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ORIGINAL ARTICLE – MELANOMA

Efficacy of Talimogene Laherparepvec (T-VEC) Therapy in Patients with In-Transit Melanoma Metastasis Decreases with Increasing Lesion Size

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ABSTRACT

Background. Talimogene laherparepvec (T-VEC) is the first injectable oncolytic viral therapy approved for in-transit melanoma metastasis, with a reported overall response rate (ORR) of 25% and complete response rate (CRR) of 10%. To ascertain the role of patient selection on outcomes in routine practice, we evaluated the impact of patient, lesion, and treatment factors on clinical response.

Methods. Medical records were extracted for patients with recurrent stage IIIB–IV melanoma completing T-VEC at Duke University Medical Center between 1 January 2016 and 1 September 2018. Kaplan–Meier analysis assessed time to response and survival, while logistic regression measured associations of clinicopathologic status, lesion burden, T-VEC dosing, and use of prior and concurrent therapy with ORR and CRR.

Results. Of 27 patients, an objective response was observed in 11 (40.7%), including one patient with partial response (3.7%) and 10 with complete response (37.0%). Time to complete response and overall response was a median 22 weeks (95% confidence interval [CI] 2.0–41.9 weeks and 15.8–28.2 weeks, respectively), and median progression-free survival was 17 weeks (95% CI 0–36 weeks). Logistic regression demonstrated each millimeter increase in maximum lesion diameter predicted decreased ORR (odds ratio [OR] 0.866, 95% CI 0.753–0.995; $p = 0.04$). Stage IV disease (OR 0.04, 95% CI 0.00–0.74; $p = 0.031$) and programmed death-1 inhibitor treatment (OR 0.06, 95% CI 0.01–0.74; $p = 0.028$) also predicted reduced clinical response.

Conclusions. This study corroborates recent data suggesting response rates to T-VEC may be higher than reported in clinical trials, arising in part from patient selection. T-VEC lesion diameter was persistently associated with clinical response and is a readily assessed predictor of successful T-VEC therapy.

After appropriate initial surgical therapy for primary melanoma, approximately 4–10% of patients will develop in-transit metastasis at a median of 18 months from primary excision.[1] In-transit melanoma represents a distinct pattern whereby disease recurs as dermal or subcutaneous nodules between the primary melanoma site and the regional lymph node basin.[2] A significant proportion of patients with advanced locoregional disease proceed to develop concurrent regional node or distant disease.[3]

Intralesional therapy for in-transit melanoma has shown promise given its ease of access to lesions of the head, neck, trunk, and extremities, as well as fewer systemic adverse effects relative to regional chemotherapy.[4] Talimogene laherparepvec (T-VEC; Imlygic™, Amgen), an attenuated herpes simplex virus I (HSV-I) modified to produce granulocyte macrophage colony-stimulating factor (GM-CSF), was the first oncolytic virus approved as first-line intralesional therapy for advanced locoregional melanoma.[5–7] In a phase III trial of 436 patients with unresectable, injectable stage IIIB–IV melanoma, T-VEC

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therapy resulted in overall response rates (ORRs) of 26.4%, complete response rates (CRRs) of 10.8%, and durable response rates (DRRs) of 16.3%.[6]

While randomized trials provide the best means to determine treatment effect size, the entry of T-VEC into real-world practice settings has demonstrated ORRs of up to 88.5%.[8–10] However, the role of patient selection in driving clinical response to therapy is not well-defined. In-transit lesion number and size, for instance, have been identified as significant predictors of distant metastasis, but not specifically of clinical response rates.[3,11] The following case series reports the experiences and outcomes of stage IIIB–IV melanoma patients with locoregional and in-transit disease treated with T-VEC by an interdisciplinary melanoma group within a single academic center, and assesses the impact of patient, lesion, and treatment characteristics on clinical response.

METHODS

With Institutional Review Board approval (IRB Pro00100097), we conducted a retrospective review of patients at Duke University Medical Center treated with T-VEC for stage IIIB–IV melanoma from 1 January 2016 to 1 September 2018. Medical records were reviewed for the following variables: demographics, clinicopathologic characteristics (disease stage [American Joint Committee on Cancer 8th edition], primary tumor location and depth, and BRAF V600 E or K mutation status), T-VEC treatment parameters (maximum treated in-transit lesion diameter at first treatment, maximum number of lesions treated, number of injection cycles performed, average dose), use of postoperative adjuvant therapy, treatment with systemic or locoregional agents after recurrence, and concurrent therapy. Patients were evaluated for treatment response based on Response Evaluation Criteria in Solid Tumors (RECIST) principles, survival, and current status (e.g. follow-up, living or deceased).[12,13]

Treatment Protocol

Patients were treated by one of three surgeons within a multidisciplinary melanoma group, and T-VEC was administered in accordance with the manufacturer guidelines. The first dose was administered at 10^6 plaque-forming units (pfu) per milliliter (mL) to evaluate safety and prime HSV-naive patients. Subsequent T-VEC doses were administered at 10^8 pfu/mL 3 weeks after the first dose and then every 2 weeks until progression of disease (PD), treatment response, or treatment-limiting toxicity.

Injections were primarily administered to cutaneous epidermotropic and subcutaneous lesions. Two patients received T-VEC for both their cutaneous in-transit disease and intranodal masses of the axilla and groin, respectively. No patients received visceral injections. At each treatment, multiple lesions were injected, with priority given to larger and newer lesions, until either eight lesions had been treated or the upper limit treatment volume of 4 mL had been administered. As with the OPTiM trial protocol, not all lesions were required to be treated during each treatment or overall treatment course.[6] For patients with more than eight lesions, injection sites were alternated between treatments. For patients whose numerous in-transit deposits presented in tighter clusters (each lesion within 2 cm of another), at least one lesion in each cluster was treated, prioritizing the most proximal lesion when located on an extremity.

At each outpatient visit, patients were clinically evaluated by physical examination and manual measurement of adequately superficial lesions. For deeper lesions not amenable to manual measurement, periodic cross-sectional imaging was used to derive measurements for response determination. PD was determined by the appearance of one or more new in-transit lesions or enlargement of existing lesions. Complete response (CR) was assigned following resolution of all documented lesions, whereas partial response (PR) was assigned for a mixed decrease in select in-transit lesions with simultaneous stability of others. In accordance with RECIST, responders to T-VEC were required to maintain their clinical status for at least 4 weeks before being confirmed as an initial CR or PR, otherwise being assigned as stable disease (SD).[13] SD was assigned for patients experiencing neither progression nor response of treated lesions for a minimum 6 weeks. Patients not meeting this criterion were recorded as not evaluable (NE) if insufficient follow-up, or PD for increased lesion burden. End-of study 'best overall response', as defined by RECIST, was also determined to capture interval PD after initial treatment response had already been recorded.[13]

For epidermotropic in-transits that were still identifiable after flattening (e.g. residual pigment), confirmatory biopsies were performed. For resolving subcutaneous lesions without overlying traces of disease or pigmentation, and given the unreliability of blind biopsy, most assessments of PR or CR were clinically determined through a combination of physical examination with manual measurement of subcutaneous deposits and cross-sectional imaging.

Statistical Analyses

The primary endpoints were ORR and CRR, where ORR represents the sum of the CR and PR rates. DRR, defined as CR or PR lasting continuously for 6 months or more, was also evaluated. Kaplan–Meier analysis was used to assess

TABLE 1 Clinicopathologic characteristics of patients undergoing T-VEC therapy

Patient characteristics	*N* = 27 patients
Age, years [median (IQR)]	67 (57.5–76.5)
Sex	
Male	12 (44.4)
Female	15 (55.6)
Location of primary tumor	
Extremities	17 (63.0)
Abdomen/trunk	4 (14.8)
Head/neck	6 (22.2)
Primary tumor stage	
I	8 (29.6)
II	10 (37.0)
III	8 (29.6)
Stage at T-VEC treatment	
IIIB	4 (14.8)
IIIC	16 (59.3)
IV	7 (25.9)
M1a	3 (11.1)
M1b	1 (3.7)
M1c	2 (7.4)
M1d	1 (3.7)
BRAF status	
Wild-type	17 (63.0)
Mutant	9 (33.3)
Unknown	1 (3.7)
Any prior treatment	17 (62.9)
Chemotherapy (including ILI)	7 (25.9)
Anti-CTLA4	8 (29.6)
Anti-PD-1	16 (59.3)
BRAF/MEK inhibitor	4 (14.8)
Interleukin-2	2 (7.4)
Interferon-α	3 (11.1)
Adjuvant treatment	8 (29.6)
Radiation	4 (14.8)
Interferon	2 (7.4)
Interferon and anti-PD-1	1 (3.7)
Anti-CTLA4	1 (3.7)
Concurrent treatment (all anti-PD-1)	7 (25.9)

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *ILI* isolated limb infusion, *T-VEC* talimogene laherparepvec, *PD-1* programmed death-1, *CTLA4* cytotoxic T-lymphocyte-associated protein 4

[a]Patients may have received one, multiple, or a combination of agents in the adjuvant setting, as well as prior to, concurrently, and/or after T-VEC therapy

the time to clinical response, as well as median overall survival (OS) and progression-free survival (PFS). Bivariate logistic regression evaluated the impact of patient, disease, and treatment characteristics on clinical response, with an alpha of 0.05 set as the threshold for significance. All statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Demographics and Clinicopathologic Characteristics

Twenty-seven patients completed T-VEC treatment for stage IIIB–IV locoregional melanoma. Fifteen (56%) patients were female, with a median age of 67 years (interquartile range [IQR] 57.5–76.5). At initiation of T-VEC therapy, 4 (14.8%) patients had stage IIIB disease, 16 (59.3%) had stage IIIC disease, and 7 (25.9%) had stage IV disease. Eight (29.6%) patients had a known BRAF V600 E or K mutation. Most patients (n = 17, 63%) had previously presented with a primary extremity melanoma, with 4 (14.8%) and 6 (22.2%) presenting with trunk and head or neck primary lesions, respectively. Patients were followed for a median of 67 weeks (range 12–133 weeks). These and other patient characteristics are summarized in Table 1.

Talimogene Laherparepvec Treatment Characteristics

A mean of 3.7 ± 2.4 standard deviation in-transit lesions were injected per treatment, with a mean maximum lesion diameter of 21.9 ± 17.7 mm at first treatment. A majority of patients (n = 23, 85.2%) had at least one lesion over 10 mm. Excluding repeat treatment courses with T-VEC (four cases), 14 patients (51.9%) received T-VEC in all noted in-transit lesions, while three patients (11.1%) with numerous in-transit deposits (e.g. more than eight lesions) received T-VEC to varied lesions on an alternating basis per the aforementioned treatment protocol. The remaining 10 patients (37.0%) did not receive T-VEC in all noted lesions. Patients underwent 1–35 cycles of treatment, at a median of four cycles (IQR 3–9 cycles). Cumulative T-VEC volume per treatment ranged from 0.1 to 4 mL, with patients receiving a median 0.50 mL (IQR 0.20–1.0 mL) at the 10^6 pfu/mL test dose, and a median 0.49 mL (0.20–0.87 mL) across 10^8 pfu/mL treatment doses.

Adjuvant and Prior Therapy

In this cohort, 24 (88.8%) patients also received some form of non-operative therapy prior to, concurrently, and/or after receiving T-VEC therapy, the specific agents for which are summarized in Table 1. Eight patients (29.6%)

TABLE 2 Clinical response to T-VEC, initial response, and best overall response

Clinical response	Initial response (N = 27)		Best overall response (N = 27)	
	n	%	*n*	%
Complete response	10	37	6	22.2
Not evaluable	3	11.1	1	3.7
Progression of disease	10	37	12	44.4
Partial response	1	3.7	1	3.7
Stable disease	3	11.1	7	25.9

Complete or partial responses were recorded only if the patient maintained their status for 4 weeks. Stable disease was recorded after a minimum of 6 weeks. Patients who met neither criteria prior to progression or were lost to follow-up were deemed 'not evaluable'. Initial response was recorded after the first definitive change in lesion status following initiation of T-VEC. Best overall response was determined at the end of the study period after accounting for interval disease progression

T-VEC talimogene laherparepvec

TABLE 3 Adverse events following T-VEC therapy

Adverse events	N = 36 events	
	n	%
Constitutional (fatigue, fever, chills, flu-like symptoms, headache)	17	47.2
Local injection site (erythema, bleeding, bruising, cellulitis)	10	27.8
Diffuse cutaneous (rash, pruritus)	3	8.3
Oral mucositis	2	5.6
Nausea, vomiting	2	5.6
Bullous pemphigoid	1	2.8
Herpes simplex virus infection	1	2.8

T-VEC talimogene laherparepvec

received therapy in the adjuvant setting following complete surgical excision. Most patients (n = 17, 62.9%) received prior systemic or locoregional therapy in the setting of recurrent or progressive disease. Of 18 (66.7%) total patients who received PD-1 inhibitor therapy, 7 (25.9%) received treatment concurrently with T-VEC. All concurrent treatments consisted solely of PD-1 inhibitor therapy (pembrolizumab or nivolumab).

Response to Therapy

Among patients' initial courses of T-VEC treatment (excluding patients undergoing retreatment following treatment cessation), ORR was 40.7% (11/27), with median time to response of 22 weeks (95% confidence interval [CI] 16–28 weeks). CRR was 37.0% (10/27) at a median 22 weeks (95% CI 2–42). Ten patients (37.0%) achieved a 6-month durable response. Median OS was not reached over the study period, while median PFS among the initial courses of T-VEC therapy was 17 weeks (95% CI 0–36 weeks). Both clinical responses to T-VEC therapy and best overall response (factoring in interval disease progression) are summarized in Table 2. Four (3.7%) patients underwent retreatment after previously stopping therapy, two of whom progressed following a prior CR, one who progressed from prior SD, and one who experienced prior treatment-limiting cellulitis. When these repeat courses of treatment were included in the analysis, median PFS increased to 21 weeks (96% CI 0–49 weeks) across the study cohort.

Treatment-Related Adverse Events

Twenty-three patients (85%) had an adverse reaction to T-VEC (Table 3). Most experienced only mild symptoms such as low-grade fever and chills. One patient developed a mild HSV infection at their injection sites, which resolved with a single course of oral valacyclovir. Two patients developed mucositis and bullous pemphigoid, respectively, each requiring treatment with oral cortisteroids. All three patients were receiving concurrent PD-1 inhibitor therapy. Three patients (11%) developed grade 3 or 4 adverse events (CRC AE v 5.0), i.e. one case of high fevers and two cases of cellulitis requiring debridement and antibiotics. One patient requiring debridement for cellulitis had received concurrent PD-1 inhibitor therapy. All patients

who developed adverse events were successfully treated and experienced complete recovery.

Predictors of Treatment Response

In logistic regression analysis including only initial courses of T-VEC treatment, each millimeter increase in maximum lesion diameter at first injection cycle was significantly associated with lower odds of overall response (odds ratio [OR] 0.866, 95% CI 0.753–0.995; $p = 0.042$) (Table 4a). The odds of CR were similarly decreased with increasing lesion diameter, although this did not achieve statistical significance (OR 0.900, 95% CI 0.804–1.007; $p = 0.067$) (Table 4b).

A history of treatment with PD-1 inhibitors predicted substantially decreased CRR and ORR (both OR 0.06, 95% CI 0.01–0.74; $p = 0.028$). Use of any prior systemic or locoregional therapies similarly predicted decreased CRR (OR 0.07, 95% CI 0.01–0.97; $p = 0.047$). Aside from the presence of stage III disease at primary tumor diagnosis (OR 0.05, 95% CI 0.00–0.67, $p = 0.024$), clinical stage was not significantly predictive of treatment response when including initial courses of T-VEC.

When considering all courses of treatment, including four cases of retreatment, increasing maximum lesion diameter was associated with a lower CRR (OR 0.89, 95% CI 0.80–0.99, $p = 0.040$) (Table 4c, d). Likewise, the use of PD-1 inhibitor therapy, in particular, predicted decreased CRR (OR 0.05, 95% CI 0.01–0.57; $p = 0.015$). The presence of both stage III disease at primary diagnosis and stage IV disease at the time of T-VEC initiation were each associated with decreased ORR (OR 0.04, 95% CI 0.00–0.56, $p = 0.017$; and OR 0.04, 95% CI 0.00–0.74, $p = 0.031$, respectively).

DISCUSSION

This single-institution study found a higher response rate than originally reported in the OPTiM trial, and reports the association of response rate with maximum treated lesion size. Over 40% of patients in our cohort achieved an overall response to therapy, with nearly all responders achieving CR, and marginally lower 6-month DRRs.

Clinical predictors of decreased response included increasing maximum lesion diameter, prior systemic therapy, and higher clinical stage. Prior PD-1 inhibitor use, but not concurrent PD-1 administration, was significantly associated with lower response. An important observation in our study is the inverse relationship between lesion size and response, which highlights the impact of patient selection when initiating T-VEC therapy. Restated in terms of probabilities, logistic regression predicted a 50% chance of overall response with a 1.5 cm lesion, $< 10\%$ with lesions exceeding 3.1 cm, and $< 1\%$ with lesions above 4.7 cm (Nagelkerke $r^2 = 0.42$, $p = 0.042$). While establishing a threshold for T-VEC treatment based on the said univariate model is not appropriate, lesion size may still provide useful means by which to identify patients at higher risk for limited clinical response. Stratification may in turn accelerate initiation of other potentially effective agents such as anti-PD-1 therapy, targeted BRAF/MEK inhibitors, isolated limb infusion, or even combination systemic therapy, with or without intralesional T-VEC.[14]

As observed in recent case series, our ORR and CRR exceed those reported in the OPTiM trial (ORR 41% vs. 26.4%; CRR 37% vs. 10.8%).[6] Disease staging at treatment likely played an important role; 70% of participants in OPTiM had stage IV disease, compared with one-quarter of patients in this study.[6] Indeed, only one stage IV patient (of seven) in this study responded to T-VEC, while response rates of 50% were seen among stage III patients. Relative burden of locoregional disease, represented by lesion size and number, comprises another potential driver of improved clinical response in this study. OPTiM participants were required to have, at minimum, one in-transit lesion exceeding 10 mm in diameter, whereas our cohort included four patients (15%) with a maximum in-transit lesion diameter < 10 mm.[6]

Differential use of systemic therapies may also explain disparate response rates between this study and OPTiM. As demonstrated previously, combination T-VEC with either pembrolizumab or ipilimumab have resulted in a near doubling of the response rates observed within OPTiM.[15,16] In our analysis, seven (25.9%) patients received concurrent T-VEC and PD-1 inhibitor, compared with only 1.4% of OPTiM patients receiving both agents together or apart at any point in their therapy.[6] Conversely, there was a non-significant trend predicting lower clinical response rates with concurrent therapy, suggesting that the use of combination therapy may not have contributed to higher observed response rates. Furthermore, use of prior systemic therapy in the setting of recurrent or progressive disease, or adjuvant therapy following oncologic resection, both predicted significantly lower odds of clinical response in our analysis. These data echo the findings of Louie et al., whereby previously treatment-naive patients undergoing T-VEC injections experienced greater DRRs than patients who had received one or more lines of pre-T-VEC therapy.[10]

The observed inverse relationship between prior therapies, including PD-1 inhibitors, and clinical response presents an apparent paradox with trials of successful concurrent therapy. However, it is critical to note that patients in our cohort with a history of prior systemic therapy also experienced progressive or recurrent disease

TABLE 4 Impact of clinicopathologic characteristics on (a) complete and (b) overall response rates after initial courses of T-VEC, and (c) complete response and (d) overall response rates after adding repeat courses of T-VEC

Predictor	OR	Lower 95% CI	Upper 95% CI	*p* value
(a) Complete response rates, initial courses of treatment				
Age (years)	0.97	0.91	1.03	0.269
Male sex	0.38	0.07	1.99	0.253
Stage at diagnosis				
I[a]	1.00			
II	0.22	0.03	1.71	0.148
III	NA	NA	NA	NA
Stage at treatment				
IIIB[a]	1.00			
IIIC	0.26	0.02	3.06	0.284
IV	NA	NA	NA	NA
Primary tumor location				
Extremity[a]	1.00			
Abdomen/trunk	0.61	0.05	7.24	0.696
Head/neck	1.83	0.28	12.07	0.528
BRAF V600 E or K mutant	0.41	0.07	2.58	0.341
Maximum number of treated lesions	0.96	0.68	1.35	0.808
Maximum initial lesion diameter (mm)	0.90	0.80	1.01	0.067
Number of treatment cycles	1.05	0.95	1.17	0.334
Average test dose (10^6 pfu/mL)	0.59	0.24	1.44	0.246
Average therapeutic dose (10^8 pfu/mL)	0.64	0.26	1.58	0.331
Any prior therapy				
None[a]	1.00			
PD-1	0.06[b]	0.01	0.74	0.028
Other	0.07[b]	0.01	0.97	0.047
Adjuvant therapy	NA	NA	NA	NA
Concurrent therapy	0.60	0.09	3.89	0.592
(b) Overall response rates, initial courses of treatment				
Age (years)	0.98	0.92	1.03	0.406
Male sex	0.29	0.06	1.53	0.144
Stage at diagnosis				
I[a]	1.00			
II	0.22	0.03	1.71	0.148
III	0.05[b]	0.00	0.67	0.024
Stage at treatment				
IIIB[a]	1.00			
IIIC	0.26	0.02	3.06	0.284
IV	0.06	0.00	1.23	0.068
Primary tumor location				
Extremity[a]	1.00			
Abdomen/trunk	0.48	0.04	5.58	0.555
Head and neck	1.43	0.22	9.26	0.708
BRAF V600 E or K mutant	0.32	0.05	2.02	0.226
Maximum number of treated lesions	1.09	0.78	1.52	0.629
Maximum lesion diameter (mm)	0.866[b]	0.75	1.00	0.042
Number of treatment cycles	1.07	0.95	1.20	0.255
Average test dose (10^6 pfu/mL)	0.57	0.24	1.37	0.206
Average therapeutic dose (10^8 pfu/mL)	0.61	0.25	1.49	0.280

TABLE 4 continued

Predictor	OR	Lower 95% CI	Upper 95% CI	*p* value
Any prior therapy				
None[a]	1.00			
PD-1	0.06[b]	0.01	0.74	0.028
Other	0.12	0.01	1.58	0.107
Adjuvant therapy	0.13	0.01	1.26	0.078
Concurrent therapy	0.49	0.08	3.15	0.451
(c) Complete response rates, including repeat treatment courses				
Age (years)	0.99	0.94	1.04	0.661
Male sex	0.50	0.12	2.14	0.350
Stage at diagnosis				
I[a]	1.00			
II	0.20	0.03	1.43	0.109
III	NA	NA	NA	NA
Stage at treatment				
IIIB[a]	1.00			
IIIC	0.25	0.02	2.70	0.253
IV	NA	NA	NA	NA
Primary tumor location				
Extremity[a]	1.00			
Abdomen/trunk	0.34	0.03	3.69	0.378
Head/neck	1.83	0.32	10.57	0.498
BRAF V600 E or K mutant	0.52	0.10	2.63	0.432
Maximum number of treated lesions	0.93	0.68	1.28	0.670
Maximum lesion diameter (mm)	0.89[b]	0.80	1.00	0.040
Number of treatment cycles	1.05	0.95	1.17	0.337
Average test dose (10^6 pfu/mL)	0.61	0.27	1.41	0.248
Average therapeutic dose (10^8 pfu/mL)	0.59	0.25	1.44	0.249
Any prior therapy				
None[a]	1.00			
PD-1	0.05[b]	0.01	0.57	0.015
Other	0.05[b]	0.00	0.67	0.024
Adjuvant therapy	NA	NA	NA	NA
Concurrent therapy	0.36	0.06	2.19	0.270
(d) Overall response rates, including repeat treatment courses				
Age (years)	0.99	0.95	1.05	0.822
Male sex	0.39	0.09	1.67	0.204
Stage at diagnosis				
I[a]	1.00			
II	0.20	0.03	1.43	0.109
III	0.04[b]	0.00	0.56	0.017
Stage at treatment				
IIIB[a]	1.00			
IIIC	0.25	0.02	2.70	0.253
IV	0.04[b]	0.00	0.74	0.031
Primary tumor location				
Extremity[a]	1.00			
Abdomen/trunk	0.28	0.03	2.97	0.278
Head and neck	1.48	0.26	8.50	0.659

TABLE 4 continued

Predictor	OR	Lower 95% CI	Upper 95% CI	*p* value
BRAF V600 E or K mutant	0.43	0.09	2.15	0.303
Maximum number of treated lesions	1.04	0.77	1.42	0.782
Maximum lesion diameter (mm)	0.86[b]	0.75	0.98	0.027
Number of treatment cycles	1.07	0.95	1.20	0.251
Average test dose (10^6 pfu/mL)	0.59	0.26	1.34	0.206
Average therapeutic dose (10^8 pfu/mL)	0.57	0.24	1.37	0.211
Any prior therapy				
None[a]	1.00			
PD-1	0.05[b]	0.01	0.57	0.015
Other	0.09	0.01	1.08	0.058
Adjuvant therapy	0.11	0.01	1.04	0.055
Concurrent therapy	0.31	0.05	1.84	0.196

T-VEC talimogene laherparepvec, *OR* odds ratio, *CI* confidence interval, *pfu* plaque-forming units, *PD-1* programmed death-1, *NA* not applicable

[a]Each predictor was evaluated against the designated reference category using bivariate logistic regression

[b]Significant at $p < 0.05$

before initiating T-VEC. Moreover, six of seven patients (85.7%) who received concurrent therapy in this study initiated PD-1 inhibitors first, and added T-VEC in the setting of minimal treatment response. While we are unable to definitively comment on the utility of T-VEC as salvage therapy given a limited patient population, heavily pre-treated patients, particularly those receiving immune checkpoint blockade inhibitors, may represent a subgroup with a more treatment refractory disease biology. Nonetheless, the optimal role and sequencing of T-VEC as a salvage or adjunctive agent to systemic therapy for in-transit melanoma requires further study.

While the objective response rate in our study exceeds that observed in the OPTiM trial, a higher response rate was also reported by Louie et al.,[10] in the largest and only multi-institutional retrospective study to date. As with the OPTiM trial, discrepancies between our study and recent retrospective studies, which report ORRs over 50%, likely arise from patient selection.[8–10] Only 30% of patients in our study were treatment-naive, relative to 43% of patients studied by Louie et al., and may thus represent a cohort less amenable to T-VEC.[10] Two other case series, reporting ORRs above 50%, reported results from patients with a maximum stage of IVM1a, whereas our study included four patients who were IVM1b or higher, nearly half of our stage IV population.[8–10]

Our analysis should be interpreted in the context of its limitations. Foremost, improved response rates observed in our cohort, relative to those studied in clinical trials, are likely attributable to selection bias from differences in staging and the use of systemic therapy. Together, these disparities limit direct comparison of therapeutic responses between in-trial and out-of-trial cohorts.

It should also be noted that measurement of treated lesions, as conducted in this study, serves best as a useful indicator, rather than global assessment, of disease burden; besides cross-sectional surveillance imaging, data for visceral lesion burden were not formally analyzed as may be expected with true RECIST response evaluation. As such, both treatment and evaluation of clinical response are subject to interprovider variation and measurement bias. Similarly, records of global lesion burden varied between providers, often without a positron emission tomography/computed tomography (PET/CT) imaging correlate immediately preceding treatment. This, in part, contributed to our reporting the maximum number of treated lesions, for which data were consistently available. While the choice of maximum lesion diameter at first treatment may limit precise characterization of overall lesion burden, this parameter favors ease of use, rapid interpretation, and offers timely risk stratification to inform conversations with patients upon starting T-VEC therapy.

Finally, our study is a retrospective single-center analysis of limited sample size. A larger analysis with greater statistical power should be conducted to validate these findings. Moreover, a true multivariate logistic regression including all posited drivers of clinical response was not feasible, given the lack of sufficient patients and variability for statistical comparison. Subgroup analyses could ameliorate residual confounding e.g. from varied therapeutic regimens, and would be feasible within a larger study population. We aim to address these concerns in the short-term by creating an institutional prospective database that will accrue additional patients, capture predictors of clinical response, and allow long-term evaluation of recurrence

and survival endpoints. In the long-term, a multicenter approach will provide more generalizable data to best characterize predictors of T-VEC response.

CONCLUSIONS

In an out-of-trial cohort, responses to T-VEC therapy may be higher than suggested by clinical trials. Application of T-VEC therapy in overall lower-stage patients with lower in-transit disease burden may play significant roles in improved clinical response. In-transit lesion diameter, as an addition to clinical stage and prior use of systemic therapy, is a rapidly assessed and useful indicator of successful T-VEC therapy. Prospective and/or larger multicenter trials would be advisable prior to implementing lesion diameter among formal patient selection criteria.

AUTHORS' CONTRIBUTION GB, PM, and JS were responsible for treating patients and recording clinical experiences in electronic medical records. SM and JH conducted a review of medical records, conducted data analysis, and prepared this manuscript.

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