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ORIGINAL REPORT

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

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ABSTRACT

Purpose
Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses. T-VEC was compared with GM-CSF in patients with unresected stage IIIB to IV melanoma in a randomized open-label phase III trial.

Patients and Methods
Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF. The primary end point was durable response rate (DRR; objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points included overall survival (OS) and overall response rate.

Results
Among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; $P < .001$). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% *v* 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; $P = .051$). T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis (2.1%). No fatal treatment-related AEs occurred.

Conclusion
T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR ($P < .001$) and longer median OS ($P = .051$), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.

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INTRODUCTION

Development of targeted therapy and immunotherapy has resulted in important advances in melanoma treatment. Improvement in overall survival (OS) has been reported with T-cell checkpoint inhibitors and BRAF inhibitors, with objective response rates ranging from 11% with single-agent ipilimumab to 76% with the combination of BRAF and MEK inhibitors, although drug resistance and recurrence are still challenges.[1-3] New strategies promoting tumor cell death and/or inducing protective host antitumor immunity are of high priority.

Oncolytic viruses are novel cancer treatments that include wild-type and modified live viruses. Talimogene laherparepvec (T-VEC) is a first-in-class oncolytic virus based on a modified herpes simplex virus (HSV) type 1 designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity. T-VEC is modified through deletion of two nonessential viral genes.[4] Functional deletion of the herpes virus

neurovirulence factor gene (*ICP34.5*) attenuates viral pathogenicity and enhances tumor-selective replication.[5-8] T-VEC is further modified by deletion of the *ICP47* gene to reduce virally mediated suppression of antigen presentation and increase the expression of the HSV *US11* gene.[9,10] Insertion and expression of the gene encoding human granulocyte macrophage colony-stimulating factor (GM-CSF) results in local GM-CSF production to recruit and activate antigen-presenting cells with subsequent induction of tumor-specific T-cell responses.[11]

T-VEC has been evaluated in early-phase studies, which demonstrated intratumoral replication and expression of GM-CSF and an acceptable safety profile (low-grade fever, chills, myalgias, and injection site reactions) after intralesional administration.[4,12] In a single-arm phase II study, an overall response rate (ORR) of 26% was reported in patients with stage IIIC to IV melanoma, with responses observed in both injected and uninjected lesions, including visceral lesions.[12] Biopsy of regressing lesions suggested an association between response and presence of interferon γ–producing MART-1–specific $CD8^+$ T cells and reduction in $CD4^+FoxP3^+$ regulatory T cells, consistent with induction of host antitumor immunity.[13] Here we report the primary analysis results from the phase III OPTiM study designed to evaluate whether treatment with T-VEC resulted in an improved durable response rate (DRR) compared with GM-CSF in patients with unresected stage IIIB to IV melanoma. ORR and OS are also reported.

PATIENTS AND METHODS

Patients

Eligible patients were age ≥ 18 years with histologically confirmed, not surgically resectable, stage IIIB to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions ≥ 10 mm in diameter). Bidimensionally measurable disease, serum lactate dehydrogenase ≤ 1.5× upper limit of normal, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and adequate organ function were also required. Patients requiring intermittent or chronic treatment with an antiviral agent (eg, acyclovir) or high-dose steroids were excluded, as were those with primary ocular or mucosal melanoma, bone metastases, active cerebral metastases, more than three visceral metastases (except lung or nodal metastases associated with visceral organs), or any visceral metastasis > 3 cm; liver metastases had to be stable for ≥ 1 month before random assignment. Patients with history of autoimmune disease, but not use of high-dose steroids, were eligible. Patients provided written informed consent; study procedures received institutional approval.

Study Design and Treatment

This open-label study was conducted at 64 centers in the United States, the United Kingdom, Canada, and South Africa and overseen by an independent data monitoring committee. Patients were assigned at a two-to-one ratio using central random assignment to receive intralesional T-VEC or subcutaneous recombinant GM-CSF. Random assignment was stratified by site of first recurrence, presence of liver metastases, disease stage, and prior nonadjuvant systemic treatment. The first dose of T-VEC was administered at 10^6 pfu/mL (to seroconvert HSV-seronegative patients). Subsequent T-VEC doses of 10^8 pfu/mL were administered 3 weeks after the first dose and then once every 2 weeks. Total T-VEC volume was up to 4.0 mL per treatment session. Injected volume per lesion ranged from 0.1 mL for lesions < 0.5 cm to 4.0 mL for lesions > 5 cm in longest diameter. Injection of all lesions was not required, and different lesions could be injected at different visits based on prioritization of injection to any new or largest lesions. Injection into visceral lesions was not allowed. GM-CSF 125 $\mu g/m^2$ was administered subcutaneously once daily for 14 days in 28-day cycles. Dose modifications for T-VEC were not permitted. GM-CSF doses could be reduced by 50% for absolute neutrophil count > 20,000/μL or platelets > 500,000/μL. If absolute neutrophil count or platelets decreased below these thresholds, GM-CSF dose could be increased 25%; if they persisted, GM-CSF was permanently discontinued.

Discontinuation of treatment because of progressive disease per response assessment criteria was not required before 24 weeks unless alternate therapy was clinically indicated. After 24 weeks, treatment continued until clinically relevant disease progression (progressive disease associated with reduced performance status), intolerability, withdrawal of consent, complete

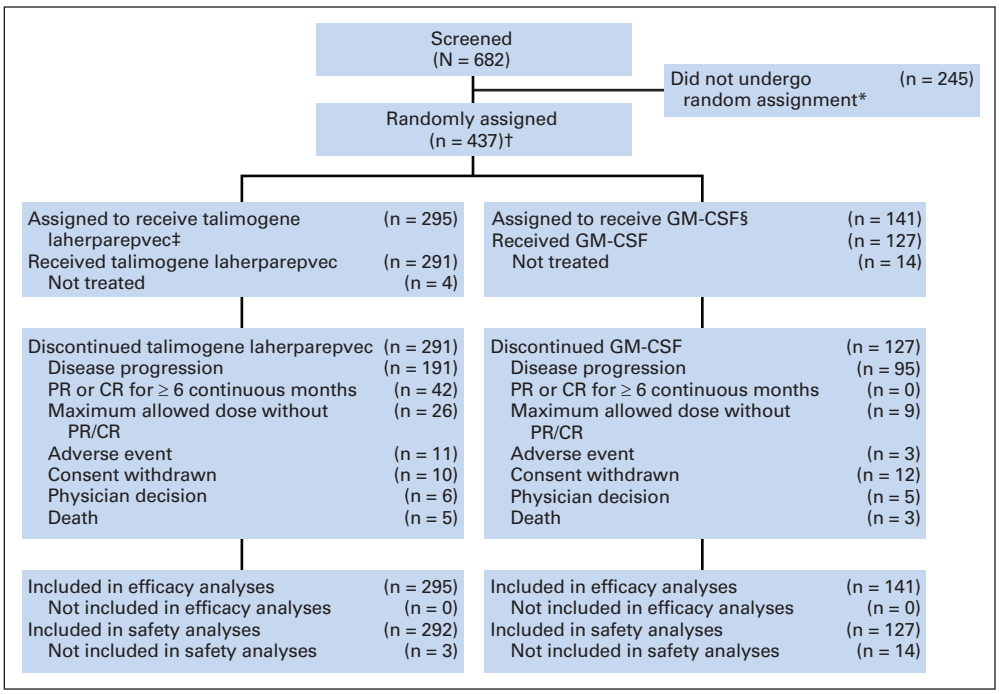

Fig 1. Disposition of patients. CR, complete response; GM-CSF, granulocyte macrophage colony-stimulating factor; PR, partial response. (*) Includes patients who were screened but did not meet eligibility criteria. Twenty-six patients in T-VEC arm (9%) and seven in GM-CSF arm (5%) were enrolled and randomly assigned but had at least one inclusion or exclusion criteria violation. (†) There were 439 random assignments; however, one patient was later determined to have been randomly assigned three times at three different sites and was excluded from intent-to-treat analysis set but was included in the safety analysis set. The patient ultimately received talimogene laherparepvec (T-VEC) after two initial random assignments to GMCSF. (‡) T-VEC was administered intralesionally ≤ 4 mL × 10^6 pfu/mL once and, after 3 weeks, ≤ 4 mL × 10^8 pfu/mL every 2 weeks. (§) GM-CSF 125 $\mu g/m^2$ subcutaneously for 14 days in 4-week cycles.

remission, lack of response by 12 months, or (T-VEC only) disappearance of all injectable lesions. After 12 months, patients with stable or responding disease could continue treatment for 6 additional months.

The primary end point was DRR, defined as the rate of complete response (CR) plus partial response (PR) lasting ≥ 6 months continuously and beginning within the first 12 months. Key secondary end points included OS (time from random assignment to death), best overall response and tumor burden, onset and duration of response, and time to treatment failure (TTF; time from baseline to first clinically relevant disease progression for which no objective response was subsequently achieved or until death).

Assessments

Visible or palpable lesions were evaluated by clinical evaluation (caliper or ruler). Deeper palpable lesions and nonpalpable subcutaneous and distant metastatic lesions were assessed by whole-body computed tomography (CT), positron emission tomography (PET) or PET-CT, and ultrasonography if appropriate. Baseline and new tumors were observed, and response was assessed per modified WHO criteria.[14] If a response was suspected to have occurred, confirmatory assessments were to be performed within 1 week. Patients with a best response per investigator of CR or PR or receiving treatment for ≥ 9 months were evaluated by a blinded end point–assessment committee (EAC). Digital photography encompassing all visible disease was required for response assessment by EAC. Clinical evaluation was performed at baseline and day 1 of each cycle; other assessments were performed at baseline and every 12 weeks. Adverse events (AEs) occurring from day 1 to 30 days after last treatment were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

The planned population size was 430 patients (randomly assigned at a two-to-one ratio). This provided 95% and 90% power for a two-sided α of 0.05 using Fisher's exact test in the intent-to-treat and per-protocol populations, respectively, to detect an estimated DRR difference of 13% versus 3%. Primary efficacy analyses were based on the intent-to-treat population. Safety analyses included patients who received at least one dose of T-VEC or GM-CSF. Interim analysis of DRR was planned after 75 patients were enrolled (one-sided $\alpha = 0.0001$) and after all patients were randomly assigned (one-sided $\alpha = 0.0005$). Primary analysis of DRR (with one-sided type I error rate of 0.0244) was planned when no additional patients had the possibility of meeting the criteria for durable response, at which time, on a positive result, an interim analysis of OS was planned after 250 events and tested (one-sided $\alpha = 0.0001$). OS was tested with an unadjusted log-rank test conditional on a statistically significant difference in DRR. Primary analysis of OS required at least 290 events with 90% power to detect a hazard ratio (HR) of 0.67 with two-sided α of 0.05, without adjustment for interim analysis.[15] Difference in DRR per EAC between treatment arms was evaluated using an unadjusted Fisher's exact test. OS, TTF, time to response, and duration of response were evaluated using unadjusted log-rank tests and Cox proportional hazards models. Difference in incidence of grade ≥ 3 AEs between arms was evaluated using χ^2 test (analysis was not prespecified). Analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics, Disposition, and Treatment

Between May 2009 and July 2011, 436 patients were assigned to treatment and included in intent-to-treat analyses (T-VEC, n = 295; GM-CSF, n = 141; Fig 1). Four patients in the T-VEC arm and 14 in the GM-CSF arm did not receive T-VEC or GM-CSF. Overall, 57% had stage IIIB, IIIC, or IVM1a disease, and 47% had not received prior systemic therapy for metastatic disease (Table 1). At time of analysis, all patients had discontinued study treatment in the main protocol but could have enrolled onto a treatment extension study if appropriate.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	T-VEC (n = 295) No.	T-VEC (n = 295) %	GM-CSF (n = 141) No.	GM-CSF (n = 141) %
Age, years				
Median	63		64	
Range	22 to 94		26 to 91	
< 65	152	52	72	51
≥ 65	143	48	69	49
Sex				
Male	173	59	77	55
Female	122	41	64	45
Disease substage				
IIIB	22	8	12	9
IIIC	66	22	31	22
IVM1a	75	25	43	30
IVM1b	64	22	26	18
IVM1c	67	23	29	21
Unknown	1	< 1	0	0
Line of therapy				
First	138	47	65	46
Second or later	157	53	76	54
ECOG performance status				
0	209	71	97	69
1	82	28	32	23
Unknown	4	1	12	9
LDH				
≤ ULN	266	90	124	88
> ULN	15	5	5	4
Unknown	14	5	12	9
HSV serostatus				
Positive	175	59	78	55
Negative	97	33	45	32
Unknown	23	8	18	13
BRAF status				
Mutation	46	16	23	16
Wild type	45	15	23	16
Unknown or missing	204	69	95	67

NOTE. Distribution of randomization stratification factors is shown in Appendix, Table A1.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; LDH, lactate dehydrogenase; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

Median duration of treatment in the T-VEC and GM-CSF arms was 23.0 weeks (range, 0.1 to 78.9 weeks) and 10.0 weeks (range, 0.6 to 72.0 weeks), respectively. Median potential follow-up (time from random assignment to analysis) was 44.4 months (range, 32.4 to 58.7 months) at the primary analysis of OS.

Durable and Overall Response

DRR per EAC assessment (primary end point) was significantly higher in the T-VEC arm (16.3%; 95% CI, 12.1% to 20.5%) compared with the GM-CSF arm (2.1%; 95% CI, 0% to 4.5%; unadjusted odds ratio, 8.9; 95% CI, 2.7 to 29.2; $P < .001$; Table 2; Fig 2A). ORR was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% *v* 5.7%; 95% CI, 1.9% to 9.5%; $P < .001$ [not prespecified]); 32 patients (10.8%) in the T-VEC arm and one patient (< 1%) in the GM-CSF arm had a CR (Table 2).

Table 2. Efficacy

Response	T-VEC (n = 295)	GM-CSF (n = 141)	*P*	Difference	
				%	95% CI
DRR			< .001		
Patients with durable response, No.	48	3			
DRR, %*	16.3	2.1			
95% CI	12.1 to 20.5	0 to 4.5			
Unadjusted odds ratio	8.9				
95% CI	2.7 to 29.2				
ORR			< .001†		
CR					
No.	32	1			
%	10.8	< 1			
PR					
No.	46	7			
%	15.6	5.0			
ORR, %*	26.4	5.7			
95% CI	21.4 to 31.5	1.9 to 9.5			
Duration of response					
Patients with response, No.	78	8			
Median	NE	2.8			
95% CI		1.2 to NE			
Probability of being in response for all responders‡					
For ≥ 9 months, %	68	47			
95% CI	55 to 78	12 to 76			
For ≥ 12 months, %	65	47			
95% CI	51 to 76	12 to 76			
OS					
Estimated OS probability, %					
At 12 months	74	69		4.6	−4.7 to 13.8
At 24 months	50	40		9.5	−0.5 to 19.6
At 36 months	39	30		8.5	−1.2 to 18.1
At 48 months	33	21		11.3	1.0 to 21.5

Abbreviations: CR, complete response; DRR, durable response rate; GM-CSF, granulocyte macrophage colony-stimulating factor; HSV, herpes simplex virus; NE, not estimable; ORR, overall response rate; OS, overall survival; PR, partial response; T-VEC, talimogene laherparepvec.
*CIs for DRR and ORR were calculated using asymptotic normal approximation.
†No α was allocated for this evaluation of statistical significance.
‡Kaplan-Meier estimate.

Median time to response among the 78 responding patients in the T-VEC arm was 4.1 months (range, 1.2 to 16.7 months), whereas among the eight patients in the GM-CSF arm with a response, it was 3.7 months (range, 1.9 to 9.1 months). Of the 78 responding T-VEC patients, 42 (54%) met criteria for disease progression before ultimately achieving a response. Among patients with a response, median duration of response in the GM-CSF arm was 2.8 months (95% CI, 1.2 to not estimable), whereas median duration of response was not estimable for the T-VEC arm. The estimated probability of being in response at 12 months from response onset was 65% (95% CI, 51% to 76%) among T-VEC responders (Table 2). At the time of the final tumor assessment included in the primary analysis of DRR (minimum follow-up for responding patients, 5.0 months), a majority (56 of 78) of T-VEC responses were ongoing (Fig 2B). Responses were observed in both injected and uninjected lesions, including a ≥ 50% decrease in size in 15% of evaluable, uninjected, measurable visceral lesions.[16,17]

TTF

Median TTF was 8.2 months (95% CI, 6.5 to 9.9 months) in the T-VEC arm versus 2.9 months (95% CI, 2.8 to 4.0 months) in the GM-CSF arm (HR, 0.42; 95% CI, 0.32 to 0.54).

OS

At the primary analysis of OS, 290 deaths had occurred (T-VEC, n = 189; GM-CSF, n = 101). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) in the T-VEC arm and 18.9 months (95% CI, 16.0 to 23.7 months) in the GM-CSF arm (HR, 0.79; 95% CI, 0.62 to 1.00; $P = .051$; Fig 3). Estimated 1-, 2-, 3-, and 4-year survival rates are listed in Table 2.

Exploratory Analyses

Subgroup analyses were performed to investigate the relative effects of treatment across a number of key covariates for DRR, ORR, and OS. Differences in DRR between the T-VEC and GM-CSF arms were more pronounced in patients with stage IIIB or IIIC (33% *v* 0%) and IVM1a disease (16% *v* 2%) than in patients with stage IVM1b (3% *v* 4%) and IVM1c disease (7% *v* 3%; Fig 4A). Differences in DRR were also more pronounced in patients with treatment-naive metastatic melanoma (24% *v* 0%) than in those receiving treatment as second-line or greater therapy (10% *v* 4%). Similar patterns were seen for ORR in these subgroups (Appendix Fig A1, online only). Effects of T-VEC on OS were also pronounced among patients with stage IIIB, IIIC, or IVM1a disease (HR, 0.57; 95% CI, 0.40 to 0.80) and previously untreated patients (HR, 0.50; 95% CI, 0.35 to 0.73; Figs 4B to 4F).

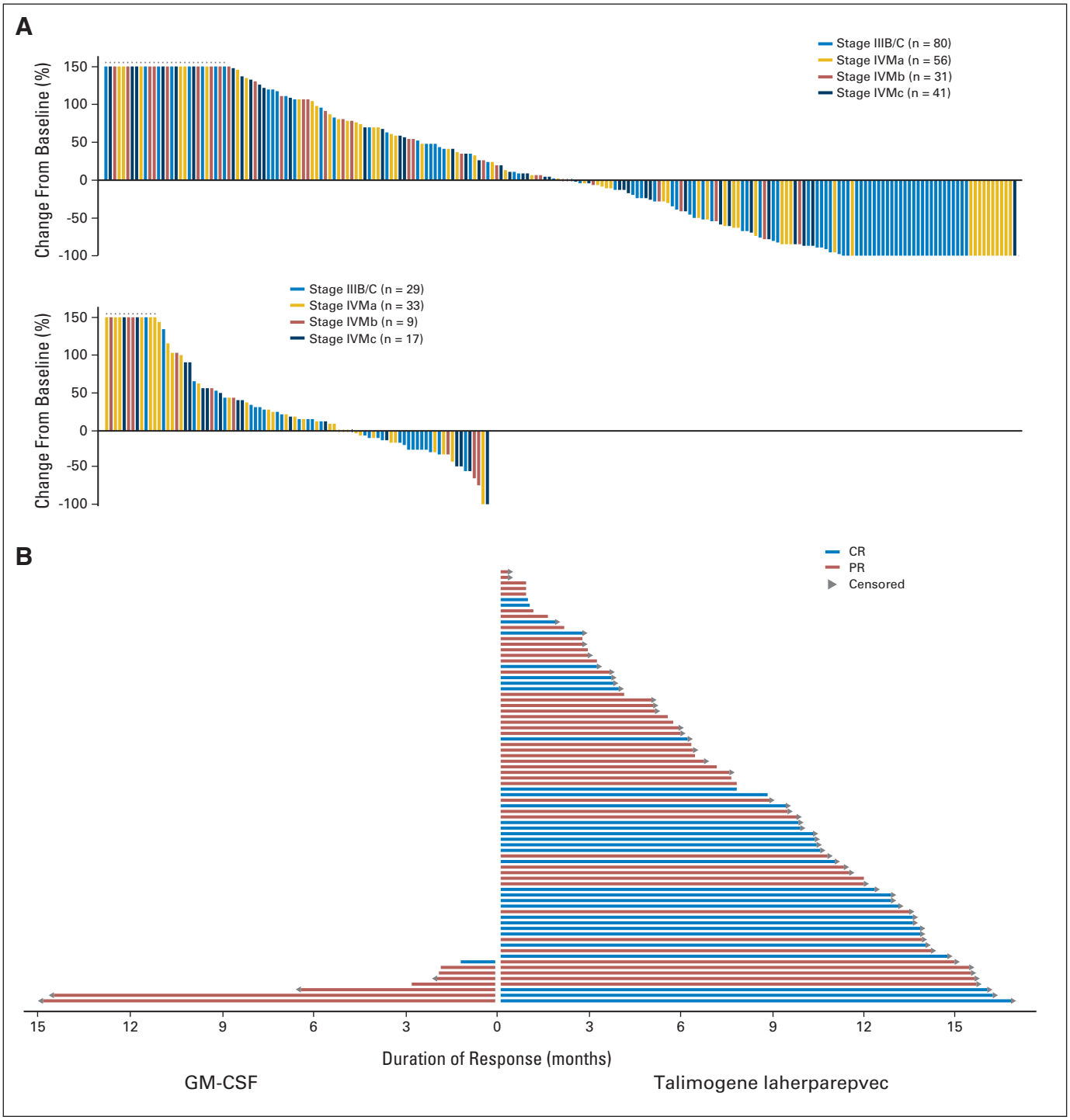

Fig 2. Antitumor activity of talimogene laherparepvec. (A) Waterfall plot of best response for all patients per investigator assessment. Response assessments per end point–assessment committee (EAC) were not available for all patients, because EAC reviewed only subset of patients with overall response per investigator or who received treatment for > 9 months (see Patients and Methods). (B) Duration of response for all patients with response per EAC assessment. Duration of response was defined as longest period of response from entering response to first documented evidence of patient no longer meeting criteria for response. Arrows indicate patients for whom duration of response was censored at last tumor assessment because there was no evidence (per EAC assessment) that their response had ended. CR, complete response; GM-CSF, granulocyte macrophage colony-stimulating factor; PR, partial response. (*) Patients with > 150% increase in tumor dimensions.

The proportion of patients receiving subsequent selected effective antimelanoma therapy was similar between arms, although T-VEC patients received treatment approximately 2 months later than GM-CSF patients (Appendix Table A2, online only). Because between-arm imbalances in nonrandomization prognostic factors of disease stage (IIIB, IIIC, or IVM1a *v* IVM1b or IVM1c) and ECOG performance status were identified, a sensitivity analysis (stratified Cox proportional hazards model) was used to adjust for

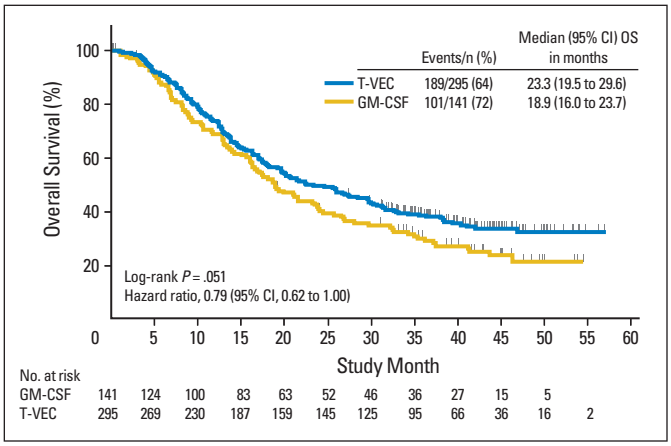

Fig 3. Primary analysis of overall survival (OS) in intent-to-treat population. GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

these factors; the HR for OS with T-VEC versus GM-CSF was 0.76 (95% CI, 0.59 to 0.98; adjusted log-rank $P = .03$; Appendix Table A3, online only).

AEs

AEs occurring more frequently among patients receiving T-VEC included chills (T-VEC, 49% *v* GM-CSF, 9%), pyrexia (43% *v* 9%), injection-site pain (28% *v* 6%), nausea (36% *v* 20%), influenza-like illness (30% *v* 15%), and fatigue (50% *v* 36%; Table 3). Vitiligo was reported in 15 T-VEC patients (5%) and one GM-CSF patient (< 1%; all grade ≤ 2). Injection-site erythema occurred more frequently among GM-CSF patients (T-VEC, 5% *v* GM-CSF, 26%). For T-VEC and GM-CSF, respectively, incidence of AEs of any grade was 99% and 95%, and incidence of treatment-related grade 3 or 4 AEs was 11% and 5%. The rate of discontinuation as a result of AEs was 4% and 2% with T-VEC and GM-CSF, respectively; disease progression was the most common reason for treatment discontinuation in both arms (Fig 1).

Grade ≥ 3 AEs occurred in 36% of patients receiving T-VEC and 21% of patients receiving GM-CSF ($P = .003$). The only grade 3 or 4 AE occurring in ≥ 2% of patients was cellulitis (T-VEC, n = 6 [2.1%]; GM-CSF, n = 1 [< 1%]). Of 10 fatal events in the T-VEC arm, none were considered treatment related per investigator, and most (80%) were associated with disease progression, with the exception of sepsis in the setting of *Salmonella* infection and myocardial infarction. Two fatal non–treatment-related AEs occurred in the GM-CSF arm, both associated with disease progression.

DISCUSSION

To our knowledge, OPTiM is the first randomized controlled phase III study evaluating an oncolytic immunotherapy to demonstrate a therapeutic benefit in melanoma. The study met its primary end point: T-VEC significantly improved the rate of responses lasting continuously for ≥ 6 months in patients with unresected stage IIIB to IV melanoma compared with subcutaneous GM-CSF. ORR was also higher.

Among responding patients in the T-VEC arm, median time to response was 4.1 months, and more than half experienced ≥ 25% increase in the size of lesions or appearance of new lesions before achieving a response. This pattern of pseudoprogression is consistent with that seen with other immunotherapies[19-23] and illustrates the importance of continuing treatment in clinically stable patients even if individual lesions increase in size or new lesions develop. In the context of the low historical CR rate reported for other single-agent immunotherapies, the 10.8% CR rate with T-VEC is high.[1,20] The duration of T-VEC responses is also notable, with two thirds of responses expected to last ≥ 1 year.

Durable responses to T-VEC were seen across all disease stages tested, including in patients within each subset of stage IV disease. More than half of the patients had skin, subcutaneous, or nodal disease only (stage IIIB, IIIC, or IVM1a disease), and DRR and ORR with T-VEC were greater among these patients than among those with lung or other visceral organ metastases (stage IVM1b or IVM1c disease). In addition, the difference in OS favoring T-VEC compared with GM-CSF in patients with stage IIIB, IIIC, or IVM1a disease (HR, 0.57; 95% CI, 0.40 to 0.80) is of particular note. Although the reasons for the apparent differences in activity by disease stage are not known, it is possible that some patients with visceral disease may have had insufficient survival time to derive benefit from T-VEC–initiated systemic antitumor immunity. Alternatively, injection of T-VEC into dermal, subcutaneous, and nodal metastases may activate T cells that preferentially traffic to metastases in similar anatomic sites.[24] Disease control in patients with stage IIIB, IIIC, or IVM1a disease can be achieved as a result of locoregional lytic effects of the virus as well as through immune effects, whereas responses in visceral lesions can only occur through systemic immune effects. Systemic immune effects of T-VEC were demonstrated, with the finding that 15% of measurable visceral (all uninjected) metastases reduced in size by ≥ 50% among T-VEC–treated patients. Development of vitiligo in T-VEC–treated patients indicates that an immune response to melanocyte antigens was induced, at least in some patients.[25] Increased numbers of MART-1–specific T cells have been observed in metastases undergoing regression after T-VEC therapy compared with untreated lesions, and T-VEC has also been shown to decrease $CD4^+FoxP3^+$ regulatory T cells and $CD8^+FoxP3^+$ suppressor T cells in injected lesions, consistent with systemic antitumor immunity.[13]

DRR and ORR were greater in patients receiving T-VEC as first-line therapy than in those receiving T-VEC after prior treatment. Similarly, the difference in OS favoring T-VEC versus GM-CSF was also notable in previously untreated patients (HR, 0.50; 95% CI, 0.35 to 0.73). This outcome might be influenced by the increased time and selective pressure under which previously treated tumors have had to develop mechanisms of immunologic escape, such as reduced antigenicity or increased immunosuppressive state.[26] Other factors to consider include prior exposure to immunosuppressive chemotherapy, higher baseline tumor burden, and potentially more indolent disease among patients receiving second-line or greater treatment in this study, because a lower tumor growth rate might affect the replicative efficiency of the virus.[27]

OS was a secondary end point; in the intent-to-treat analysis (based on 290 events), patients in the T-VEC arm had a 21% reduced risk of death (HR, 0.79; 95% CI, 0.62 to 1.00; $P = .051$) and 4.4-month longer median OS compared with patients treated with GM-CSF. Median TTF was 5.3 months longer with T-VEC. Combined with the limited toxicity observed, these are clinically important results.

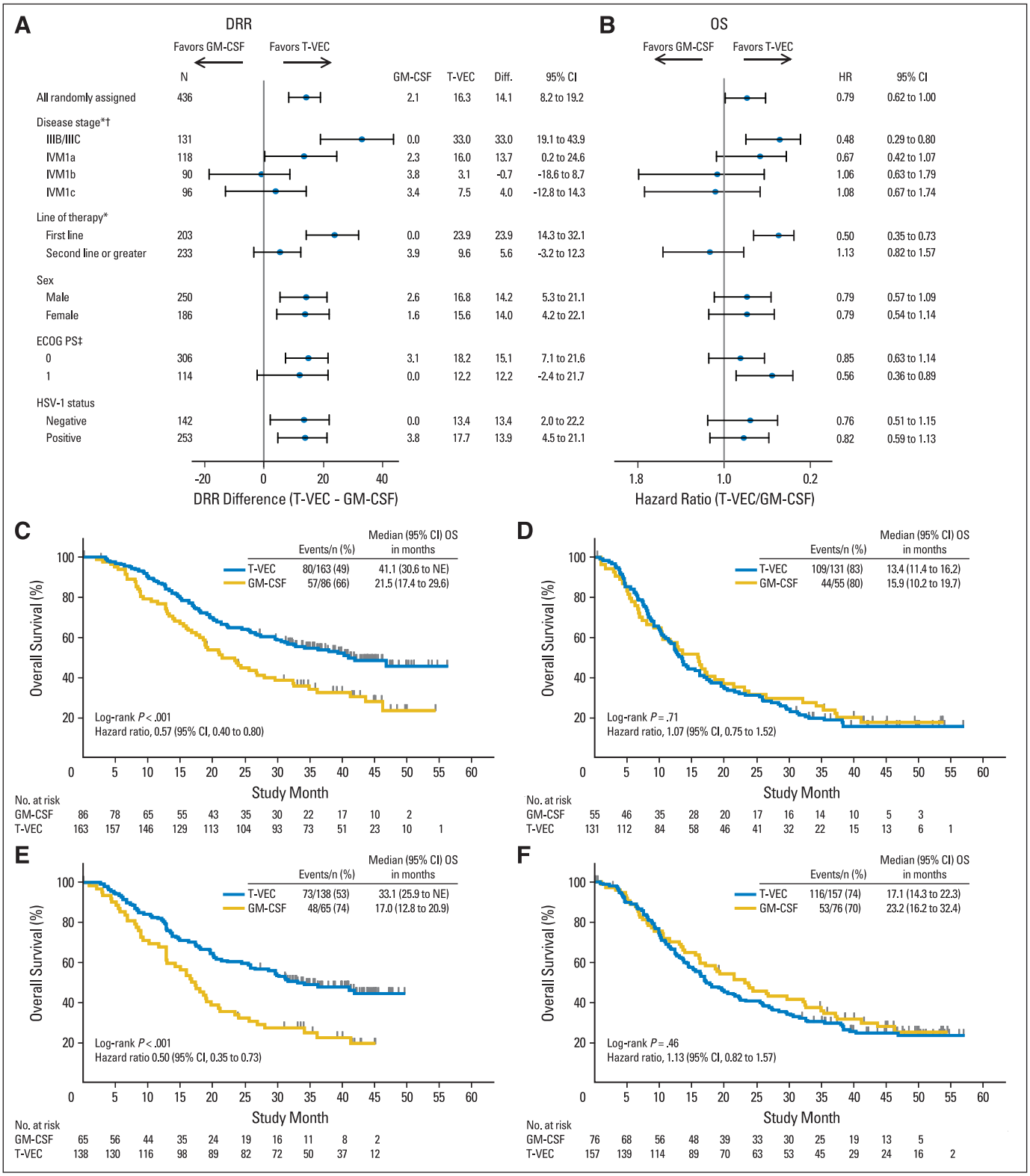

Fig 4. Outcomes in patient subgroups. (A) Durable response rate (DRR) and (B) overall survival (OS) in patient subgroups defined by key baseline characteristics. OS in patients with (C) stage IIIB, IIIC, or IVM1a or (D) stage IVM1b or IVM1c disease. OS in patients receiving study treatment as (E) first- or (F) second-line or greater therapy. No α was allocated for evaluations of statistical significance. ECOG, Eastern Cooperative Oncology Group; diff, difference; GM-CSF, granulocyte macrophage colony-stimulating factor; HSV, herpes simplex virus; NE, not estimable; PS, performance status; T-VEC, talimogene laherparepvec. (*) $P < .001$ per Gail and Simon[18] quantitative treatment by covariate interaction test (for DRR). (†) One patient in the T-VEC arm had unknown disease stage. (‡) Twelve patients in the GM-CSF arm and four in the T-VEC arm had unknown ECOG status.

Table 3. Patient Incidence of AEs

	T-VEC (n = 292)				GM-CSF (n = 127)			
	Any Grade		Grade 3 or 4		Any Grade		Grade 3 or 4	
AE*	No.	%	No.	%	No.	%	No.	%
Fatigue	147	50.3	5	1.7	46	36.2	1	0.8
Chills	142	48.6	0	0	11	8.7	0	0
Pyrexia	125	42.8	0	0	11	8.7	0	0
Nausea	104	35.6	1	0.3	25	19.7	0	0
Influenza-like illness	89	30.5	2	0.7	19	15.0	0	0
Injection-site pain	81	27.7	3	1.0	8	6.3	0	0
Vomiting	62	21.2	5	1.7	12	9.4	0	0
Diarrhea	55	18.8	1	0.3	14	11.0	0	0
Headache	55	18.8	2	0.7	12	9.4	0	0
Myalgia	51	17.5	1	0.3	7	5.5	0	0
Arthralgia	50	17.1	2	0.7	11	8.7	0	0
Pain in extremity	48	16.4	4	1.4	12	9.4	1	0.8
Pain	47	16.1	2	0.7	13	10.2	1	0.8
Peripheral edema	35	12.0	2	0.7	12	9.4	2	1.6
Constipation	34	11.6	0	0	8	6.3	1	0.8
Cough	31	10.6	0	0	10	7.9	0	0
Decreased appetite	30	10.3	0	0	14	11.0	0	0
Pruritus	28	9.6	0	0	19	15.0	0	0
Cellulitis	17	5.8	6	2.1	2	1.6	1	0.8
Injection-site erythema	15	5.1	0	0	33	26.0	0	0
Dyspnea	13	4.5	3	1.0	13	10.2	2	1.6
Injection-site pruritus	5	1.7	0	0	21	16.5	0	0

Abbreviations: AE, adverse event; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.
*Treatment-emergent AEs of any grade with incidence ≥ 10% in either arm and/or grade 3 to 4 AEs with incidence of ≥ 2% in either arm.

Several factors might have influenced the efficacy outcomes. GM-CSF was selected as a comparator based on its immune-mediated mechanism of action, established safety profile, and preliminary evidence of clinical benefit as adjuvant therapy in resectable stage III to IV melanoma.[11,28,29] Although the duration of treatment was shorter in the GM-CSF arm, the reported activity of single-agent GM-CSF in advanced melanoma has been modest[11]; it is unlikely that shorter exposure contributed meaningfully to the reduced treatment effect. Effective subsequent antimelanoma therapies were received earlier by GM-CSF patients and could have overcome some of the OS benefit achieved with T-VEC. Furthermore, it is plausible that prior GM-CSF treatment may have had a beneficial impact on subsequent therapies, because concomitant administration of GM-CSF and ipilimumab has been shown to increase OS over ipilimumab alone.[30] There were also small but meaningful imbalances in prognostic factors (disease stage and ECOG performance status) favoring the GM-CSF arm that may have affected the overall result, as suggested by a sensitivity analysis adjusting for these imbalances. In addition, the open-label study design may have influenced assessment of some end points (particularly TTF).

Both treatments administered in this study had tolerable safety profiles, and few patients discontinued because of toxicity in either arm. Frequently occurring AEs with T-VEC were flu-like symptoms (including fatigue, chills, and pyrexia). The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis; there were no treatment-related deaths. In the context of toxicity reported for some other melanoma therapies,[1,20,31] the low rate of grade 3 or 4 AEs with T-VEC is notable, particularly when considering combined immunotherapy approaches. The evidence of local and systemic immune responses with T-VEC supports combination with other immunotherapies as a rational approach. A phase 1b/2 study of T-VEC and ipilimumab is evaluating the safety and efficacy of this combination.[32]

In conclusion, this randomized phase III study demonstrated that treatment with T-VEC, an oncolytic virus immunotherapy, improved DRR compared with GM-CSF in patients with unresected stage IIIB, IIIC, or IV melanoma. T-VEC treatment resulted in long-lasting CRs, suggesting T-VEC could delay or prevent relapses or preclude progression to later stages of disease. T-VEC represents a novel potential new treatment option for patients with injectable metastatic melanoma and limited visceral disease.

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Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

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Appendix

Table A1. Random Assignment Stratification Factors*

Factor	T-VEC (n = 295)		GM-CSF (n = 141)	
	No.	%	No.	%
Disease substage				
IIIB or IIIC	92	31	46	33
IVM1a or IVM1b	144	49	67	48
IVM1c	59	20	28	20
Line of therapy				
First	138	47	65	46
Second or later	157	53	76	54
Site of first recurrence				
Visceral	15	5	8	6
In transit or distant skin	177	60	84	60
Lymph node	103	35	49	35
Presence of liver metastases				
Yes	20	7	8	6
No	275	93	133	94

Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.
*As reported by investigators at patient enrollment using interactive voice response system.

Table A2. Subsequent Treatment With Selected Systemic Targeted Therapies

Subsequent Treatment	GM-CSF (n = 141)			T-VEC (n = 295)		
	Incidence			Incidence		
	No.	%	Median Time to Use (months)	No.	%	Median Time to Use (months)
Ipilimumab, vemurafenib, dabrafenib, or trametinib	60	43	6.9	116	39	8.9
Ipilimumab	49	35	7.4	106	36	8.6
Vemurafenib	21	15	13.6	26	9	14.6
Dabrafenib	2	1	7.1	7	2	12.8
Trametinib	0	0	—	3	1	18.0
Anti–PD-1 antibody*	3	2	—	4	1	—

Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; PD-1, programmed death 1; T-VEC, talimogene laherparepvec.
*Excludes pidilizumab (CT-001).

Table A3. OS Sensitivity Analysis Correcting for Imbalances in Nonrandomization Factors

Factor	Between-Arm Difference (T-VEC − GM-CSF)	HR*	95% CI	Log-Rank *P*
ITT		0.79	0.62 to 1.00	.05
Disease stage†				
IIIB, IIIC, or IVM1a (n = 249)	−6%	0.78	0.62 to 1.00	.05
IVM1b or IVM1c (n = 187)	+5%			
ECOG performance status				
0 (n = 306)	+2%	0.78	0.61 to 1.00	.04
1 (n = 114)	+5%			
Unknown (n = 16)	−7%			
Disease stage and ECOG‡	—	0.76	0.59 to 0.98	.03

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating factor; HR, hazard ratio; ITT, intent to treat; OS, overall survival; T-VEC, talimogene laherparepvec.
*HR from stratified Cox proportional hazards model in which prognostic factors were used to stratify model rather than included in model as covariates.
†Per case-report form using imputation from interactive voice response for one patient with missing case-report form value.
‡Analysis stratified by ECOG performance status (three levels) and disease stage (two levels).

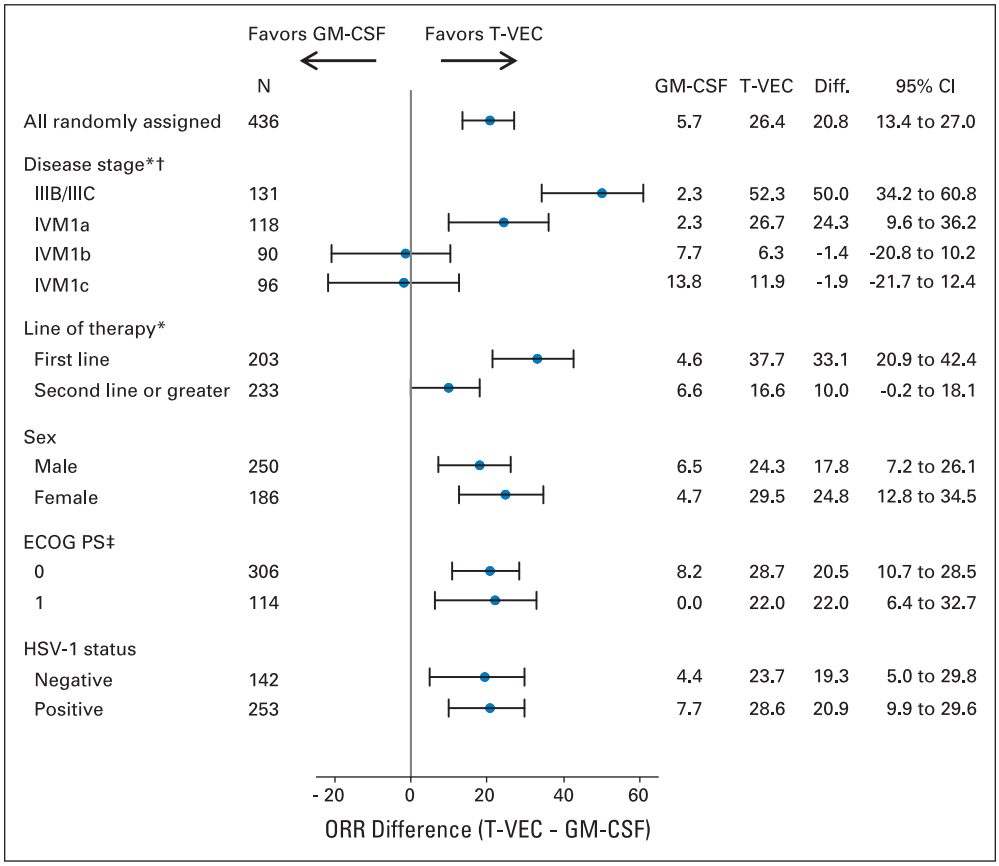

Fig A1. Overall response rate (ORR) by key subgroups. ECOG, Eastern Cooperative Oncology Group; diff, difference; GM-CSF, granulocyte macrophage colony-stimulating factor; HSV, herpes simplex virus; PS, performance status; T-VEC, talimogene laherparepvec. (*) $P < .05$ per Gail and Simon[18] quantitative treatment by covariate interaction test. (†) One patient in the T-VEC arm had unknown disease stage. (‡) Twelve patients in the GM-CSF arm and four in the T-VEC arm had an unknown ECOG status.