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# Talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone for advanced melanoma: 5-year final analysis of a multicenter, randomized, open-label, phase II trial

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## ABSTRACT

Talimogene laherparepvec (T-VEC) plus ipilimumab has demonstrated greater antitumor activity versus ipilimumab alone, without additional toxicity, in patients with advanced melanoma. Here, we report the 5-year outcomes from a randomized phase II study. These data provide the longest efficacy and safety follow-up for patients with melanoma treated with a combination of an oncolytic virus and a checkpoint inhibitor.

Eligible patients with unresectable stage IIIB–IV melanoma were randomized 1:1 to receive T-VEC plus ipilimumab or ipilimumab alone. T-VEC was administered intralesionally at $10^6$ plaque-forming units (PFU)/mL in week 1, followed by $10^8$ PFU/mL in week 4 and every 2 weeks thereafter. Ipilimumab (3 mg/kg every 3 weeks; ≤4 doses) was administered intravenously starting at week 1 in the ipilimumab arm and week 6 in the combination arm. The primary end point was investigator-assessed objective response rate (ORR) per immune-related response criteria; key secondary end points included durable response rate (DRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Overall, 198 patients were randomized to receive the combination (n=98) or ipilimumab (n=100). The combination improved the ORR versus ipilimumab (35.7% vs 16.0%; OR 2.9; 95% CI 1.5 to 5.7; p=0.003). DRR was 33.7% and 13.0% (unadjusted OR 3.4; 95% CI 1.7 to 7.0; descriptive p=0.001), respectively. Among the objective responders, the median DOR was 69.2 months (95% CI 38.5 to not estimable) with the combination and was not reached with ipilimumab. Median PFS was 13.5 months with the combination and 6.4 months with ipilimumab (HR 0.78; 95% CI 0.55 to 1.09; descriptive p=0.14). Estimated 5-year OS was 54.7% (95% CI 43.9 to 64.2) in the combination arm and 48.4% (95% CI 37.9 to 58.1) in the ipilimumab arm. Forty-seven (48.0%) and 65 (65.0%) patients in the combination and ipilimumab arms, respectively, received subsequent therapies. No new safety signals were reported.

At the 5-year follow-up, the improved response rates observed with T-VEC plus ipilimumab were durable. This is the first randomized controlled study of the combination of an oncolytic virus and a checkpoint inhibitor that meets its primary end point.Trial registration number: NCT01740297.

## BACKGROUND

Recent advances in treatment options, including checkpoint inhibitors and BRAF/MEK inhibitors, have significantly improved survival in patients with advanced melanoma.[1–6] Therapies with complementary mechanisms of action are attractive candidates to improve outcomes without increased toxicities. Talimogene laherparepvec (T-VEC), an oncolytic viral immunotherapy, is designed to produce granulocyte-macrophage colony-stimulating factor and enhance antitumor immunity.[7–10] Ipilimumab blocks inhibition of antitumor T-cells and promotes T-cell expansion.[11] The combination of these different yet complementary mechanisms is hypothesized to further augment the magnitude of the antitumor immune responses.

This phase Ib/II, multicenter, open-label study in patients with advanced melanoma was designed to provide proof of concept that the combination of an oncolytic virus and a checkpoint inhibitor was tolerable and would enhance clinical efficacy (NCT01740297). The phase Ib study evaluated the safety and tolerability of T-VEC plus ipilimumab (T-VEC-ipilimumab) in patients with treatment-naïve, unresectable, stage IIIB–IVM1c melanoma and has been reported previously.[12] The randomized phase II study further assessed the

safety and efficacy of the combination versus ipilimumab and met its primary end point; a significantly improved objective response rate (ORR) was observed with T-VEC-ipilimumab versus ipilimumab (39.0% vs 18.0%; OR 2.9; 95% CI 1.5 to 5.5; p=0.002) without increased toxicity.[13] Here, we report the final analysis of the study performed 5 years after the last patient was randomized.

## METHODS

### Patients

Eligible patients (≥18 years) had histologically confirmed stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c malignant melanoma not suitable for surgical resection; measurable and injectable disease; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate hematological, renal, hepatic, and coagulation function; either be treatment naïve or have received only one line of systemic anticancer therapy for cancers with *BRAF* wild-type or ≤2 lines for cancers with *BRAF* mutations; and have had no clinically active cerebral metastases.

### Study design

The study design and protocol were described previously.[13] Briefly, the phase II portion was an open-label, multicenter, randomized study conducted at 33 centers in the USA, France, and Germany between February 2013 and March 2021. Patients were randomized 1:1 to receive T-VEC-ipilimumab or ipilimumab (online supplemental figure 1). Thereafter, patients were followed up for safety until approximately 30 days after the last dose of T-VEC or 60 days after the last dose of ipilimumab, whichever occurred later, and long-term survival until approximately 60 months after the last patient was randomized in phase II. Data cut-off for this final analysis was March 31, 2021.

### Treatment

T-VEC was administered intralesionally at ≤4 mL of $10^6$ plaque-forming units (PFU)/mL (first dose), followed by ≤4 mL of $10^8$ PFU/mL 3 weeks later and every 2 weeks thereafter. T-VEC treatment continued until a complete response (CR), disappearance of all injectable lesions, confirmed disease progression (PD) per modified immune-related response criteria (irRC), or treatment intolerance, whichever occurred first. Ipilimumab (intravenous; 3 mg/kg every 3 weeks; ≤4 doses) was administered with the third dose of T-VEC in the combination arm and at week 1 in the ipilimumab arm.[13]

### End points and assessments

The primary end point was investigator-assessed confirmed ORR per modified irRC. Secondary end points included best overall response, disease control rate, durable response rate, time to response, duration of response, and progression-free survival (PFS) evaluated by the investigator using modified irRC, overall survival (OS), landmark OS by year, and safety. All adverse events (AEs), grade ≥3 AEs, serious AEs (SAEs), and AEs leading to treatment discontinuation were recorded and graded using the Common Terminology Criteria for Adverse Events v3.0.

### Statistical analysis

The planned sample size of approximately 200 patients was based on the comparison between the treatment arms for the primary efficacy end point of ORR using the intent-to-treat (ITT) analysis set using an overall two-sided 5% significance level to test the null hypothesis of no treatment effect. Efficacy was analyzed using the ITT set. Safety was analyzed using the safety analysis set, per the treatment received. Treatment effects on efficacy end points were evaluated and compared between the treatment arms according to the treatment as randomized. Summary statistics, including mean, standard deviation, median, and first and third quartiles, were provided for continuous variables. Frequency and percentage were summarized by treatment arm for the binary and categorical variables. For binary end points, exact binomial two-sided 95% CIs were provided. A $\chi^2$ test with continuity correction was used as appropriate. Unstratified log-rank tests were performed to test for time-to-event end points, which were estimated using the Kaplan-Meier method. HRs and corresponding 95% CIs were estimated using unstratified Cox proportional hazards models. Data presented for secondary end points, including p values, are strictly descriptive. Statistical analyses are detailed in the online supplemental material.

## RESULTS

### Patient disposition and characteristics

Overall, 198 patients were randomized to receive T-VEC-ipilimumab (n=98) or ipilimumab (n=100) (ITT set) (online supplemental figure 2). The safety analysis set included 95 patients in each treatment arm who received ≥1 dose of the study treatment. All 95 patients in the combination arm had discontinued T-VEC; the most frequently reported reasons for discontinuation were PD (40.0%), protocol-specified criteria (32.6%), and patient request (11.6%). Sixty-six (67.3%) patients in the combination arm and 66 (66.0%) patients in the ipilimumab arm had completed ipilimumab treatment. Among patients who discontinued ipilimumab early, the most frequently reported reasons for discontinuation in the combination arm and the ipilimumab arm were AEs (46.2% and 48.3%, respectively), PD (34.6% and 34.5%), and patient request (11.5% and 13.8%).

Baseline characteristics were generally balanced between the treatment arms (online supplemental material). In the combination arm, patients received T-VEC for a median (range) of 10.0 (1, 66) visits over 21.1 (0.1, 132.1) weeks. The median (range) total number of doses of ipilimumab (in patients who received ≥1 dose of ipilimumab) was 4.0 (0, 4) in the combination arm and 4.0 (1, 4) in the ipilimumab arm; the median (range) treatment duration was 9.1 (0.0, 14.1) weeks and 9.1 (0.1,

15.7) weeks, respectively. The median (range) actual follow-up time was 49.4 (0.2, 89.3) months and 35.8 (0.1, 87.4) months in the combination and ipilimumab arms, respectively.

### Response rate

The confirmed ORR improved significantly with the combination (35.7%; 95% CI 26.3 to 46.0) compared with ipilimumab (16.0%; 95% CI 9.4 to 24.7), with an unadjusted OR of 2.9 (95% CI 1.5 to 5.7; p=0.003) (table 1). Overall, 20 (20.4%) and 6 (6.0%) patients in the combination and ipilimumab arms, respectively, achieved CR, while 15 (15.3%) and 10 (10.0%) achieved partial response (table 1). Twenty (20.4%) patients in the combination arm and 24 (24.0%) patients in the ipilimumab arm had stable disease (SD); 30 (30.6%) and 35 (35.0%) patients, respectively, had progressive disease.

The disease control rate was higher with the combination (56.1%; 95% CI 45.7 to 66.1) than with ipilimumab (40.0%; 95% CI 30.3 to 50.3), with a significant rate difference of 16.1% (95% CI 1.5 to 29.9) and an unadjusted OR of 1.9 (95% CI 1.1 to 3.4; descriptive p=0.033).

The durable response rate was higher with the combination (33.7%; 95% CI 24.4 to 43.9) than with ipilimumab (13.0%; 95% CI 7.1 to 21.2), with an unadjusted OR of 3.4 (95% CI 1.7 to 7.0; descriptive p=0.001) (table 1). The median time to response was 8.4 months (95% CI 5.5 to 11.0) in the combination arm and was not reached in the ipilimumab arm (range: 0.0+, 49.1+), where '+' indicates the value is a censoring time. Among the 35 responders in the combination arm, the median time to response was 5.2 months (95% CI 2.7 to 5.4). Among the 16 responders in the ipilimumab arm, the median time to response was 2.8 months (95% CI 2.7 to 5.1). Among the 35 objective responders in the combination arm, the median duration of response was 69.2 months (95% CI 38.5 to not estimable [NE]). Among the 16 objective responders in the ipilimumab arm, the median duration of response was not reached (range: 2.8+, 61.1+ months).

Of the five patients who previously progressed on programmed cell death protein (PD)-1 inhibitors, four (n=1, combination arm; n=3, ipilimumab arm) had a best overall response of PD, and one patient in the combination arm had a best overall response of SD per modified irRC (data not shown). All five patients died by the end of the study.

### Progression-free survival

At the final analysis, 49.0% of patients in the combination arm and 45.0% in the ipilimumab arm had progression events. The median PFS was 13.5 months (95% CI 5.2 to 25.0) with the combination and 6.4 months (95% CI 3.8 to 17.1) with ipilimumab (HR 0.78; 95% CI 0.55 to 1.09; descriptive p=0.14) (figure 1A). Analyses of PFS among prespecified subgroups showed that the median PFS was 13.9 and 6.4 months in the combination and ipilimumab arms, respectively, in patients enrolled in the USA (HR 0.70; 95% CI 0.49 to 1.00), 13.9 and 4.2 months in those aged ≥65 years (HR 0.56; 95% CI 0.35 to 0.90), and 19.1 and 7.3 months in those with baseline lactate dehydrogenase (LDH) ≤upper limit of normal (ULN) (HR 0.65; 95% CI 0.43 to 0.97) (figure 1B).

### Overall survival and landmark overall survival by year

At the final analysis, 45.9% of patients in the combination arm and 52.0% in the ipilimumab arm had died. The median OS was 84.9 months (95% CI 41.0 to NE) with the combination and 50.1 months (95% CI 32.0 to NE) with ipilimumab (HR 0.83; 95% CI 0.56 to 1.24, descriptive p=0.37) (figure 2A). The 1–5-year OS landmarks for the combination and ipilimumab arms, respectively, were 83.3% and 79.9%, 72.7% and 69.3%, 62.9% and 55.2%, 57.2% and 50.7%, and 54.7% and 48.4% (table 1). Median OS was 56.7 months with the combination and 32.0 months with ipilimumab in patients aged ≥65 years (HR 0.59; 95% CI 0.35 to 1.00) (figure 2B).

### Safety

Ninety-two (96.8%) patients in the combination arm and 90 (94.7%) patients in the ipilimumab arm had ≥1 AE; 46.3% and 43.2% in the combination and ipilimumab arms, respectively, had at least one ≥grade 3 AE (table 2). AEs attributed to T-VEC were reported in 82 (86.3%) patients in the combination arm. A total of 75 (78.9%) and 78 (82.1%) patients in the combination and ipilimumab arms, respectively, had AEs attributed to ipilimumab. Six (6.3%) patients in the combination arm discontinued T-VEC due to AEs; 13 (13.7%) patients in the combination arm and 17 (17.9%) patients in the ipilimumab arm discontinued ipilimumab due to AEs. SAEs were reported in 34 (35.8%) patients in the combination arm and 34 (35.8%) patients in the ipilimumab arm. Ten (10.5%) patients in the combination arm had SAEs considered related to T-VEC; 14 (14.7%) patients in the combination arm and 19 (20.0%) patients in the ipilimumab arm had SAEs considered related to ipilimumab. Fatal AEs were reported for five (5.3%) patients in the combination arm (autoimmune hepatitis, malignant melanoma, malignant neoplasm progression, central nervous system metastases, and myocardial infarction) and one (1.1%) patient in the ipilimumab arm (malignant melanoma).

### Subsequent therapies

Forty-seven (48.0%) patients in the combination arm and 65 (65.0%) patients in the ipilimumab arm received subsequent therapies, primarily PD-1 inhibitors (n=33 (33.7%) and n=48 (48.0%), respectively). The median (95% CI) time to the first subsequent anticancer therapy

**Table 1** Response to therapy (intent-to-treat analysis set)

| Variable | Primary analysis | | Final analysis | | |
|---|---|---|---|---|---|
| | T-VEC plus ipilimumab (n=98) | Ipilimumab (n=100) | T-VEC plus ipilimumab (n=98) | Ipilimumab (n=100) | Statistical results |
| Objective response rate (CR/PR) | 38 (39.0) | 18 (18.0) | 35 (35.7) | 16 (16.0) | 19.7 (6.8 to 31.9)* |
| 95% CI† | | | (26.3 to 46.0) | (9.4 to 24.7) | 0.003‡ |
| | | | | | 2.9 (1.5 to 5.7)§ |
| Best overall response | | | | | |
| CR | 13 (13.0) | 7 (7.0) | 20 (20.4) | 6 (6.0) | |
| PR | 25 (26.0) | 11 (11.0) | 15 (15.3) | 10 (10.0) | |
| SD | 19 (19.0) | 24 (24.0) | 20 (20.4) | 24 (24.0) | |
| PD | 31 (32.0) | 33 (33.0) | 30 (30.6) | 35 (35.0) | |
| Unevaluable | 4 (4.0) | 17 (17.0) | 7 (7.1) | 16 (16.0) | |
| Not done | 6 (6.0) | 8 (8.0) | 6 (6.1) | 9 (9.0) | |
| Disease control | | | | | |
| Disease control rate (CR/PR/SD) | 57 (58.0) | 42 (42.0) | 55 (56.1) | 40 (40.0) | 16.1 (1.5 to 29.9)* |
| 95% CI† | | | (45.7 to 66.1) | (30.3 to 50.3) | 0.033‡ |
| | | | | | 1.9 (1.1 to 3.4)§ |
| Durable response | | | | | |
| Durable response rate | | | 33 (33.7) | 13 (13.0) | 20.7 (8.2 to 32.4)* |
| 95% CI† | | | (24.4 to 43.9) | (7.1 to 21.2) | 0.001‡ |
| | | | | | 3.4 (1.7 to 7.0)§ |
| Progression-free survival (KM) (months) | | | | | |
| Median (95% CI) | 8.2 (4.2 to 21.5) | 6.4 (3.2 to 16.5) | 13.5 (5.2 to 25.0) | 6.4 (3.8 to 17.1) | |
| OS | | | | | |
| Deaths | | | 45 (45.9) | 52 (52.0) | |
| Median¶ (95% CI), months | | | 84.9 (41.0 to NE) | 50.1 (32.0 to NE) | |
| Estimated OS at 12 months¶, % (95% CI) | | | 83.3 (74.2 to 89.4) | 79.9 (70.4 to 86.7) | 3.4 (–7.6 to 14.4)* |
| Estimated OS at 24 months¶, % (95% CI) | | | 72.7 (62.5 to 80.5) | 69.3 (58.9 to 77.5) | 3.4 (–9.5 to 16.3)* |
| Estimated OS at 36 months¶, % (95% CI) | | | 62.9 (52.3 to 71.7) | 55.2 (44.5 to 64.6) | 7.7 (–6.4 to 21.8)* |
| Estimated OS at 48 months¶, % (95% CI) | | | 57.2 (46.5 to 66.5) | 50.7 (40.1 to 60.3) | 6.5 (–7.8 to 20.8)* |
| Estimated OS at 60 months¶, % (95% CI) | | | 54.7 (43.9 to 64.2) | 48.4 (37.9 to 58.1) | 6.3 (–8.1 to 20.7)* |

Data presented as number (%) of patients unless specified otherwise.
Confirmed CR/PR/PD per modified irRC refers to the initiating CR/PR/PD of two consecutive CR/PR/PD that are ≥4 weeks apart. The PD without confirmation was not considered as confirmed PD with only one exception: if the last tumor assessment was an initialization of PD and patients had ended radiographic follow-up due to rapid clinical deterioration.
Durable response rate was defined as the incidence rate of patients with a duration of response per modified irRC of ≥6 months; 1 month=365.25/12 days.
Progression-free survival was defined as the time from randomization to the first confirmed disease progression per modified irRC, or death.
OS was defined as the time from randomization to death from any cause.
*Rate difference (95% CI) (T-VEC plus ipilimumab–ipilimumab).
†The Clopper-Pearson method was used to calculate exact CIs for binary end points. Wilson score method with continuity correction was used to calculate an approximate CI for between-arm differences in binary rates.
‡p value from the $\chi^2$ test with continuity correction.
§Unadjusted OR (95% CI) obtained from the unstratified logistic regression model.
¶Calculated using the KM method.
CR, complete response; irRC, immune-related response criteria; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; T-VEC, talimogene laherparepvec.

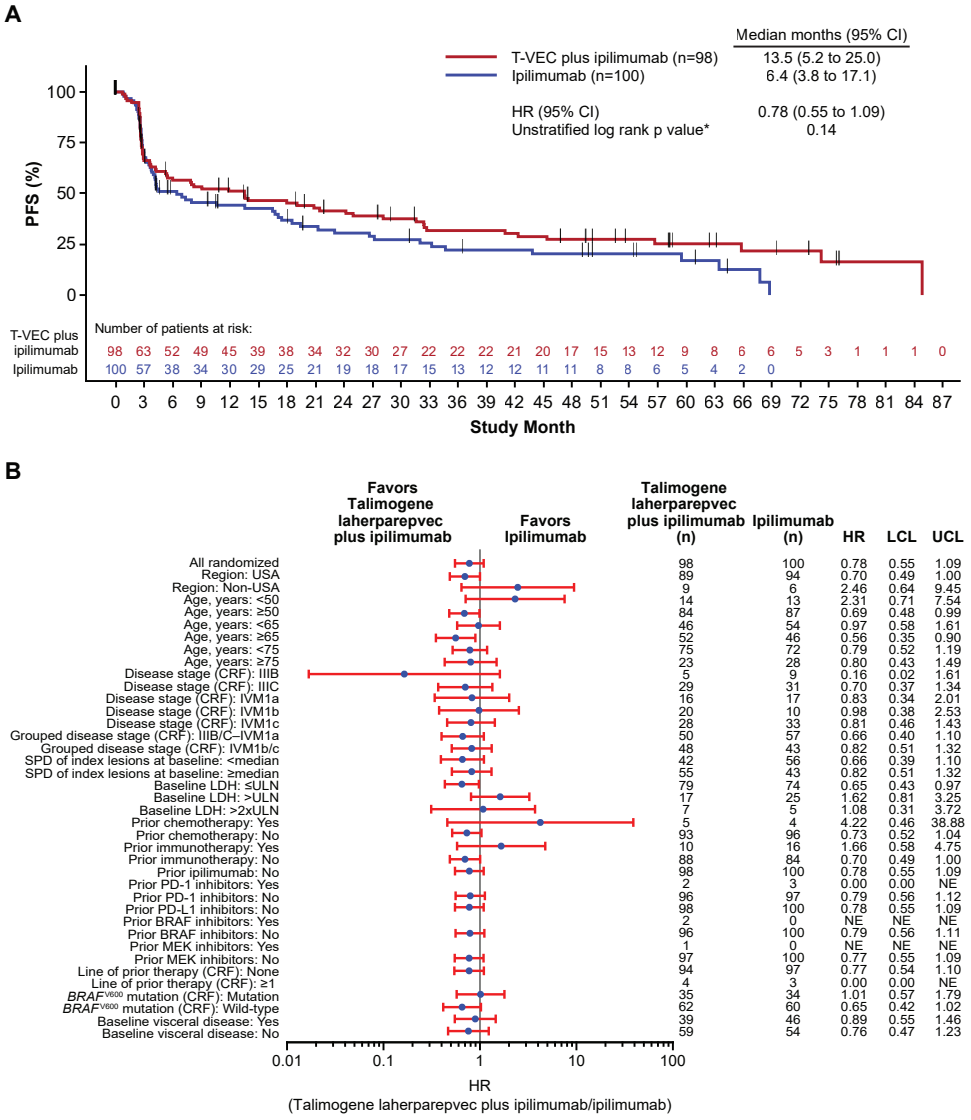


**Figure 1** (A) Kaplan-Meier estimate of PFS in the intent-to-treat population. (B) Forest plot for PFS in subgroups. *p value is descriptive. Vertical lines indicate censoring. LCL and UCL denote the lower and upper limits of 95% CI, respectively. The intent-to-treat analysis set included all randomized patients regardless of whether they received study treatment. PFS was defined as the time from randomization to the first confirmed disease progression per modified immune-related response criteria, or death, whichever occurred earlier. Patients without documented death or disease progression were censored at their last evaluable tumor assessment date. CRF, case report form; LCL, lower confidence limit; LDH, lactate dehydrogenase; NE, not estimable; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SPD, sum of the products of the two largest perpendicular diameters; T-VEC, talimogene laherparepvec; UCL, upper confidence limit; ULN, upper limit of normal.

was 27.7 months (15.9 to NE) with the combination and 8.3 months (4.8 to 14.3) with ipilimumab.

## DISCUSSION

At the 5-year follow-up, T-VEC-ipilimumab continued to provide durable and improved ORR versus ipilimumab in patients with advanced melanoma. The combination did not provide statistically significant PFS or OS benefits in the overall patient population. Survival may have been confounded by subsequent anticancer therapies because patients receiving ipilimumab alone had greater utilization of subsequent therapies and shorter time to initiation of subsequent therapies after ending study treatment than those receiving the combination. However, when accounting for the confounding effects of starting selected subsequent anticancer medication (ipilimumab, vemurafenib, dabrafenib, trametinib, nivolumab, and pembrolizumab), OS was not different between the treatment arms (HR 0.84; 95% CI 0.53 to 1.34). No new safety signals were reported.

Patients who responded to the combination treatment continued to have durable responses, lasting a median of 69.2 months. The prolonged duration of response achieved with the combination appeared to be an

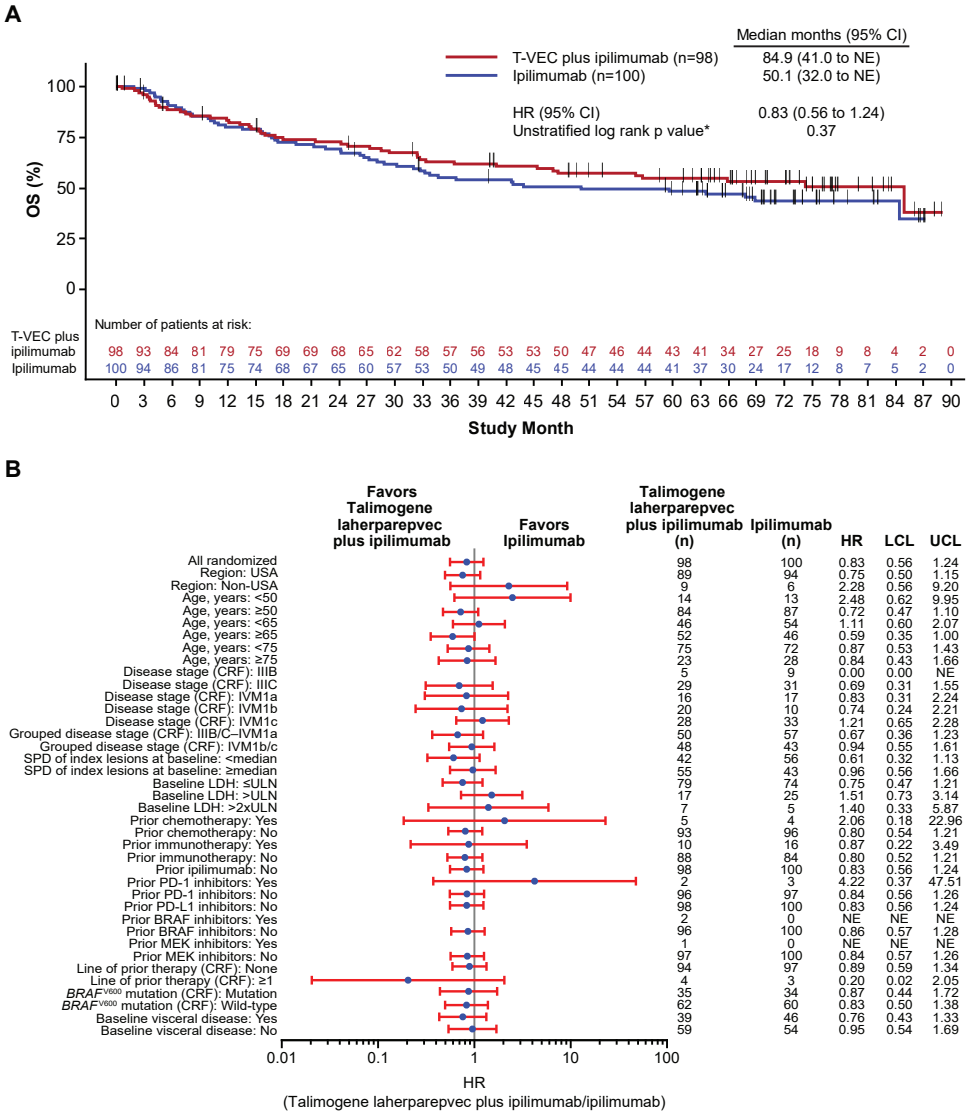


**Figure 2** (A) Kaplan-Meier estimate of OS in the intent-to-treat population. (B) Forest plot for OS in subgroups. *p value is descriptive. Vertical lines indicate censoring. LCL and UCL denote the lower and upper limits of 95% CI, respectively. The intent-to-treat analysis set included all randomized patients regardless of whether they received study treatment. OS was defined as the time from randomization to death from any cause. Patients without documented death at the time of analysis were censored on the date that they were last known to have been alive. One month=365.25/12 days. CRF, case report form; LCL, lower confidence limit; LDH, lactate dehydrogenase; NE, not estimable; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; SPD, sum of the products of the two largest perpendicular diameters; T-VEC, talimogene laherparepvec; UCL, upper confidence limit; ULN, upper limit of normal.

important contributor to the improved outcomes. The confirmed ORR (35.7%) with the combination was more than double that observed with ipilimumab (16.0%; OR 2.9; 95% CI 1.5 to 5.7; p=0.0003). This ORR was also higher than that elicited by either agent administered as monotherapy (ipilimumab, 11%–19%; T-VEC, 26.4%).[2 8 14 15] The median PFS with the combination (13.5 months) was longer than that observed with ipilimumab (6.4 months), consistent with that observed at the primary analysis.[13] As observed at the 4-year follow-up, median OS was not reached for the combination and was 50.1 months for ipilimumab (HR 0.82; 95% CI 0.54 to 1.25; p=0.36).[16] Sustained 5-year OS was observed in a greater percentage of patients who received the combination (54.7%) than in those who received ipilimumab (48.4%). The durable response rate with T-VEC-ipilimumab in this study was 33.7%, compared with 13.0% with ipilimumab in this study and 16.3% with T-VEC monotherapy in OPTiM.[8] PFS favored the combination arm in specific subgroups (age ≥65 years; baseline LDH ≤ULN), whereas no differences in OS outcomes between treatment arms were seen in any subgroup. Collectively, these findings highlight the promising efficacy of T-VEC-ipilimumab in this overall patient population.

Although a vast majority of the patients were treatment naïve, a small subset (5/198) enrolled had received prior PD-1 inhibitors (pembrolizumab or nivolumab); these patients had a best overall response of either PD or SD

**Table 2** Incidence of treatment-emergent AEs (safety analysis set)

| Parameter | T-VEC plus ipilimumab (n=95) | | Ipilimumab (n=95) | |
|---|---|---|---|---|
| Any grade AEs | 92 (96.8) | | 90 (94.7) | |
| Grade ≥3 AEs | 44 (46.3) | | 41 (43.2) | |
| Grade ≥4 AEs | 6 (6.3) | | 4 (4.2) | |
| Serious AEs | 34 (35.8) | | 34 (35.8) | |
| Fatal AEs | 5 (5.3) | | 1 (1.1) | |
| AEs leading to discontinuation of T-VEC | 6 (6.3) | | NA | |
| AEs leading to discontinuation of ipilimumab | 13 (13.7) | | 17 (17.9) | |
| Any grade AEs occurring in ≥10% of patients in either arm | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Fatigue | 56 (58.9) | 1 (1.1) | 40 (42.1) | 3 (3.2) |
| Chills | 50 (52.6) | 0 | 4 (4.2) | 0 |
| Diarrhea | 40 (42.1) | 3 (3.2) | 35 (36.8) | 3 (3.2) |
| Rash | 40 (42.1) | 1 (1.1) | 29 (30.5) | 1 (1.1) |
| Pruritus | 39 (41.1) | 0 | 35 (36.8) | 0 |
| Pyrexia | 38 (40.0) | 1 (1.1) | 9 (9.5) | 0 |
| Nausea | 37 (38.9) | 2 (2.1) | 26 (27.4) | 0 |
| Headache | 34 (35.8) | 0 | 22 (23.2) | 1 (1.1) |
| Influenza-like illness | 29 (30.5) | 4 (4.2) | 1 (1.1) | 0 |
| Injection site pain | 27 (28.4) | 0 | 0 | 0 |
| Arthralgia | 21 (22.1) | 0 | 16 (16.8) | 1 (1.1) |
| Cough | 21 (22.1) | 0 | 11 (11.6) | 0 |
| Vomiting | 19 (20.0) | 0 | 13 (13.7) | 0 |
| Abdominal pain | 16 (16.8) | 1 (1.1) | 12 (12.6) | 1 (1.1) |
| Injection site reaction | 15 (15.8) | | 0 | |
| Constipation | 14 (14.7) | 0 | 9 (9.5) | 1 (1.1) |
| Edema peripheral | 14 (14.7) | 1 (1.1) | 5 (5.3) | 0 |
| Decreased appetite | 12 (12.6) | | 14 (14.7) | |
| Anemia | 11 (11.6) | 2 (2.1) | 6 (6.3) | 1 (1.1) |
| Back pain | 11 (11.6) | 2 (2.1) | 8 (8.4) | 2 (2.1) |
| Dizziness | 11 (11.6) | | 4 (4.2) | |
| Pain | 11 (11.6) | 1 (1.1) | 4 (4.2) | 1 (1.1) |
| Insomnia | 10 (10.5) | | 16 (16.8) | |
| Lymphopenia | 10 (10.5) | 4 (4.2) | 3 (3.2) | 2 (2.1) |
| Myalgia | 10 (10.5) | | 4 (4.2) | |
| Dyspnea | 9 (9.5) | 3 (3.2) | 10 (10.5) | 1 (1.1) |
| Asthenia | 8 (8.4) | 2 (2.1) | 10 (10.5) | 0 |
| Colitis | 8 (8.4) | 5 (5.3) | 14 (14.7) | 7 (7.4) |

Data presented as number (%) of patients.
Safety analysis set included all patients who received ≥1 dose of T-VEC or ipilimumab. Treatment-emergent AEs were defined as any AE occurring after initiation of the first dose of any study treatment through 30 days after the last administration of T-VEC or 60 days after the last dose of ipilimumab, whichever occurred later.
If a patient had multiple AEs of the same PT, the one with the worst grade is presented.
AE, adverse event; NA, not applicable; PT, preferred term; T-VEC, talimogene laherparepvec.

at the final analysis. This study was initiated at a time when the PD-1–refractory patient population was scarce and therefore was not a focus of our analysis. With the current broader adoption of PD-1 inhibitors, the promising durable responses observed with T-VEC-ipilimumab in the treatment-naïve setting could support further

investigation of this combination in the immunotherapy-refractory setting, which remains an unmet need in advanced melanoma.

T-VEC was tested in combination with pembrolizumab in treatment-naïve patients with advanced melanoma (MASTERKEY-265).[17 18] While phase Ib reports showed promising tumor responses, in the randomized phase III portion, T-VEC-pembrolizumab treatment did not significantly improve PFS (HR 0.86; 95% CI 0.71 to 1.04; p=0.13) or OS (HR 0.96; 95% CI 0.76 to 1.22; p=0.74) compared with placebo-pembrolizumab, although the subgroup-specific PFS trends were similar to those observed in the current study.[17 18] Different checkpoint inhibitors likely have different mechanisms of action, which might explain why T-VEC-ipilimumab conferred significant benefits whereas T-VEC-pembrolizumab did not.

Toxicity observed with T-VEC-ipilimumab was consistent with that observed at the primary analysis, the patients' underlying disease, and other T-VEC and ipilimumab studies.[8 12 14] Five-year outcomes from this study represent the longest follow-up of patients who received T-VEC-ipilimumab.[13]

In conclusion, this is the first randomized controlled study of an oncolytic virus combined with a checkpoint inhibitor that meets its primary end point. T-VEC-ipilimumab provided durable responses with tolerable safety in patients with advanced melanoma. These data support the potential of T-VEC-ipilimumab treatment to improve long-term outcomes in patients with advanced melanoma without additional toxicity.

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