Title

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Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined With Pembrolizumab for Advanced Melanoma

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abstract

PURPOSE The combination of talimogene laherparepvec (T-VEC) and pembrolizumab previously demonstrated an acceptable safety profile and an encouraging complete response rate (CRR) in patients with advanced melanoma in a phase Ib study. We report the efficacy and safety from a phase III, randomized, double-blind, multicenter, international study of T-VEC plus pembrolizumab (T-VEC-pembrolizumab) versus placebo plus pembrolizumab (placebo-pembrolizumab) in patients with advanced melanoma.

METHODS Patients with stage IIIB-IVM1c unresectable melanoma, naïve to antiprogrammed cell death protein-1, were randomly assigned 1:1 to T-VEC-pembrolizumab or placebo-pembrolizumab. T-VEC was administered at $\leq 4 \times 10^6$ plaque-forming unit (PFU) followed by $\leq 4 \times 10^8$ PFU 3 weeks later and once every 2 weeks until dose 5 and once every 3 weeks thereafter. Pembrolizumab was administered intravenously 200 mg once every 3 weeks. The dual primary end points were progression-free survival (PFS) per modified RECIST 1.1 by blinded independent central review and overall survival (OS). Secondary end points included objective response rate per mRECIST, CRR, and safety. Here, we report the primary analysis for PFS, the second preplanned interim analysis for OS, and the final analysis.

RESULTS Overall, 692 patients were randomly assigned (346 T-VEC-pembrolizumab and 346 placebo-pembrolizumab). T-VEC-pembrolizumab did not significantly improve PFS (hazard ratio, 0.86; 95% CI, 0.71 to 1.04; $P = .13$) or OS (hazard ratio, 0.96; 95% CI, 0.76 to 1.22; $P = .74$) compared with placebo-pembrolizumab. The objective response rate was 48.6% for T-VEC-pembrolizumab (CRR 17.9%) and 41.3% for placebo-pembrolizumab (CRR 11.6%); the durable response rate was 42.2% and 34.1% for the arms, respectively. Grade ≥ 3 treatment-related adverse events occurred in 20.7% of patients in the T-VEC-pembrolizumab arm and in 19.5% of patients in the placebo-pembrolizumab arm.

CONCLUSION T-VEC-pembrolizumab did not significantly improve PFS or OS compared with placebo-pembrolizumab. Safety results of the T-VEC-pembrolizumab combination were consistent with the safety profiles of each agent alone.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Advances in treatment for patients with advanced melanoma, including immune checkpoint inhibitors and targeted agents blocking BRAF and MEK, have significantly improved survival with the highest 5-year landmark overall survival (OS) rates above 50%.[1-5] Novel combination strategies to further improve this survival rate are currently being evaluated.

Several combination therapies showed improved survival over monotherapy; however, increased toxicities were observed. Ipilimumab, an anti–cytotoxic T lymphocyte–associated antigen-4 checkpoint inhibitor, plus nivolumab, a programmed cell death protein-1 (PD-1) inhibitory antibody, showed significantly longer progression-free survival (PFS) and OS than ipilimumab alone (PFS hazard ratio [HR], 0.42; $P < .001$; OS HR, 0.55; $P < .001$).[6,7] In addition, triple therapy with

CONTEXT

Key Objective

Immune checkpoint inhibitors have greatly improved clinical outcomes for patients with advanced melanoma; however, resistance is common. Intratumoral administration of agents that increase T-cell infiltration, such as talimogene laherparepvec (T-VEC), has the potential to safely boost immune responses in combination with immune checkpoint inhibitor therapy. This phase III clinical trial evaluated the efficacy and safety of T-VEC-pembrolizumab versus placebo-pembrolizumab in patients with unresectable/metastatic melanoma.

Knowledge Generated *(G.K. Schwartz)*

The combination of T-VEC-pembrolizumab did not statistically improve progression-free survival or overall survival relative to placebo-pembrolizumab. However, T-VEC-pembrolizumab demonstrated a numerical progression-free survival improvement and safety was consistent with the known safety profiles of each agent.*

Relevance *(G.K. Schwartz)*

This phase III clinical trial evaluated the combination of an agent that increases tumor infiltration of T cells with the one that blocks inhibitory T-cell checkpoints. As life expectancy improves for patients with melanoma, combination strategies that do not increase toxicities while improving survival warrant further study.*

*Knowledge Generated and Relevance sections written by *JCO* Associate Editor Gary K. Schwartz, MD.

cobimetinib, vemurafenib, and atezolizumab showed statistically significantly improved PFS (PFS HR 0.78, $P = .025$; OS HR, 0.85; $P = .23$) compared with cobimetinib plus vemurafenib.[8] Both these combination treatments resulted in a high rate of grade ≥ 3 adverse events (AEs).[2,6,8] Recently, the combination of relatlimab, an anti–LAG-3 antibody, with nivolumab was also reported to significantly improve PFS (PFS HR, 0.75; $P = .006$; OS HR, 0.80; $P = .059$) compared with nivolumab alone.[9,10]

Talimogene laherparepvec (T-VEC) is a herpes simplex virus-1–based immunotherapy that promotes intratumoral T-cell infiltration.[11,12] A recent study in B-cell lymphoma demonstrated that injected T-VEC infects malignant and nonmalignant cells causing infiltration of natural killer cells, monocytes, and dendritic cells, followed by cytotoxic T cells, with an associated decrease in regulatory T cells.[13] Pembrolizumab targets PD-1, blocking the interaction between the receptor and its ligands, thereby augmenting the expansion and function of antitumor T cells. Combining an agent that increases tumor infiltration of innate and adaptive immune cells with the one that blocks inhibitory T-cell checkpoints may further improve the antitumor activity of either agent. The phase Ib, single-arm trial (MASTERKEY-265) testing the combination of T-VEC plus pembrolizumab in 21 patients with advanced melanoma showed promising tumor responses (objective response rate [ORR] 62%; complete response rate [CRR] 43%), and the combination was generally well tolerated with no dose-limiting toxicities.[14] Given the phase Ib results, a randomized, double-blind, placebo-controlled, multicenter, international phase III trial was conducted to evaluate the efficacy and safety of T-VEC combined with pembrolizumab versus placebo plus pembrolizumab in patients with unresectable/metastatic melanoma.

METHODS

Patients

Our study enrolled patients with histologically confirmed stage IIIB-IV M1c unresectable melanoma[15] who were age ≥ 18 years and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligible patients had at least one visceral or nodal/soft tissue melanoma lesion that could be accurately and serially measured in at least one dimension and for which the longest diameter was ≥ 10 mm as measured by a computed tomography scan or magnetic resonance imaging. To be considered measurable by a computed tomography scan or magnetic resonance imaging, lymph nodes were eligible only if they measured at least 15 mm at their short axis. Patients with $BRAF^{V600}$ wild-type melanoma must not have received prior systemic anticancer therapy in a nonadjuvant setting for stage IIIB-IVM1c unresectable melanoma. Patients with $BRAF^{V600}$-mutated melanoma may have received prior BRAF inhibitor therapy as their only prior line of systemic therapy; however, the patient must have ended the therapy at least 14 days before enrollment. Prior adjuvant therapy was allowed except T-VEC or other viral-based anticancer treatments and PD-1, programmed cell death ligand 1 (PD-L1), or programmed cell death-1 ligand 2 inhibitors.

Key exclusion criteria included active untreated brain metastases, primary uveal or mucosal melanoma, prior therapy with T-VEC or any other oncolytic viruses, prior therapy with anti–PD-1/PD-L1/PD-L2 agents, prior therapy with tumor vaccine in the nonadjuvant setting, history of autoimmune diseases, evidence of immunosuppression therapy for greater than 2 weeks or within 7 days prior to the first dose of study treatment (including oral steroid doses greater than 10 mg/day of prednisone or equivalent except

for management of adverse events and CNS metastases during the course of the study), active herpetic skin lesions, and current treatment with an antiherpetic drug.

Protocols (online only) and subsequent amendments were approved by the institutional review board or ethics committees at each participating site. Written informed consent was provided by all patients.

Study Design and Treatment

MASTERKEY-265 was a multicenter, double-blind, placebo-controlled, randomized phase III study (Fig 1). Patients were randomly assigned 1:1 to receive the combination of T-VEC plus pembrolizumab (T-VEC-pembrolizumab) or placebo plus pembrolizumab (placebo-pembrolizumab). Random assignment was stratified by disease stage per the American Joint Committee on Cancer seventh edition[15] (less advanced stages [IIIB, IIIC, and IVM1a] *v* more advanced stages [IVM1b and IVM1c]) and prior anti-BRAF therapy (no prior anti-BRAF therapy *v* prior anti-BRAF therapy with or without MEK inhibitor).

Treatment with T-VEC plus pembrolizumab and placebo plus pembrolizumab was initiated simultaneously. T-VEC/placebo was administered via intratumoral injection once at 10^6 plaque-forming unit (PFU)/mL for up to 4 mL on day 1 of week 0, followed by up to 4 mL of 10^8 PFU/mL on day 1 of week 3 and once every 2 weeks until the fifth injection at week 9. T-VEC/placebo was then administered synchronously with pembrolizumab every 3 weeks thereafter. Pembrolizumab was administered intravenously at 200 mg once every 3 weeks.

The dual primary end points were PFS per modified RECIST 1.1 by a blinded independent central review (BICR) and OS. Key secondary end points included CRR and PFS per modified Immune-related Response Criteria (irRC)-RECIST per BICR and OS in patients with stages IIIB-IVM1b. Other secondary end points included ORR, best overall response (BOR), durable response rate (DRR), duration of response, and disease control rate by BICR per both modified RECIST 1.1 and modified irRC-RECIST, as well as safety.

Assessments

PFS was defined as the time from random assignment to documented disease progression or death, whichever occurred first, per modified RECIST 1.1.[16] OS was defined as the time from random assignment to death from any cause. The PFS primary end point and the secondary end points related to tumor response were assessed by a BICR using both modified RECIST 1.1[16] and a modified version of the irRC-RECIST.[17] Tumor response was assessed at week 0, week 12, and every 12 weeks thereafter until confirmed progressive disease by irRC-RECIST or the start of a new anticancer treatment, whichever occurred first. Response or progressive disease was confirmed by a consecutive scan at least 4 weeks after the initial detection.

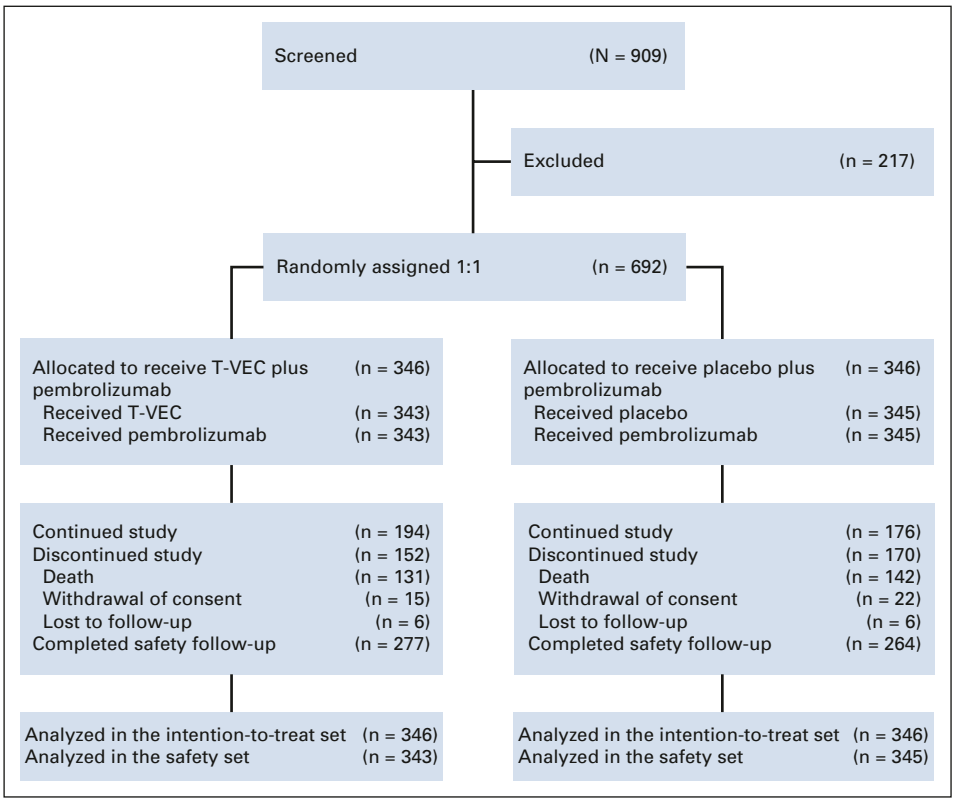

FIG 1. CONSORT diagram. T-VEC, talimogene laherparepvec.

The severity of AEs was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A safety follow-up was conducted approximately 30 days after the last dose of T-VEC or placebo or pembrolizumab, whichever was later. Patients were followed up for survival every 12 weeks from the date of safety follow-up visit for up to 60 months after the last patient was randomly assigned to the trial.

PD-L1 expression was assessed at a central laboratory using an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA) and was characterized by the MEL score[18]; PD-L1 positivity was defined as MEL scores $\geq$ 2 (ie, membranous staining in $\geq$ 1% of cells within tumor nests, including neoplastic cells and intercalated and contiguous immune cells).

Statistical Analysis

The planned sample size of 660 (330 per arm) patients was based on the dual primary end points of PFS and OS; initial allocation of significance level, overall two-sided 0.05, was two-sided 0.005 for PFS and two-sided 0.045 for OS (see the Data Supplement, online only for more information). A group sequential design was used for four analyses of OS. Lost to follow-up proportions of 10% for PFS and 5% for OS were assumed over 5 years. The analyses of PFS and OS were performed using a stratified log-rank test for the null hypothesis of no treatment effect, with the stratification factors mentioned above and by baseline PD-L1 status. Assuming a piecewise exponential distribution, we hypothesized an HR of 0.67 with 90% power for PFS (T-VEC-pembrolizumab *v* placebo-pembrolizumab) and an HR of 0.70 with 90% power for OS. The Cox proportional hazards model was used to estimate HRs and two-sided 95% CIs.

The primary analysis of PFS was to be performed after 407 PFS events occurred, as assessed by BICR using modified RECIST 1.1. At the time of the PFS primary analysis, an interim OS analysis occurred, including all observed deaths at the time of analysis. The second interim OS analysis was planned for efficacy and futility after 282 events had been observed. The futility boundary was HR, 0.89 assuming a constant treatment effect and HR, 0.93 assuming a nonconstant treatment effect. A third interim OS analysis for efficacy was planned after 315 events, and a primary analysis of OS was to be performed after 346 OS events occurred. The final analysis was planned to include all observed events at the time of analysis.

If neither the PFS nor the OS was statistically significant, all secondary end points were to be descriptive. The analysis of PFS per modified irRC-RECIST (iPFS) occurred at 256 events; analysis of other secondary end points included all events/observations.

Data cutoff dates are as follows: March 2, 2020, for the PFS primary analysis; September 29, 2020, for the second interim OS analysis; and March 26, 2021, for the final analysis.

RESULTS

Patients and Treatment

From March 17, 2016, through April 26, 2018, 692 patients were enrolled in 21 countries with 346 patients randomly assigned to each arm (Fig 1 and Data Supplement). Baseline patient characteristics were generally balanced between the arms (Table 1).

On June 12, 2020, the data monitoring committee (DMC) met to review data from the PFS primary analysis and recommended that the study continues as planned. The DMC then met on December 22, 2020, to review the efficacy and safety data from the second OS interim analysis. The DMC indicated that the futility boundary for OS was crossed and recommended that no further study-related procedures are conducted. On January 8, 2021, the study was unblinded and proceeded directly to a final analysis conducted in an unblinded manner. All patients were off study treatment as of April 2020. The last visit date for the final analysis was March 11, 2021.

The median follow-up time was 25.58 (range, 0.3-45.8) months for the PFS primary analysis, 31.0 (range, 0.3-53.0) months for the second OS interim analysis, and 35.56 (range, 0.3-58.4) months for the final analysis (Data Supplement).

Efficacy

In the planned PFS primary analysis, treatment with T-VEC-pembrolizumab did not result in a statistically significant improvement in PFS per BICR using modified RECIST 1.1 compared with placebo-pembrolizumab (overall stratified HR, 0.86; 95% CI, 0.71 to 1.04; $P = .13$; Fig 2A). PFS favored the T-VEC-pembrolizumab arm over the placebo-pembrolizumab arm for three predefined subgroups: (1) patients enrolled in the United States (overall HR, 0.59; 95% CI, 0.37 to 0.92), (2) patients with baseline lactate dehydrogenase (LDH) $\leq$ the upper limit of normal (ULN; overall HR, 0.76; 95% CI, 0.59 to 0.99), and (3) patients with baseline sum of the longest diameters of target lesions (SLD) $\leq$ the median (overall HR, 0.70; 95% CI, 0.51 to 0.96; Fig 2B and Data Supplement).

In the planned second interim OS analysis, 136 (39.3%) and 146 (42.2%) deaths had occurred in the T-VEC-pembrolizumab and placebo-pembrolizumab arms, respectively. Treatment with T-VEC-pembrolizumab did not result in a statistically significant improvement in OS compared with placebo-pembrolizumab; the observed HR of 0.96 (95% CI, 0.76 to 1.22; $P = .74$) was beyond both prespecified futility boundaries for efficacies of 0.89 assuming a constant treatment effect and 0.93 assuming a nonconstant

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	T-VEC-Pembrolizumab (n = 346)	Placebo-Pembrolizumab (n = 346)
Age, years, median (range)	64 (26-92)	64 (19-94)
Sex, male	199 (57.5)	219 (63.3)
Race		
White	327 (94.5)	335 (96.8)
Asian	7 (2.0)	4 (1.2)
Black	2 (0.6)	1 (0.3)
ECOG performance status		
0	259 (74.9)	249 (72.0)
1	87 (25.1)	97 (28.0)
Region of enrollment		
US	87 (25.1)	71 (20.5)
Non-US	259 (74.9)	275 (79.5)
Baseline HSV-1 status		
Negative	58 (16.8)	63 (18.2)
Positive	275 (79.5)	273 (78.9)
Unknown	13 (3.8)	10 (2.9)
BRAF mutation status		
Present	124 (35.8)	116 (33.5)
Absent	211 (61.0)	215 (62.1)
Unknown	11 (3.2)	15 (4.3)
Baseline LDH		
≤ ULN	214 (61.8)	241 (69.7)
> ULN	129 (37.3)	97 (28.0)
> 2 × ULN	22 (6.4)	21 (6.1)
Baseline PD-L1 status		
Negative	78 (22.5)	85 (24.6)
Positive	231 (66.8)	218 (63.0)
Indeterminate	34 (9.8)	36 (10.4)
Missing	3 (0.9)	7 (2.0)
Disease stage		
IIIB	18 (5.2)	20 (5.8)
IIIC	66 (19.1)	53 (15.3)
IVM1a	69 (19.9)	81 (23.4)
IVM1b	48 (13.9)	49 (14.2)
IVM1c	145 (41.9)	143 (41.3)

NOTE. Data are No. (%) unless otherwise specified.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HSV-1, herpes simplex virus 1; LDH, lactate dehydrogenase; PD-L1, programmed cell death ligand 1; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

treatment effect (Fig 3A). No improvement in OS was observed in any of the predefined subgroups (Fig 3B).

Subsequent anticancer therapies did not appear to confound the OS analysis because second-line therapies were generally balanced between the arms, and the crossover rate from the placebo arm to receive subsequent T-VEC treatment was < 5% (Data Supplement). A sensitivity analysis was also performed, which censored patients at the time of subsequent anticancer therapy (Table 2), and no difference in OS was observed between treatment arms in this analysis (overall stratified HR, 0.90; 95% CI, 0.67 to 1.20).

To determine if the T-VEC-pembrolizumab combination benefited patients with earlier-stage disease, an OS sensitivity analysis excluding patients with stage IVM1c disease was performed, and no difference between treatment arms was observed (overall stratified HR, 0.87; 95% CI, 0.61 to 1.24; Table 2).

Tumor responses to treatment were assessed in the primary analysis. ORR, CRR, and DRR by BICR using RECIST 1.1 were 48.6 (95% CI, 43.3 to 53.8), 17.9% (95% CI, 13.9 to 22.0), and 42.2% (95% CI, 37.0 to 47.4) for the T-VEC-pembrolizumab arm and 41.3% (95% CI, 36.1 to 45.5), 11.6% (95% CI, 8.2 to 14.9), and 34.1% (95% CI, 29.1 to 39.1) for the placebo-pembrolizumab arm, respectively (Table 3). The median duration of response was 43.7 months (95% CI could not be estimated) for the T-VEC-pembrolizumab arm and could not be estimated for the placebo-pembrolizumab arm. An analysis of BOR using irRC-RECIST was performed, and the results were consistent with BOR via mRECIST (Data Supplement).

In the primary analysis, iPFS by BICR per irRC-RECIST was analyzed to account for potential progression before response with immunotherapies. No difference between treatment arms was observed for iPFS (overall stratified HR, 1.05; 95% CI, 0.82 to 1.34; Data Supplement). After overlaying the iPFS curve on the PFS primary analysis curve (Data Supplement), it became apparent that the iPFS curve primarily represents the early part of the PFS curve when there was no difference between the arms.

AEs

Overall, 339 patients (98.3%) receiving T-VEC-pembrolizumab and 330 patients (96.2%) receiving placebo-pembrolizumab had at least one treatment-emergent AE. Treatment-related AEs (TRAEs) were experienced by 305 patients (88.4%) receiving T-VEC-pembrolizumab and 256 patients (74.6%) receiving placebo-pembrolizumab (Table 4); the most common AEs were pyrexia (35.1% and 5.0%) and fatigue (31.3% and 22.2%). Grade ≥ 3 TRAEs occurred in 70 (20.3%) patients in the T-VEC-pembrolizumab arm and 54 (15.7%) patients in the placebo-pembrolizumab arm. Forty-five patients (13.1%) receiving T-VEC-pembrolizumab and 42 patients (12.2%) receiving placebo-pembrolizumab had a fatal AE. There were four treatment-related fatal events (1.2%; one each of atypical pneumonia, cardiac arrest, delirium, and pulmonary sepsis) in the T-VEC-pembrolizumab arm and one (0.3%; respiratory failure) in the placebo-pembrolizumab arm. Death from progressive disease occurred in 7.8% and 8.2% of patients, respectively.

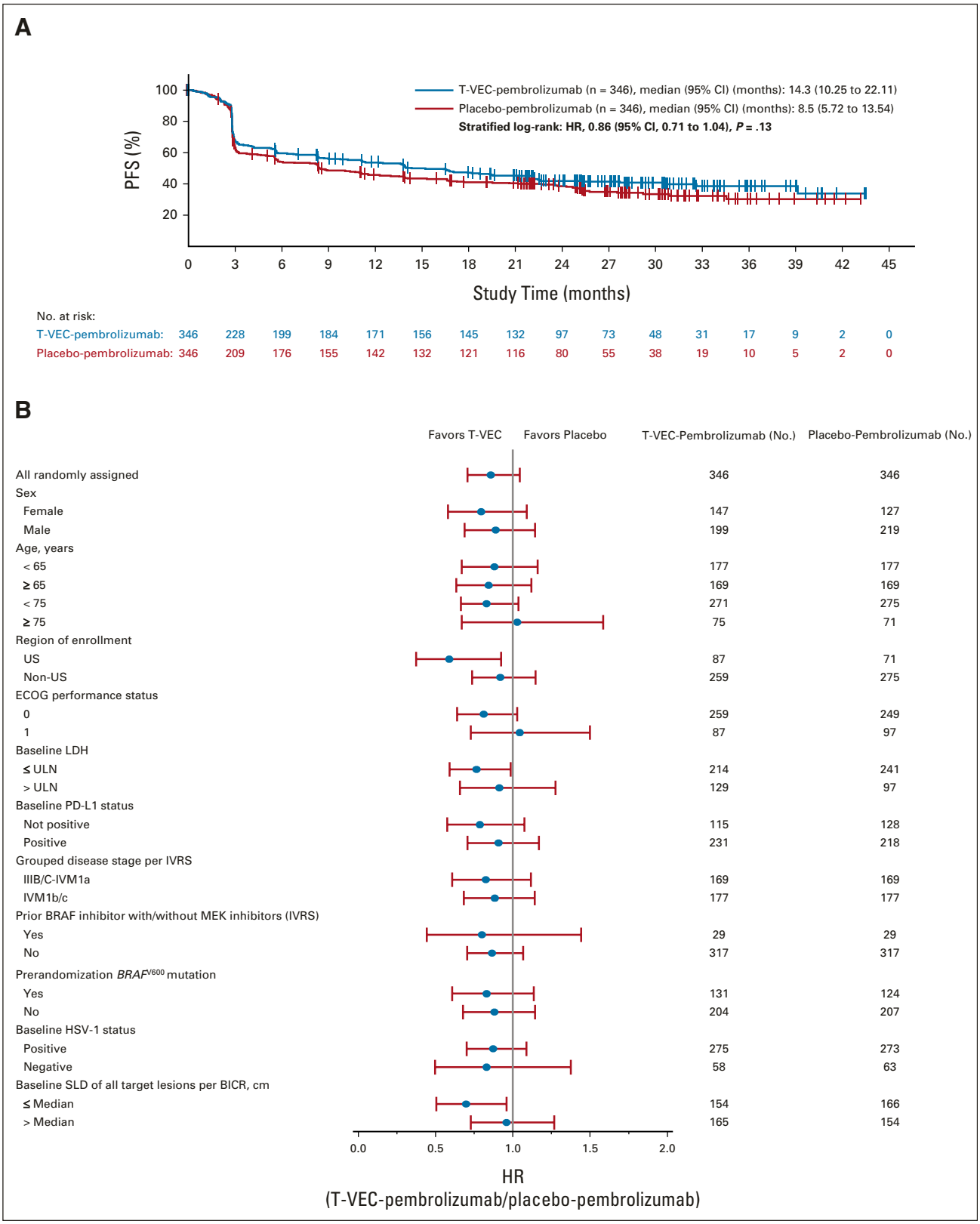

FIG 2. (A) Kaplan-Meier estimate of PFS in the intention-to treat population. Vertical lines indicate censoring. (B) Forest plots for PFS in subgroups. HRs are shown for subgroups as defined by baseline patient and tumor characteristics. BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HSV, herpes simplex virus; IVRS, interactive voice response system; LDH, lactate dehydrogenase; PFS, progression-free survival; SLD, sum of lesion diameters; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

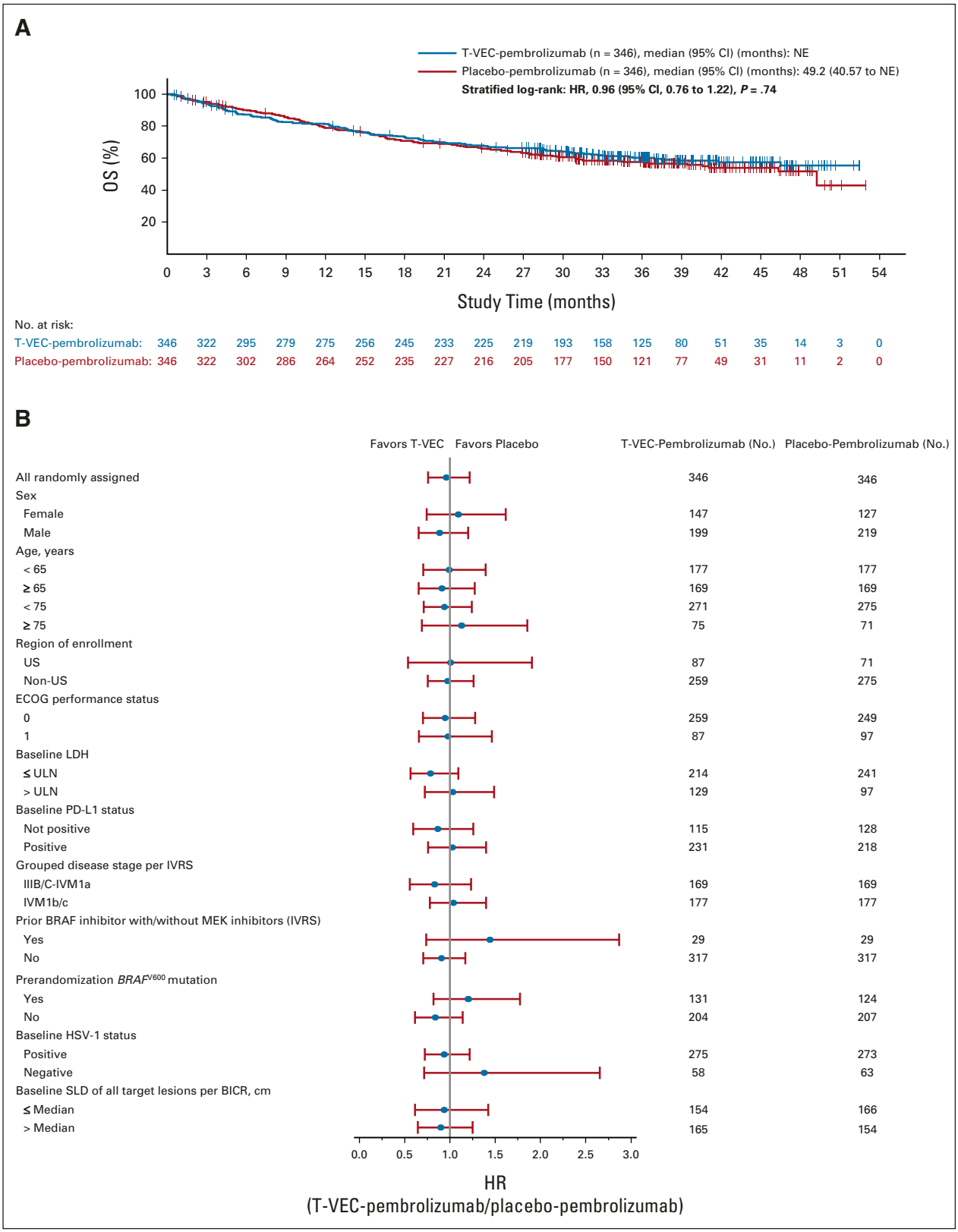

FIG 3. (A) Kaplan-Meier estimate of OS in the intention-to treat population. Vertical lines indicate censoring. (B) Forest plots for OS in subgroups. HRs are shown for subgroups as defined by baseline patient and tumor characteristics. BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HSV, herpes simplex virus; IVRS, interactive voice response system; LDH, lactate dehydrogenase; NE, not estimable; OS, overall survival; SLD, sum of lesion diameters; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

TABLE 2. OS in the Second Interim Analysis and the Final Analysis

OS	Second Interim Analysis		Final Analysis	
	T-VEC-Pembrolizumab (n = 346)	Placebo-Pembrolizumab (n = 346)	T-VEC-Pembrolizumab (n = 346)	Placebo-Pembrolizumab (n = 346)
OS, overall	136 (39.3)	146 (42.2)	146 (42.2)	156 (45.1)
Overall stratified HR (95% CI)	0.96 (0.76 to 1.22)		0.97 (0.77 to 1.21)	
Stratified log-rank *P* value	.74		.77	
OS after excluding patients with IVM1c disease	57 (28.4)	70 (34.5)	65 (32.3)	76 (37.4)
Overall stratified HR (95% CI)	0.87 (0.61 to 1.24)		0.88 (0.63 to 1.24)	
OS sensitivity for subsequent anticancer therapy	88 (25.4)	96 (27.7)	93 (26.9)	99 (28.6)
Overall stratified HR (95% CI)	0.90 (0.67 to 1.20)		0.92 (0.69 to 1.22)	

NOTE. Intention-to-treat population. Data are deaths (%). *P* value for the final analysis was descriptive.
Abbreviations: HR, hazard ratio; OS, overall survival; T-VEC, talimogene laherparepvec.

Immune-related AEs (irAEs) of any grade occurred in 27.5% of the patients receiving T-VEC-pembrolizumab and 24.8% receiving placebo-pembrolizumab; the most frequently reported AEs were hypothyroidism (12.5% and 13.4%) and hyperthyroidism (5.8% and 5.0%; Data Supplement).

Final Analysis Update

As of April 2020, all patients had discontinued study treatments. The final analysis was performed early given the futility noted in the second interim analysis and included an additional follow-up of 6 months. At the cutoff date for the final analysis, PFS and OS results were consistent with those from the PFS primary analysis and the second OS interim analysis. Treatment with T-VEC-pembrolizumab did not result in improved PFS per BICR using modified RECIST 1.1 (overall stratified HR, 0.87; 95% CI, 0.72 to 1.06) or OS (overall stratified HR, 0.97; 95% CI, 0.77 to 1.21) compared with placebo-pembrolizumab. No new safety signals were observed.

TABLE 3. Response to Treatment per Modified RECIST 1.1 by Blinded Independent Central Review in the Primary Analysis

Response	T-VEC-Pembrolizumab (n = 346)	Placebo-Pembrolizumab (n = 346)
Best overall tumor response		
CR	62 (17.9)	40 (11.6)
PR	106 (30.6)	103 (29.8)
SD	28 (8.1)	30 (8.7)
Progressive disease	106 (30.6)	120 (34.7)
Unable to evaluate	3 (0.9)	11 (3.2)
Not assessed	30 (8.7)	26 (7.5)
CRR	62 (17.9)	40 (11.6)
95% CI	13.88 to 21.96	8.19 to 14.93
ORR (CR/PR)	168 (48.6)	143 (41.3)
95% CI	43.29 to 53.82	36.14 to 46.52
Disease control rate (CR/PR/SD)	196 (56.6)	173 (50.0)
95% CI	51.43 to 61.87	44.73 to 55.27
Durable response rate	146 (42.2)	118 (34.1)
95% CI	36.99 to 47.40	29.11 to 39.10

NOTE. Intention-to-treat population. Data are No. (%).
Abbreviations: CR, complete response; CRR, complete response rate; ORR, objective response rate; PR, partial response; SD, stable disease; T-VEC, talimogene laherparepvec.

DISCUSSION

This randomized, double-blinded, placebo-controlled, multicenter, international phase III trial did not show improved PFS or OS for the combination of T-VEC plus pembrolizumab compared with placebo plus pembrolizumab for immunotherapy-naïve patients with advanced melanoma in the frontline setting. There were no new safety concerns with the addition of T-VEC to pembrolizumab, and the safety profile of the combination was consistent with the known safety profile of each drug.

OPTiM was a pivotal phase III trial that led to the approval of T-VEC monotherapy for patients with advanced melanoma. Because of the requirement for radiographically measurable disease in MASTERKEY-265, some patients with stage IIIB/C/IVM1a disease enrolled in OPTiM were not represented in our study.[19] Additional criteria in OPTiM that limited the population to patients with less aggressive disease included serum LDH $\leq$ 1.5 ULN, excluding patients with more than three visceral metastases or any visceral metastasis $>$ 3 cm and only including patients with liver metastases that were stable for $\geq$ 1 month.[19] It is uncertain if the patient population with more advanced disease in MASTERKEY-265 has an impact on the results presented here. Another difference was that T-VEC was delivered once every 2 weeks in OPTiM, whereas in our study, T-VEC was delivered once every 2 weeks until week 9 then every 3 weeks to align with pembrolizumab dosing. These differences make it

TABLE 4. TRAEs in All Treated Patients

	T-VEC-Pembrolizumab (n = 345)			Placebo-Pembrolizumab (n = 343)		
TRAE	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
All	232 (67.2)	63 (18.3)	7 (2.0)	201 (58.6)	50 (14.6)	4 (1.2)
Pyrexia	119 (34.5)	2 (0.6)		17 (5.0)		
Fatigue	103 (29.9)	5 (1.4)		72 (21.1)	4 (1.2)	
Chills	68 (19.7)	2 (0.6)		11 (3.2)	1 (0.3)	
Nausea	63 (18.3)	1 (0.3)		35 (10.2)		
Pruritus	57 (16.5)			39 (11.4)	3 (0.9)	
Influenza-like illness	56 (16.2)			14 (4.1)		
Arthralgia	54 (15.7)	1 (0.3)		40 (11.7)	1 (0.3)	
Rash	49 (14.2)	2 (0.6)		21 (6.1)		
Diarrhea	45 (13.0)	4 (1.2)	1 (0.3)	37 (10.8)	3 (0.9)	
Hypothyroidism	43 (12.5)			46 (13.4)		
Vitiligo	42 (12.2)			31 (9.0)		
Headache	38 (11.0)	1 (0.3)		15 (4.4)	1 (0.3)	
Vomiting	32 (9.3)	3 (0.9)		11 (3.2)		
Myalgia	26 (7.5)			8 (2.3)		
Decreased appetite	22 (6.4)			8 (2.3)		
Hyperthyroidism	20 (5.8)			16 (4.7)	1 (0.3)	
Rash maculopapular	19 (5.5)	1 (0.3)		11 (3.2)	3 (0.9)	
ALT increased	15 (4.3)	2 (0.6)		15 (4.4)	2 (0.6)	
Pneumonitis	15 (4.3)	3 (0.9)	1 (0.3)	6 (1.7)	3 (0.9)	
AST increased	12 (3.5)	1 (0.3)		8 (2.3)	5 (1.5)	
Pain	11 (3.2)	1 (0.3)		5 (1.5)		
Anemia	10 (2.9)	2 (0.6)		8 (2.3)	1 (0.3)	
Extremity pain	10 (2.9)			6 (1.7)	1 (0.3)	
Dyspnea	8 (2.3)	2 (0.6)		7 (2.0)	1 (0.3)	
Blood alkaline phosphatase increased	7 (2.0)	1 (0.3)		2 (0.6)		
Dermatitis	6 (1.7)	1 (0.3)		5 (1.5)		
Cellulitis	5 (1.4)	1 (0.3)		2 (0.6)	2 (0.6)	
Colitis	4 (1.2)	3 (0.9)			1 (0.3)	
Gamma-glutamyl transferase increased	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	
Infusion-related reaction	4 (1.2)	1 (0.3)				
Peripheral edema	4 (1.2)	2 (0.6)		6 (1.7)		
Hyperglycemia	3 (0.9)	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.3)
Hypophosphatemia	3 (0.9)	3 (0.9)				
International normalized ratio increased		1 (0.3)				
Lipase increased	3 (0.9)	1 (0.3)		3 (0.9)	1 (0.3)	1 (0.3)
Pruritic rash	3 (0.9)	1 (0.3)		2 (0.6)		
Arthritis	2 (0.6)	1 (0.3)		2 (0.6)	1 (0.3)	
Diabetes mellitus	2 (0.6)	2 (0.6)		1 (0.3)	1 (0.3)	
Mucosal inflammation	2 (0.6)	1 (0.3)				
Musculoskeletal pain	2 (0.6)	1 (0.3)				
Neck pain	2 (0.6)	1 (0.3)		1 (0.3)		

(continued on following page)

TABLE 4. TRAEs in All Treated Patients (continued)

	T-VEC-Pembrolizumab (n = 345)			Placebo-Pembrolizumab (n = 343)		
TRAE	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Pneumonia	2 (0.6)	1 (0.3)				
Hepatitis	1 (0.3)	2 (0.6)		1 (0.3)	1 (0.3)	
Hypopituitarism	1 (0.3)	1 (0.3)				
Inflammation	1 (0.3)	1 (0.3)				
Lymphocytic hypophysitis	1 (0.3)	2 (0.6)			1 (0.3)	
Papilledema	1 (0.3)	1 (0.3)				
Respiratory failure	1 (0.3)	1 (0.3)				
Skin infection	1 (0.3)	1 (0.3)				
Tumor hemorrhage	1 (0.3)	1 (0.3)				
Syncope		2 (0.6)				
Acute cardiac failure		1 (0.3)				
Autoimmune arthritis		1 (0.3)		1 (0.3)		
Chorioretinitis		1 (0.3)				
Condition aggravated		1 (0.3)				
Dehydration		1 (0.3)		1 (0.3)		
Diabetic ketoacidosis		1 (0.3)	1 (0.3)			
Gastritis		1 (0.3)		1 (0.3)		
Gout		1 (0.3)				
Hematochezia		1 (0.3)				
Hypotension		1 (0.3)				
Joint effusion		1 (0.3)				
Lymph gland infection		1 (0.3)				
Malignant melanoma		1 (0.3)				
Mental status change		1 (0.3)				
Polyarthritis		1 (0.3)				
Psoriatic arthropathy		1 (0.3)				
Retinal edema		1 (0.3)				
Tumor-associated fever		1 (0.3)				
Type 1 diabetes mellitus			1 (0.3)			

NOTE. Safety analysis population. Data are No. (%). Grade 1-2 TRAEs listed above occurred in ≥ 5% of the patients receiving T-VEC-pembrolizumab. All grade 3 and grade 4 TRAEs for T-VEC-pembrolizumab are listed.

Abbreviations: TRAE, treatment-related adverse event; T-VEC, talimogene laherparepvec.

difficult to compare our results with those of the OPTiM study.

MASTERKEY-265 had a greater percentage of patients with stage IIIB/C/IVM1a disease than the pivotal KEYNOTE-006 trial, which evaluated the safety and efficacy of pembrolizumab versus ipilimumab in patients with advanced melanoma (44% *v* 16% in KN-006).[20] The most likely reason is the requirement for injectable lesion(s) in the current study. Compared with other frontline phase III advanced melanoma trials, our trial had the largest population of patients with unresectable stage III and IVM1a melanoma. The median PFS of 8.5 months in the placebo-pembrolizumab control arm of our study was similar to that observed in the KEYNOTE-006 trial for the combined pembrolizumab group (median PFS, 8.4 months; 95% CI, 6.6 to 11.3).[1,20] Although we did not observe a statistically significant difference in the median PFS between the treatment arms, there was a numerical difference of 5.8 months favoring the T-VEC-pembrolizumab arm (14.3 *v* 8.5). In addition, PFS favored the T-VEC-pembrolizumab combination for three subgroups: patients enrolled in the United States, patients with baseline LDH ≤ ULN, and patients with baseline SLD ≤ the median. The observed difference between regions may be explained by the United States enrolling more patients with baseline LDH ≤ ULN

(75.3% *v* 62.9% from non-US) and lower median baseline SLD (4.2 cm *v* 5.2 cm from non-US). Nevertheless, the observed PFS benefit in these subgroups of patients did not translate into an OS benefit.

A high incidence of progression before response was observed in the OPTiM study.[19] The lower incidence of pseudoprogression in our trial than that observed in OPTiM (< 5% *v* 14%) might explain why there was no difference in iPFS between the treatment arms in our study.[19] In addition, the pseudoprogression rate that we observed is consistent with that reported for anti–PD-1 monotherapy.[21-23]

Our study's OS landmarks for the pembrolizumab control arm were higher than those reported in the KEYNOTE-006 and KEYNOTE-001 trials. For example, our 2-year OS landmark was 66% compared with 58% in the KEYNOTE-006 study and 60% in the KEYNOTE-001 study.[6,20] Many factors might have contributed to a better performing control arm in our trial; for example, the higher percentage of patients with stage IIIB/C/IVM1a disease and lower disease burden and the availability of better second-line treatments. Baseline PD-L1 status was used as a stratification factor in our study and did not appear to contribute directly to the better performance of the control arm. Other clinical trials have reported a wide variability for positive baseline PD-L1 status ranging from 23% to 83%.[6,20,24,25] Our observed rate for the positive baseline PD-L1 of 67% for the combination arm and 63% for the control arm is aligned with the range seen in other trials. Differences in execution of PD-L1 testing may be responsible for discrepancies in the detection of positive PD-L1 patients.

Compared with the placebo-pembrolizumab arm, the ORR, CRR, and DRR were numerically higher in the T-VEC-pembrolizumab arm. The observed difference in DRR for T-VEC-pembrolizumab over pembrolizumab monotherapy in our study is consistent with the DRR results reported in OPTiM.[19] Combination strategies that provide clinical benefit without additional toxicities are highly sought. The addition of T-VEC to pembrolizumab did not add significant toxicities, and no increase in irAEs was noted. Overall, the incidence of TRAEs including ≥ grade 3 AEs and fatal AEs was similar between arms. TRAEs that occurred with ≥ 5% higher incidence for the T-VEC-pembrolizumab arm over the placebo-pembrolizumab arm were known adverse drug reactions for T-VEC and pembrolizumab; most were nonserious grade 1/2 in severity. Despite the favorable safety results of the combination, no statistically significant efficacy advantages were observed.

There is a continuing unmet need in the field for combination strategies to improve the efficacy of currently available therapies without added toxicities. Although the combination of T-VEC-pembrolizumab did not result in OS benefit compared with placebo-pembrolizumab in the frontline treatment of advanced melanoma, this combination is still under active investigation in patients who are refractory to anti–PD-1 inhibitor therapy for melanoma and other tumor types.

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Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined with Pembrolizumab for Advanced Melanoma

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Research Funding: ISDIN, Sun Pharma (Inst), Almirall (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Almirall, ISDIN, Roche Posay, Pierre Fabre

Bernardo Leon Rapoport
Honoraria: Lilly, MSD, Janssen, Novartis South Africa
Consulting or Advisory Role: Janssen, Lilly, Novartis South Africa
Speakers' Bureau: Merck, Bristol Myers Squibb, Novartis South Africa, Roche, Lilly, Astellas Pharma, Amgen, Janssen, AstraZeneca, Mylan, ECS Progastrin
Research Funding: Roche, Sandoz, Cancer Association of South Africa, ECS Progastrin, GlaxoSmithKline, HalioDx

Ari Vanderwalde
Employment: Caris Life Sciences
Consulting or Advisory Role: Bristol Myers Squibb, Caris Life Sciences, Compugen, Concerto HealthAI, Elsevier, Inivata
Research Funding: Amgen (Inst), Merck (Inst), Genentech/Roche (Inst), Millennium (Inst), AstraZeneca (Inst), Lilly (Inst), Bristol Myers Squibb (Inst), Replimune (Inst), Caris Life Sciences (Inst), EMD Serono (Inst), Immunomedics/Gilead (Inst)

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Employment: Merck Sharp & Dohme
Stock and Other Ownership Interests: Merck Sharp & Dohme

James R. Anderson
Employment: Merck
Stock and Other Ownership Interests: Merck Sharp & Dohme
Travel, Accommodations, Expenses: Merck Sharp & Dohme

Sheryl Treichel
Employment: Amgen
Stock and Other Ownership Interests: Amgen

Edward L. Chan
Employment: Amgen, Arvinas
Stock and Other Ownership Interests: Amgen
Travel, Accommodations, Expenses: Amgen, Arvinas

Sumita Bhatta
Employment: Amgen
Stock and Other Ownership Interests: Amgen

Jennifer Gansert
Employment: Amgen
Stock and Other Ownership Interests: Amgen
Patents, Royalties, Other Intellectual Property: Talimogene laherparepvec patents. No royalties

Helen Gogas
Honoraria: Bristol Myers Squibb, MSD Oncology, Pierre Fabre, Sanofi/Regeneron
Consulting or Advisory Role: Bristol Myers Squibb, MSD Oncology, Amgen, Pierre Fabre, Sanofi/Regeneron
Research Funding: Bristol Myers Squibb (Inst), Roche (Inst), MSD Oncology (Inst), Amgen (Inst), Novartis (Inst), Iovance Biotherapeutics (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Amgen, Pfizer

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