advised to engage in safe practices, as elaborated on by Harrington and colleagues.[13,15,27,29]

T-VEC is stored at −90°C to −70°C and should be thawed at room temperature immediately before injection. T-VEC is to be injected directly into cutaneous, subcutaneous, and nodal lesions that are visible, palpable, or detectable by ultrasonography guidance using a single insertion point to create multiple tracts covering the radial distance of the needle (**Fig. 2**). Before rotating the needle to create a new tract, the needle should be withdrawn until the tip is just deep to the puncture site. This method prevents the possibility of a needle fracture from undue torque within fibrotic lesions. T-VEC does not have approval for visceral lesion injections. Lesion prioritization, T-VEC dosing, and injection frequency are summarized in **Tables 4** and **5**. Multiple injection sites, using a separate needle for each injection, may be used if the lesion is larger than the needle radial distance. If necrosis is present, injecting the border of

Fig. 2. Radial injection of (*left*) cutaneous, (*middle*) subcutaneous, and (*right*) nodal lesions. (Used with permission of Amgen Inc.)

the lesion theoretically increases chances of injecting viable tumor cells. Topical or local anesthesia may be used, but do not directly inject the lesion with anesthetic or mix anesthetic with T-VEC. The authors recommend using needles of 26 to 30 gauge for patient comfort. Small unit syringes (eg, 0.5-mL insulin syringes) enhance injection control. Needle withdrawal should be slow to prevent leakage from injection sites. After withdrawal, apply pressure with sterile gauze for 30 seconds, sterilize injection site and surrounding area with alcohol, change gloves or remove the top glove of 2 gloves, then apply an absorbent pad and dry occlusive dressing. Maintain dressing for 1 week, or longer if injection site oozing is present. Used dressings should be placed in a sealed plastic bag and discarded in the garbage.[13]

T-VEC has a biosafety level 1 classification and the risk for transmission to a healthy, adult health care worker using appropriate personal protective equipment (gowns, face shields, and gloves) is low.[15,28,29] The authors are aware of 2 reports of herpetic whitlow occurring in health care providers from accidental needle sticks during T-VEC administration.[15,27,30] T-VEC should not be prepared or administered by immunocompromised or pregnant individuals.[13,15] Some investigators have suggested the use of Luer-Lock needles to prevent needle detachment as the syringe develops high pressure when injecting fibrotic lesions.[15] Should an infection in a patient or health care provider occur, T-VEC has been designed to retain susceptibility to thymidine kinase inhibitors.[29,30] Of note, avoidance of thymidine kinase inhibitors in patients receiving T-VEC is recommended because of the potential to decrease oncolytic effect.[13]

Talimogene Laherparepvec Systemic Immune Effects and Pseudoprogression

The systemic immune effects of T-VEC are theorized to be caused by release of local tumor-derived antigens and virally encoded GM-CSF on destruction of injected tumor cells. Biopsies of regressing lesions, both injected and uninjected, from 11 T-VEC–treated patients were associated with the presence of MART-1 (melanoma antigen recognized by T cells 1)–specific cluster of differentiation (CD) $^{+}$8 T cells and a reduction in CD4^{+} regulatory T cells, providing evidence for systemic immune effects.[16,17] Benefits of systemic immune effects of T-VEC are noticed clinically (see **Table 3**).

A well-reported phenomenon related to the immunotherapies, including T-VEC, is pseudoprogression.[31,32] Pseudoprogression has been defined as a greater than 25% increase in total baseline tumor area or tumor burden or the appearance of a new lesion before clinical improvement.[17] Forty-eight percent of the T-VEC–treated OPTiM subjects who had a durable response experienced pseudoprogression before response (PPR). Importantly, PPR led to a delay in achieving durable response by approximately 3 months compared with those who did not experience PPR; however, there was no difference in duration of response or survival for those experiencing PPR.[17]

Pseudoprogression can create challenging clinical assessments of worsening tumor burden in the face of forthcoming improvement. There is not enough evidence to stratify T-VEC patients at greatest risk of pseudoprogression.[17] Immune-related response criteria or immune-related Response Evaluation Criteria in Solid Tumors (RECIST) can account for pseudoprogression and are more clinically appropriate for monitoring response to immunotherapies compared with the World Health Organization (WHO) criteria or RECIST.[15,32,33] Investigators have recommended maintaining T-VEC treatment for at least 6 months, as clinically appropriate, in anticipation of improvement of lesions.[13,15,19] This recommendation is consistent with OPTiM methodology of continuing treatment for at least 6 months regardless of occurrence of progressive disease (unless clinically appropriate alternative therapies are indicated).[18]

Table 6
Noteworthy ongoing clinical trials of injectables in melanoma

Study Agent	Description	Interventions	Phase	Clinical Trial
Nonviral Agents				
PV-10	Rose Bengal (inflammatory dye)	PV-10 vs systemic dacarbazine, temozolomide, or intralesional T-VEC	Phase III	NCT02288897
		PV-10 + pembrolizumab vs pembrolizumab	Phase Ib/II	NCT02557321
Tilsotolimod (IMO-2125)	TLR9 agonist	Intratumoral tilsotolimod + ipilimumab vs ipilimumab	Phase III	NCT03445533
CMP-001	TLR9 agonist	CMP-001 + nivolumab	Phase II	NCT03618641
		CMP-001 + pembrolizumab	Phase IB	NCT02680184
IL-2 and BCG	Inflammatory cytokine and attenuated *M bovis*	IL-2 + BCG vs IL-2	Phase II/III	NCT03928275
Viral Agents				
T-VEC	Herpesvirus	T-VEC + pembrolizumab vs placebo + pembrolizumab	Phase Ib/III	NCT02263508
		T-VEC neoadjuvant + surgery vs immediate surgery	Phase II	NCT02211131
		T-VEC + pembrolizumab	Phase II	NCT02965716
		Autologous CD1c (BDCA-1)$^{+}$ myeloid dendritic cells + T-VEC	Phase II	NCT03747744
		T-VEC + hypofractionated radiotherapy vs T-VEC	Phase I	NCT02819843
		T-VEC + nivolumab	Phase II	NCT04330430
		T-VEC + pembrolizumab	Phase II	NCT03842943
		T-VEC + dabrafenib + trametinib	Phase Ib	NCT03088176
HF10	Herpesvirus	HF10 + nivolumab	Phase II	NCT03259425
ONCOS-102	Adenovirus	ONCOS-102 + pembrolizumab	Phase I	NCT03003676
OBP-301	Adenovirus	OBP-301	Phase 2	NCT03190824
CVA21	Coxsackievirus	CVA21 + pembrolizumab	Phase I	NCT02565992
		CVA21 + ipilimumab	Phase I	NCT02307149
PVSRIPO	Poliovirus/rhinovirus	PVSRIPO	Phase I	NCT03712358

Abbreviations: BCG, bacillus Calmette-Guérin; TLR, toll-like receptor.

Postmarket Studies

Although a large portion of OPTiM study subjects (45%) had advanced-stage disease (IV1b/IV1c), postmarketing case series of T-VEC monotherapy have shown better efficacy data than the OPTiM study owing to these primarily evaluating melanoma stage IIIB to IVM1a disease.[34–37] A case series, COSMUS-1 (Clinical Observational Study of talimogene laherparepvec use among Melanoma patients in routine clinical practice in the United States), included 76 patients, of whom 39% had stage IVM1b/c disease (compared with 45% in OPTiM). Patients received T-VEC as monotherapy (22%) or any combination of immunotherapy, targeted therapy, radiation, or chemotherapy occurring before, concurrent with, or after T-VEC therapy. Of patients completing T-VEC therapy, 19.7% achieved CR or no remaining injectable lesions, findings comparable with OPTiM (16.9% CR).[38]

Advancing the Clinical Utility of Talimogene Laherparepvec

T-VEC has the potential to advance melanoma treatment in a variety of situations. It can be considered for salvage therapy in patients having failed systemic chemotherapy and immunotherapy.[37,39,40] Given the lack of approved neoadjuvant treatment of resectable stage IIIB to IVM1a melanoma, an ongoing randomized controlled trial is assessing the utility of T-VEC as a neoadjuvant therapy (ClinicalTrials.gov identifier: NCT02211131).[41] One-year analysis of 150 patients with stage IIIB to IVM1a melanoma allocated in a 1:1 ratio for T-VEC neoadjuvant plus surgical resection versus surgical resection alone revealed recurrence-free rates of 33.5% versus 21.9% (HR, 0.73; $P = .048$) in favor of T-VEC neoadjuvant therapy.[41]

Other Available Injectables

Intralesional IL-2 is characterized as having a strong local response rate, minimal systemic response, and tolerable side effect profile. A phase II study evaluating IL-2 in 51 patients with metastatic melanoma found CR rates for 6 months or longer in 70% of injected metastases. However, there was no response in distant, uninjected metastases, which is a major limitation.[42] A 2014 systematic review analyzed 49 studies of IL-2 use for in-transit melanoma and found 78% CR rate per lesion and 50% CR rate per subject.[43] In contrast with the severe side effects seen with systemic IL-2, intralesional IL-2 is well tolerated from an AE perspective.[42,43] IL-2 is expensive, and each lesion requires multiple injections per week, which limits its clinical utility.

Rose Bengal is a photosensitizing dye selectively taken up by tumor-cell lysosomes. PV-10, a 10% Rose Bengal solution, has preliminary results suggesting efficacy in injected and uninjected metastatic melanoma lesions. PV-10 is only available in the clinical trial setting. The phase II study revealed an ORR of 51% in injected lesions and an ORR of 33% in uninjected lesions.[44] In addition, a phase Ib/II study comparing PV-10 plus pembrolizumab versus pembrolizumab alone is currently recruiting [NCT02557321].

Ongoing Clinical Trials

Table 6 summarizes ongoing investigations into intralesional treatments for melanoma.

SUMMARY

Head and neck cutaneous melanomas are challenging to treat, often because of the limited potential for surgical resection. Intratumoral injectables offer the benefit of local and potentially systemic responses, which are of particular value in unresectable

lesions. T-VEC, an attenuated oncolytic HSV-1, is currently the most clinically relevant injectable for cutaneous melanoma. T-VEC has been shown to improve DRR, with suggested OS advantages compared with systemic GM-CSF therapy in patients with stage IIIB to IVM1a unresectable melanoma. These benefits are also most noticed in treatment-naive patients. The efficacy of T-VEC is maintained in patients with head and neck melanoma. The benefits of T-VEC are supported by real-world-use postmarketing studies. T-VEC plus systemic immunotherapies are being studied with promising preliminary data; however, the clinical utility of combination therapy is limited until more data are available. There are numerous ongoing clinical trials investigating other viral and nonviral injectables.

CLINICS CARE POINTS

- Ultrasound guidance can make injection of deeper tumors easier and more accurate.
- T-VEC is generally well tolerated with manageable flu-like reactions.
- Viral shedding risk is low but pregnant and immunocompromised individuals should be guarded against handing post injection drainage or contaminated bandages.
- T-VEC has been designed to retain susceptibility to thymidine kinase inhibitors.

DISCLOSURE

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