

**Article Category:** Clinical Trial: Research Articles

**Article Title:** **Talimogene Laherparepvec and Pembrolizumab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (MASTERKEY-232): A Multicenter, Phase 1b Study**

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**Journal:** *Clinical Cancer Research*

**Running title:** T-VEC in combination with pembrolizumab in R/M HNSCC

**Key words:** talimogene laherparepvec; pembrolizumab; R/M HNSCC; oncolytic virus; combination immunotherapy.

**Funding:** This study is funded by Amgen Inc.

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**Word count:** Abstract: 249 / 250  
Manuscript: 3587 / 5000  
Tables/Figures: 6 / 6

**Disclosures:** Harrington: honoraria from Amgen Inc., AstraZeneca, BMS, Merck & Co, MSD, and Pfizer; consulting or advisory role for Amgen Inc., AstraZeneca, BMS, Merck & Co, MSD, and Pfizer; speakers bureau for Amgen Inc., AstraZeneca, BMS, Merck & Co, MSD, and Pfizer; research funding from AstraZeneca and MSD; travel accommodation from MSD

Kong: honoraria from Merck & Co and BMS; consulting or advisory role for Centauri Therapeutics, Amgen Inc., Puma Biotechnology, and Merck & Co; speakers bureau for BMS, MSD and Merck & Co; research funding from Puma Biotechnology, and AstraZeneca; travel accommodation from MSD, and Merck & Co

Mach: stock or other ownership in MaxiVAX SA; honoraria from BMS; consulting or advisory role for Amgen Inc., BMS, Roche, MSD, and AstraZeneca; research funding from MaxiVAX SA

Chesney: consulting or advisory role for Replimune and Amgen Inc.; research funding from Amgen Inc., Merck & Co, and BMS; patents royalties, or other intellectual property with University of Louisville; travel accommodations from Replimune.

Fernandez: consulting or advisory role for EISAI.

Rischin: advisory role for Amgen, Merck, BMS, GSK, Regeneron, Sanofi – all uncompensated; Travel accommodation – Merck, GSK; Research Funding – Sanofi, Roche-Genentech

Cohen: consulting or advisory role for Amgen, AstraZeneca, Bayer, BMS, Incyte, MSD, and Merck

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## **Abstract**

### **Background**

The prognosis for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is poor, and only a minority of patients benefit from checkpoint immunotherapy. Talimogene laherparepvec (T-VEC), an oncolytic immunotherapy approved for advanced melanoma, in combination with pembrolizumab may yield enhanced antitumor activity over either agent alone.

### **Methods**

This was a phase 1b/3, multicenter trial testing intratumoral T-VEC combined with intravenous pembrolizumab in R/M HNSCC refractory to platinum-based chemotherapy. For phase 1b, primary endpoint was incidence of dose-limiting toxicity (DLT). Key secondary endpoints included objective response rate and progression-free survival (PFS) per irRECIST, overall survival (OS), and safety.

### **Results**

Thirty-six patients were enrolled into the phase 1b study. The data cutoff date was August 28, 2018. Median follow up was 5.8 months (range: 0.3–24.2). One DLT of T-VEC-related fatal arterial hemorrhage was reported. Twenty (55.6%) and 21 (58.3%) patients experienced adverse events (AEs) related to T-VEC and pembrolizumab, respectively. Besides the DLT, there were no treatment-related fatal AEs. A confirmed partial response was observed in 5 (13.9%) patients. Ten (27.8%) patients were unevaluable for response due to early death. Median PFS and OS were 3.0 months (95% CI, 2.0–5.8) and 5.8 months (95% CI, 2.9–11.4), respectively.

### **Conclusions**

The combination of T-VEC and pembrolizumab demonstrated a tolerable safety profile in R/M HNSCC. The efficacy with the combination was similar to that with pembrolizumab monotherapy

in historical HNSCC studies. Phase 3 part of this study was not further pursued (ClinicalTrials.gov Identifier: NCT02626000).

### **Translational Relevance**

Recurrent or metastatic squamous cell carcinoma of the head and neck (R/M HNSCC) represents a disease setting with considerable clinical complexity and a poor prognosis. In this phase 1b study, we tested a novel combination of talimogene laherparepvec, a genetically modified herpes simplex virus-1–based oncolytic immunotherapy, and pembrolizumab, a humanized monoclonal antibody against PD-1, in R/M HNSCC. We hypothesized that combining these two agents with complementary roles in activating antitumor immune responses might augment the activity of either agent alone. This combination demonstrated manageable toxicities and antitumor efficacy comparable to that with single-agent pembrolizumab in historical HNSCC studies. Responses were durable, with most responders having responses still ongoing at data cutoff. Even though the response to the combination did not appear to be superior to previous reports of pembrolizumab monotherapy, this study provides insights into the design of future trials testing combinatorial immunotherapeutic regimens.

## Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is a common and frequently lethal malignancy, with approximately 800,000 newly diagnosed cases and 400,000 deaths worldwide in 2018 (1). For most patients with recurrent or metastatic (R/M) HNSCC, the previous first-line treatment options included platinum-based agents, fluorouracil, and cetuximab in various combinations, depending on the patient's performance status, comorbidities, prior treatments, and geographical variations in therapies supported by different healthcare systems (2,3). The median overall survival (OS) was 7.4 months with chemotherapy and 10.1 months with chemotherapy plus cetuximab in the first-line setting. (3) Checkpoint inhibitor immunotherapies are now approved as a single agent (first-line or second-line) or in combination with chemotherapy (first-line) in these patients (4-6).

The programmed death 1 (PD-1) receptor is expressed on activated T cells and interacts with its ligands, PD-L1 and PD-L2, to prevent healthy cells from autoimmune attacks. Excessive expression of PD-L1 or PD-L2 tumor or stromal cells can result in immune evasion, leading to recurrence and metastasis of the tumor (7). Pembrolizumab is a humanized, monoclonal PD-1 antibody that has demonstrated antitumor activity and a tolerable safety profile in multiple tumor types. It is currently approved as a single agent or in combination with platinum and fluorouracil, with certain restrictions based on PD-L1 combined positive score (CPS) in some jurisdictions, for the first-line treatment of patients with R/M HNSCC, replacing the previous use of EXTREME regimen (platinum and fluorouracil chemotherapy with cetuximab) in this setting; single-agent pembrolizumab is also approved for the treatment of patients with disease progression on or after platinum-based chemotherapy (5,8,9). In the phase 3 KEYNOTE-048 trial comparing pembrolizumab alone or with platinum and fluorouracil chemotherapy versus cetuximab with chemotherapy in patients with previously untreated R/M HNSCC, the objective response rate (ORR) with pembrolizumab was 17% in the total population, 23% in the population with PD-L1 CPS

of  $\geq 20$ , and 19% in the population with PD-L1 CPS of  $\geq 1$ . Pembrolizumab alone or with chemotherapy improved OS versus cetuximab with chemotherapy in the CPS of  $\geq 20$  and CPS of  $\geq 1$  populations. In the total population, the median OS associated with pembrolizumab plus chemotherapy was significantly longer than that associated with cetuximab plus chemotherapy (13.0 months vs 10.7 months, HR 0.77 [95% CI 0.63–0.93],  $p=0.0034$ ) (6). In the phase 2 KEYNOTE-055 and phase 3 KEYNOTE-040 HNSCC trials of pembrolizumab that required disease progression during or after platinum-based chemotherapy, the ORR was 16% and 14.6%, respectively (10,11). In the KEYNOTE-040 comparing pembrolizumab against investigator's choice of methotrexate, docetaxel, or cetuximab (standard of care), pembrolizumab prolonged OS as compared with standard of care (8.4 months, 95% confidence interval [CI] 6.4–9.4 vs. 6.9 months, 95% CI 5.9–8.0, hazard ratio 0.80, 0.65–0.98; nominal  $p = 0.0161$ ) (11).

Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex virus-1–based oncolytic immunotherapy designed to preferentially replicate in tumors, produce granulocyte-macrophage colony-stimulating factor, and stimulate antitumor immune responses (12). T-VEC was the first U.S. Food and Drug Administration (FDA)-approved oncolytic viral therapy for the treatment of unresectable, cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery (13). T-VEC has been previously studied in a phase 1/2 clinical trial, where patients with untreated stage III/IV HNSCC received chemoradiation with concomitant cisplatin and 4 intratumoral injections of T-VEC at escalating doses, followed by neck dissection (14). Fourteen of 17 patients (82.4%) had a response, with 4 (23.5%) complete and 10 (58.8%) partial responses (CR and PR), and 93% of patients reached confirmed pathologic complete remission at the neck dissection.

Combining T-VEC, which increases tumor-specific immune activation, with pembrolizumab may yield an enhanced antitumor response over either agent alone. The combination of an oncolytic virus with a checkpoint inhibitor was previously tested in melanoma. In a phase 1b clinical trial of

T-VEC in combination with systemic administration of pembrolizumab in patients with advanced melanoma, the confirmed ORR was 67% with a CR rate of 43% (15). Increased CD8+ T cells and upregulation of PD-L1 and IFN- $\gamma$  were observed in tumors from responders (16). Another randomized, phase 2 trial of T-VEC in combination with ipilimumab, which blocks cytotoxic T lymphocyte-associated antigen 4, met its primary endpoint: intratumoral T-VEC plus systemic ipilimumab resulted in a significantly higher ORR without additional safety signals than ipilimumab alone in patients with advanced melanoma (39% vs. 18%,  $p = 0.002$ ) (17). The treatment effect of T-VEC as a monotherapy or in combination with checkpoint inhibitors has been observed in both injected and uninjected (including visceral) melanoma lesions, indicating that a systemic antitumor immune response was triggered (18,19). These results suggest that T-VEC may improve the efficacy of checkpoint inhibitor immunotherapies by changing the tumor microenvironment and support the rationale that combining immunotherapies with complementary mechanisms of action may yield augmented antitumor responses.

The objective of this study was to evaluate the safety and preliminary efficacy of the combination of intratumoral injection of T-VEC and intravenous pembrolizumab in patients with R/M HNSCC.



## **Methods**

### ***Patients***

Eligible patients had an age of 18 years or older; the Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that was not suitable for curative surgical resection; disease progression after treatment with a platinum-based regimen, defined as one of the following: (1) disease progression or recurrence between 3 and 6 months of prior curatively intended multimodal therapy, which includes platinum therapy, for locoregionally advanced HNSCC (this criterion was applicable only to patients who had not received treatment in the R/M setting), or (2) disease progression or recurrence after prior platinum-based therapy in the R/M setting; disease suitable for intratumoral therapy administration through the skin (non-visceral injection); and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Key exclusion criteria included known active central nervous system metastases and any systemic or local therapy 28 days prior to enrollment (including chemotherapy, targeted therapy, radiotherapy, surgery). Following 1 dose-limiting toxicity (DLT) of fatal arterial hemorrhage (see Results section), the protocol was amended to exclude patients with tumor that directly contacts or encases a major blood vessel and ulceration and/or fungation onto the skin surface and patients who had undergone re-irradiation.

### ***Study Design***

This was a phase 1b/3, multicenter trial. In the phase 1b part of the study, T-VEC was administered in combination with pembrolizumab to 36 patients with R/M HNSCC. The first dose of T-VEC was administered at the concentration of  $10^6$  plaque-forming units (PFU)/mL for up to 8 mL, followed by up to 8 mL of  $10^8$  PFU/mL every 3 weeks ( $\pm$  3 days). The study allowed for multiple injection sites. T-VEC was administered by intratumoral injection into cutaneous, subcutaneous, and nodal lesions if injectable (with or without ultrasound-based image guidance) but was not

administered into mucosal or visceral lesions. T-VEC was administered before pembrolizumab on treatment days, and investigators injected as many lesions as possible to the maximum volume of 8 mL. Pembrolizumab was given intravenously at the dose of 200 mg every 3 weeks ( $\pm$  3 days). Treatment continued until CR, no injectable lesions, confirmed progressive disease per immune-related RECIST (irRECIST) (20), intolerance of study treatment, or 24 months from the date of the first dose, whichever occurred first. DLTs were evaluated in the first 16 DLT-evaluable patients. An additional 20 patients were enrolled to further evaluate safety and efficacy of the combination to support a decision to initiate the phase 3 part of the study.

The phase 3 part of the study was planned as a multicenter, placebo-controlled, double-blind, randomized study to evaluate the efficacy, as assessed by OS, of the treatment with T-VEC plus pembrolizumab versus placebo plus pembrolizumab in patients with R/M HNSCC. Statistical considerations for proceeding to the phase 3 study are described below.

### ***Endpoints***

For the phase 1b study, the primary endpoint was incidence of DLT. Secondary endpoints included ORR per irRECIST (CR + PR), best overall response, duration of response, disease control rate (DCR, CR + PR + stable disease [SD]), and progression-free survival (PFS) per irRECIST, OS, and safety.

### ***Assessments***

DLTs were evaluated among the first 16 DLT-evaluable patients. An additional 20 treated patients were enrolled to further evaluate safety and to estimate efficacy. The DLT evaluation period was 6 weeks from the initial administration of the treatment.

A modified version of RECIST 1.1, irRECIST, was used by the investigators to assess tumor response. Radiographic tumor assessments were performed independent of treatment cycle at baseline, week 9 ( $\pm$  1 week), week 18 ( $\pm$  1 week), and then every 9 weeks ( $\pm$  1 week) until confirmed progressive disease per irRECIST or the start of a new anticancer treatment. Patients

completed a safety follow-up visit approximately 30 ( $\pm$  7) days after the last dose of study treatment. After safety follow-up, patients entered long-term follow-up and were followed up for survival and subsequent anticancer therapies every 12 weeks ( $\pm$  28 days) for approximately 36 months after the last patient was enrolled. PD-L1 positivity used in this manuscript was defined using a CPS  $\geq$  1 cutoff.

### ***Statistical Analyses***

The DLT analysis set was used to summarize the incidence of DLT and included DLT-evaluable patients who had the opportunity to be on treatment for at least 6 weeks from the initial dosing and had received at least 2 doses of T-VEC and 2 doses of pembrolizumab in combination or had a DLT during the DLT evaluation period after at least 1 dose of T-VEC and pembrolizumab in combination. According to a sequential stopping rule, up to 18 DLT-evaluable patients could be enrolled to assess the DLT profile of the combination therapy. The design achieved a 7.7% 1-sided significance level and 81.6% power to test the null hypothesis of a DLT rate  $\leq$  10% versus the alternative hypothesis of a rate  $\geq$  33%.

The safety analysis set, which included all enrolled patients who received at least 1 dose of T-VEC or pembrolizumab, was used for all analyses of safety endpoints except DLT, including incidence of treatment-emergent and treatment-related adverse events (AEs). The full analysis set, including all patients who had received at least 1 dose of T-VEC and 1 dose of pembrolizumab in combination, was used for all efficacy analyses.

One key secondary endpoint was ORR per irRECIST by investigator assessment with or without confirmation. The expected ORR for pembrolizumab in the study population with 9 weeks minimum potential follow-up was assumed to be approximately 11%. A Bayesian analysis was performed to calculate the posterior probability that the true ORR of the T-VEC and pembrolizumab combination exceeded the expected ORR for pembrolizumab by an absolute

amount, with the assumption that observed efficacy would be minimally consistent with monotherapy historical data.

## Results

### ***Patients and Treatment***

From April 06, 2016 to August 28, 2017, a total of 36 patients were enrolled into this phase 1b study. The data cutoff for this analysis was August 28, 2018. The first 16 patients were DLT-evaluable and constituted the DLT analysis set. A cohort of an additional 20 patients was enrolled to further evaluate safety and estimate efficacy. All 36 patients received at least 1 dose of T-VEC and pembrolizumab in combination and were included in both the safety and full analysis sets.

Baseline and demographic characteristics are summarized in **Table 1**. The median age was 62 years (range: 35–77), and most patients were male (80.6%). The primary tumor sites were oral cavity (20/36, 55.6%), oropharynx (9/36, 25.0%), larynx (4/36, 11.1%), and hypopharynx (3/36, 8.3%). Of the 9 patients with oropharyngeal cancer, 5 were human papillomavirus (HPV)-positive, and 4 were HPV-negative at baseline. Most patients (63.9%) had locoregionally recurrent disease. Thirteen patients (36.1%) had metastatic disease (patients with both locoregional and metastatic disease were considered as having metastatic disease). All patients had received prior anticancer therapies. Type of prior therapy (all lines) included chemotherapy (100.0%), radiotherapy (91.7%), targeted biologics (16.7%), and immunotherapy (8.3%). Nineteen patients (52.8%) had prior lines of therapy in the R/M setting, with 3 patients (8.3%) having received 4 lines. Twenty-eight patients (77.8%) were positive for PD-L1 at baseline.

As of the data cutoff, 1 year after the last patient was enrolled, 25 patients (69.4%) had died, and 11 patients (30.6%) were continuing study (**Figure 1**). The median follow-up time was 5.8 months (range: 0.3–24.2).

### ***Safety***

One DLT (6.3%), fatal arterial hemorrhage related to T-VEC, was observed in the DLT analysis set. The DLT occurred in a 45-year old female with an initial diagnosis of stage III HNSCC of oral cavity and no history of tobacco or alcohol use. After tumor resection followed by adjuvant

radiation, disease progressed in the right cervical lymph node and recurred after platinum-based chemotherapy in combination with cetuximab. Tumor surrounded the right carotid artery, and there was ulceration of the right cervical lymph node to the skin surface. The patient then received 2 doses of the combination of T-VEC plus pembrolizumab. T-VEC was injected into the right cervical lymph node 1cm away from the ulcerated tumor. The size of the tumor ulcer further increased. After the 2nd dose, the patient presented to the emergency department with bleeding from the tumor wound on the right neck and died of acute arterial hemorrhage. The DLT led to a protocol amendment to exclude high-risk patients with tumor that directly contacted or encased a major blood vessel, and in whom there was ulceration and/or fungation onto the skin surface, as well as patients with a history of re-irradiation to a portal, which included the carotid arteries.

Safety results are summarized in **Table 2**. Twenty of 36 (55.6%) patients experienced T-VEC-related AEs of any grade, with the most common events (reported in more than 1 patient) being pyrexia (22.2%), influenza-like illness (11.1%), asthenia (8.3%), injection site pain (8.3%), body temperature increase (5.6%), fatigue (5.6%), nausea (5.6%), and vomiting (5.6%). Two patients (5.6%) discontinued T-VEC due to T-VEC-related AEs, mucosal hemorrhage and tumor ulceration, respectively. Except for the DLT, there were no T-VEC-related fatal AEs.

Pembrolizumab-related AEs of any grade were reported in 21 of 36 patients (58.3%), and the most common events (reported in more than 1 patient) were pyrexia (19.4%), fatigue (16.7%), asthenia (8.3%), hypothyroidism (8.3%), body temperature increase (5.6%), diarrhea (5.6%), influenza-like illness (5.6%), nausea (5.6%), stomatitis (5.6%), and vomiting (5.6%). Pembrolizumab-related AEs led to pembrolizumab discontinuation in 2 patients (5.6%, euglycemic diabetic ketoacidosis and hepatitis, respectively) and T-VEC discontinuation in 1 patient (2.8%, euglycemic diabetic ketoacidosis). There were no fatal AEs related to pembrolizumab.

Seven patients (19.4%) reported T-VEC-related serious AEs, which included pyrexia (5.6%), arterial hemorrhage (2.8%), chills (2.8%), mucosal hemorrhage (2.8%), odynophagia (2.8%), and pain (2.8%). Seven patients (19.4%) reported pembrolizumab-related SAEs, which included pyrexia (5.6%), eczema (2.8%), euglycemic diabetic ketoacidosis (2.8%), hepatitis (2.8%), infusion-related reaction (2.8%), musculoskeletal chest pain (2.8%), and pain (2.8%). Three patients (8.3%) had 2 SAEs related to both agents: pyrexia (occurred in 2 patients) and pain (at the right supraclavicular region, occurred in 1 patient).

### ***Efficacy***

Of the 36 enrolled patients, 5 had a confirmed objective response to the combination of T-VEC plus pembrolizumab, resulting in an ORR of 13.9% (95% CI, 4.7–29.5) per irRECIST. No patient achieved CR (**Table 3**). Nine patients (25%) had SD, which together with 5 confirmed PRs, resulted in a DCR (CR + PR + SD) of 38.9%. The first tumor assessment at week 9 could not be done in 10 patients (27.8%, shown as “Not Done” in Table 3, indicating radiographic imaging was not performed at the time point to evaluate response) due to early death. Best overall response was unevaluable for 6 additional patients (16.7%, shown as “Unevaluable” in Table 3), 1 of whom withdrew prior to week 9 due to clinical progression; 5 had progressive disease at week 9 and died of progression prior to the subsequent confirmatory assessment.

All 5 responders were among the 28 patients who had positive baseline PD-L1 status per CPS cutoff of 1. This leads to a higher ORR of 17.9% in the PD-L1-positive subgroup than in the full analysis set. Four of the 5 responders had tumors with baseline PD-L1 CPS  $\geq$  50 (**Supplementary Table S1**).

Analyses of lesion-level responses in injected and uninjected lesions were conducted. In 33 injected lesions, 2 (6.1%) complete responses and 5 (15.2%) partial responses were seen, resulting in an overall response rate of 21.2% (95% CI, 9.0, 38.9). In 40 uninjected lesions, 3 (7.5%) had complete response, 3 (7.5%) had partial response, and the overall response rate was

15.0% (95% CI, 5.7, 29.8) (**Supplementary Table S2**). At patient level, responses were observed across both injected and uninjected lesions in responders (**Supplementary Figure S1**).

Of the 4 HPV-negative patients with oropharyngeal cancer, 1 achieved confirmed PR, 1 progressed, and 1 was unevaluable, and 1 was not done due to early death. Of the 5 HPV-positive patients, 1 had confirmed PR, 3 had SD, and 1 was not done due to early death. The DCR was 80.0% (95% CI, 28.4–99.5) in the HPV-positive subgroup and 25% (95% CI, 0.6–80.6) in the HPV-negative subgroup.

Twenty-two patients had tumor assessment available at both baseline and data cutoff. Eight patients, including 2 with the primary tumor location in oropharynx, 5 in oral cavity, and 1 in hypopharynx, had a  $\geq 25\%$  reduction in tumor burden; 7 of them were PD-L1-positive at baseline (**Figure 2A, 2B**).

The median duration of response was not reached, with 4 of 5 responders remaining in response as of the data cutoff. Among 5 responders, 3 with oral cavity cancer had a duration of response of 37 weeks, 63 weeks, and 80 weeks, and 2 with oropharyngeal cancer had a duration of response of 64 weeks and 37 weeks (**Figure 2B**). One responder with oropharyngeal cancer had a sustained reduction in tumor burden until week 45, after which, the tumor burden started to gradually increase and reached a level comparable to baseline at week 63. The duration of response for this patient lasted 37 weeks (**Figure 2B**). Among 5 responders, 1 progressed and died in March 2019, 4 remained alive without disease progression as of October 2019. As of the data cutoff, 4 patients—3 with PR and 1 with SD—remained on treatment (**Figure 2C**). None of these 4 patients had received immunotherapy prior to this trial.

The median PFS was 3.0 months (95% CI, 2.0–5.8), and the median OS was 5.8 months (95% CI, 2.9–11.4). The estimated survival rate at 12 months was 30.6%.



## Discussion

This phase 1b study evaluated for the first time the combination of T-VEC, an oncolytic virus, and pembrolizumab, an anti-PD1 antibody, in patients with R/M HNSCC refractory to platinum-based chemotherapy. Overall, this combination regimen demonstrated a manageable safety profile and antitumor activity in R/M HNSCC. One DLT of fatal arterial hemorrhage, related to T-VEC, was observed.

Most treatment-related AEs were grade 1 or 2; 13.9% and 16.7% of patients experienced grade  $\geq 3$  AEs related to T-VEC and pembrolizumab, respectively. Apart from the DLT, there were no treatment-related fatal AEs. The safety results of pembrolizumab in this study were consistent with the previously known safety profile of pembrolizumab in HNSCC or other tumor types (11,21).

It is worth noting that in our study, 4 of 5 objective responses were durable and still ongoing as of the data cutoff, 1 year after the last patient was enrolled. One patient with oropharyngeal cancer and 1 patient with oral cavity cancer had a response that lasted 80 and 64 weeks, respectively. The historical ORR with pembrolizumab monotherapy in R/M HNSCC ranged from 14.6% to 18% in the phase 1b KEYNOTE-012 (18%, 8 of 45 patients), phase 2 KEYNOTE-055 (16%, 28 of 171), and phase 3 KEYNOTE-040 (14.6%, 36 of 247) studies (5,10,11). In the present study, the confirmed ORR per irRECIST with the combination did not appear to be superior to previous reports.

Of note, unlike other HNSCC trials of monotherapy checkpoint inhibitors, our trial had a disproportionate group of patients with no post-baseline tumor assessment data. Ten patients in the current study—27.8% of the full analysis set—missed the first postbaseline tumor assessment at week 9 due to early death, whereas this proportion was 11% in KEYNOTE-012 and 17% in KEYNOTE-040 (11,22). The high percentage of missing post-baseline assessment in this study significantly limited the comparison. In addition, the present study required patients to have injectable lesions (non-visceral), which are usually present in locoregionally advanced HNSCC,

whereas previous HNSCC studies of pembrolizumab or nivolumab monotherapy did not have such requirement. Therefore, our study enrolled a different patient population with locoregional disease and often a heavy disease burden in the head and neck region, as compared with patients in other HNSCC studies of anti-PD1 agents, which might have included patients without locoregional recurrence and with metastatic disease only.

Ten patients (27.8%) had received  $\geq 2$  lines of prior therapy in the metastatic or recurrent setting. There were no responders in this patient subset (4 had SD and 6 were not evaluable due to early death prior to week 9). The incidences of grade  $\geq 3$ , grade  $\geq 4$ , and serious treatment-emergent AEs in this subset were higher than in the rest of the patients.

The approach of intratumoral injection may have an impact on the efficacy. Similar to studies of T-VEC in melanoma, our study allowed for multiple injection sites, and T-VEC was injected into cutaneous, subcutaneous, or nodal lesions. In a previous study of T-VEC combined with ipilimumab in advanced melanoma, 70% (62/89) of injected lesions had tumor reduction of any magnitude, with 56% (50/89) and 34% (30/89) having  $\geq 50\%$  and 100% of tumor burden reduction. These responses appeared to be higher than those in uninjected lesions receiving T-VEC plus ipilimumab (57% had tumor burden reduction of any magnitude, 35% had  $\geq 50\%$  reduction, and 24% had 100% reduction).(17) In the current study with a relatively small sample size, the response rate for injected lesions appeared to be numerically higher than that for uninjected lesions, even though we observed responses across injected and uninjected lesions.

For patients with oropharyngeal cancer, tumor HPV status is commonly assessed by p16 immunohistochemical testing, which is rarely tested in non-oropharyngeal cancers due to the low incidence of HPV and lack of specificity of the p16 test for HPV status outside the oropharynx (23,24). The clinical outcomes are generally better for patients with locoregionally advanced HPV-positive oropharyngeal cancer treated with chemoradiation or cetuximab than for those with HPV-

negative tumors (25,26). As for the impact of baseline HPV status on the response to pembrolizumab, it appeared that numerically more patients in HPV-positive subgroup than in HPV-negative subgroup responded in the phase 1b KEYNOTE-012. However, subsequent large-scale prospective studies proved that response rates were similar, irrespective of HPV status (10,11,21). Our study enrolled 9 patients (25%) with oropharyngeal cancer; 5 and 4 were HPV-positive and HPV-negative at baseline, respectively. Two patients in the HPV-positive group and 1 in the HPV-negative group achieved PR. More HPV-positive patients than HPV-negative ones had disease control (80% vs. 25%). However, the sample sizes were too small to draw any conclusions.

A growing body of clinical evidence indicates that the level of PD-L1 expression is predictive of best overall response and improved PFS with PD-1 inhibitors (4,5,21). In this study, a large proportion of enrolled patients (78%) were PD-L1 positive at baseline per CPS cutoff of 1, with only 3 patients (8.3%) being confirmed as PD-L1 negative. All 5 responders were PD-L1-positive. Of those, 4 had tumors with baseline PD-L1 CPS  $\geq$  50, suggesting a potential association between high PD-L1 CPS at baseline and response. This is consistent with results from previous HNSCC study of pembrolizumab as monotherapy or in combination with chemotherapy (6). A large sample size is needed to draw concrete conclusions on the impact of PD-L1 status and the most relevant threshold.

In summary, the combination of intratumoral administration of T-VEC and systemic intravenous pembrolizumab showed a tolerable safety profile in patients with R/M HNSCC refractory to platinum-based chemotherapy; however, the evaluation of efficacy was limited by the high percentage of missing post-baseline assessment and the inconsistencies in patient characteristics between this study and other historical anti-PD-1 monotherapy HNSCC studies. Because of the evolving treatment landscape, the phase 3 part of this trial as written in the protocol was not further pursued. However, further clinical and translational studies are needed to better

understand the potential benefit of the combination of an oncolytic virus and an immune checkpoint inhibitor in HNSCC.

### **Data Sharing**

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <http://www.amgen.com/datasharing>

### **Acknowledgment**

Medical writing assistance was provided by Yang Li PhD (Amgen Inc.). KJH acknowledges funding support from The Royal Marsden Hospital/The Institute of Cancer Research National Institute for Health Research Biomedical Research Centre.

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**Tables.**

**Table 1: Baseline and demographic characteristics**

	T-VEC + Pembrolizumab (N = 36)
Age – year	
Median (range)	62.0 (35–77)
Sex – n (%)	
Male	29 (80.6)
Female	7 (19.4)
ECOG performance status – n (%)	
0	9 (25.0)
1	27 (75.0)
Distant metastatic disease – n (%)	
Yes	13 (36.1)
No	23 (63.9)
Primary tumor site – n (%)	
Oropharynx	9 (25.0)
HPV-positive	5 (13.9)
HPV-negative	4 (11.1)
Larynx	4 (11.1)
Oral cavity	20 (55.6)
Hypopharynx	3 (8.3)
PD-L1 status – n (%) <sup>a</sup>	
Positive	28 (77.8)
Not positive	3 (8.3)
Unknown	5 (13.9)
Number of patients reporting prior anti-cancer therapies – n (%)	36 (100.0)
Prior lines of therapy in recurrent/metastatic setting – n (%)	
None	17 (47.2)
1 <sup>st</sup> line	9 (25.0)
2 <sup>nd</sup> line	7 (19.4)
3 <sup>rd</sup> line	0 (0.0)
4 <sup>th</sup> line	3 (8.3)
Type of prior therapy – n (%)	
Chemotherapy	36 (100.0)
Curative intent, locally advanced	16 (44.4)
Palliative intent, 1 <sup>st</sup> -line recurrent or metastatic	9 (25.0)
Palliative intent, 2 <sup>nd</sup> -line recurrent or metastatic	7 (19.4)
Palliative intent, 3 <sup>rd</sup> -line recurrent or metastatic	0 (0.0)
Palliative intent, 4 <sup>th</sup> -line recurrent or metastatic	3 (8.3)
Other	1 (2.8)
Immunotherapy	3 (8.3)
Targeted biologics	6 (16.7)
Radiotherapy	33 (91.7)

	T-VEC + Pembrolizumab (N = 36)
Number of injected lesions – N <sup>b</sup>	57
Cutaneous – n (%) <sup>c</sup>	5 (8.8)
Face	2 (3.5)
Neck	3 (5.3)
Subcutaneous – n (%) <sup>c</sup>	15 (26.3)
Face	5 (8.8)
Neck	10 (17.5)
Nodal – n (%) <sup>c</sup>	37 (64.9)
Neck	31 (54.4)
Axilla	2 (3.5)
Sub-Mandibular	2 (3.5)
Sub-Mental	1 (1.8)
Chest	1 (1.8)

<sup>a</sup>PD-L1 cutoff: CPS of 1

<sup>b</sup>Includes both target and non-target lesions injected on day 1 from all patients

<sup>c</sup>Calculations used “number of injected lesions” as the denominator

**Table 2: Patient incidence of treatment-related AEs**

	T-VEC-related AEs T-VEC + Pembrolizumab (N = 36), n (%)			Pembro-related AEs T-VEC + Pembrolizumab (N = 36), n (%)	
	Any grade	Grade ≥ 3		Any grade	Grade ≥ 3
Any event	20 (55.6)	5 (13.9)	Any event	21 (58.3)	6 (16.7)
Pyrexia	8 (22.2)		Pyrexia	7 (19.4)	
Influenza-like illness	4 (11.1)		Fatigue	6 (16.7)	
Asthenia	3 (8.3)		Asthenia	3 (8.3)	
Injection site pain	3 (8.3)		Hypothyroidism	3 (8.3)	
Body temperature increased	2 (5.6)		Body temperature increased	2 (5.6)	
Fatigue	2 (5.6)		Diarrhea	2 (5.6)	
Nausea	2 (5.6)		Influenza-like illness	2 (5.6)	
Vomiting	2 (5.6)		Nausea	2 (5.6)	
Application site pruritus	1 (2.8)		Stomatitis	2 (5.6)	
Arterial hemorrhage	1 (2.8)	1 (2.8)	Vomiting	2 (5.6)	
Blister	1 (2.8)		Cervix disorder	1 (2.8)	
Cervix disorder	1 (2.8)		Cytokine release syndrome	1 (2.8)	
Chills	1 (2.8)	1 (2.8)	Decreased appetite	1 (2.8)	
Cytokine release syndrome	1 (2.8)		Dyspnea	1 (2.8)	
Decreased appetite	1 (2.8)		Eczema	1 (2.8)	1 (2.8)
Dysphagia	1 (2.8)		Euglycemic diabetic ketoacidosis	1 (2.8)	1 (2.8)
Dyspnea	1 (2.8)		Glucose tolerance impaired	1 (2.8)	
Fistula	1 (2.8)		Hepatitis	1 (2.8)	1 (2.8)
Hot flush	1 (2.8)		Hypoesthesia oral	1 (2.8)	
Hypoesthesia oral	1 (2.8)		Infusion-related reaction	1 (2.8)	
Injection site infection	1 (2.8)		Musculoskeletal chest pain	1 (2.8)	1 (2.8)
Injection site laceration	1 (2.8)		Odynophagia	1 (2.8)	
Lip blister	1 (2.8)		Orthopnea	1 (2.8)	
Mucosal hemorrhage	1 (2.8)	1 (2.8)	Pain	1 (2.8)	1 (2.8)
Odynophagia	1 (2.8)	1 (2.8)	Pain in extremity	1 (2.8)	
Oropharyngeal pain	1 (2.8)		Temporomandibular joint syndrome	1 (2.8)	
Pain	1 (2.8)	1 (2.8)	Transaminases increased	1 (2.8)	1 (2.8)
Pain in extremity	1 (2.8)				
Pruritus	1 (2.8)				
Rash maculo-papular	1 (2.8)				
Rhinitis	1 (2.8)				
Stomatitis	1 (2.8)				
Tumor ulceration	1 (2.8)	1 (2.8)			

**Table 3: Confirmed best overall response per irRECIST by baseline PD-L1 status**

	T-VEC + Pembrolizumab (N=36), n (%)	PD-L1 Positive (CPS ≥ 1) (N=28), n (%)	PD-L1 Negative (CPS < 1) (N=3), n (%)
Response assessment based on investigator			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	5 (13.9)	5 (17.9)	0 (0.0)
Stable disease	9 (25.0)	6 (21.4)	2 (66.7)
Progressive disease	6 (16.7)	3 (10.7)	0 (0.0)
Unevaluable <sup>a</sup>	6 (16.7)	5 (17.9)	0 (0.0)
Not done <sup>b</sup>	10 (27.8)	9 (32.1)	1 (33.3)
Complete response rate	0 (0.0)	0 (0.0)	0 (0.0)
95% CI	(0.0, 9.7)	(0.0, 12.3)	(0.0, 70.8)
Objective response rate	5 (13.9)	5 (17.9)	0 (0.0)
95% CI	(4.7, 29.5)	(6.1, 36.9)	(0.0, 70.8)
Duration of response <sup>c</sup>			
≥ 6 months	5 (100.0)	5 (100.0)	0 (0.0)
< 6 months	0 (0.0)	0 (0.0)	0 (0.0)
Disease control rate	14 (38.9)	11 (39.3)	2 (66.7)
95% CI	(23.1, 56.5)	(21.5, 59.4)	(9.4, 99.2)

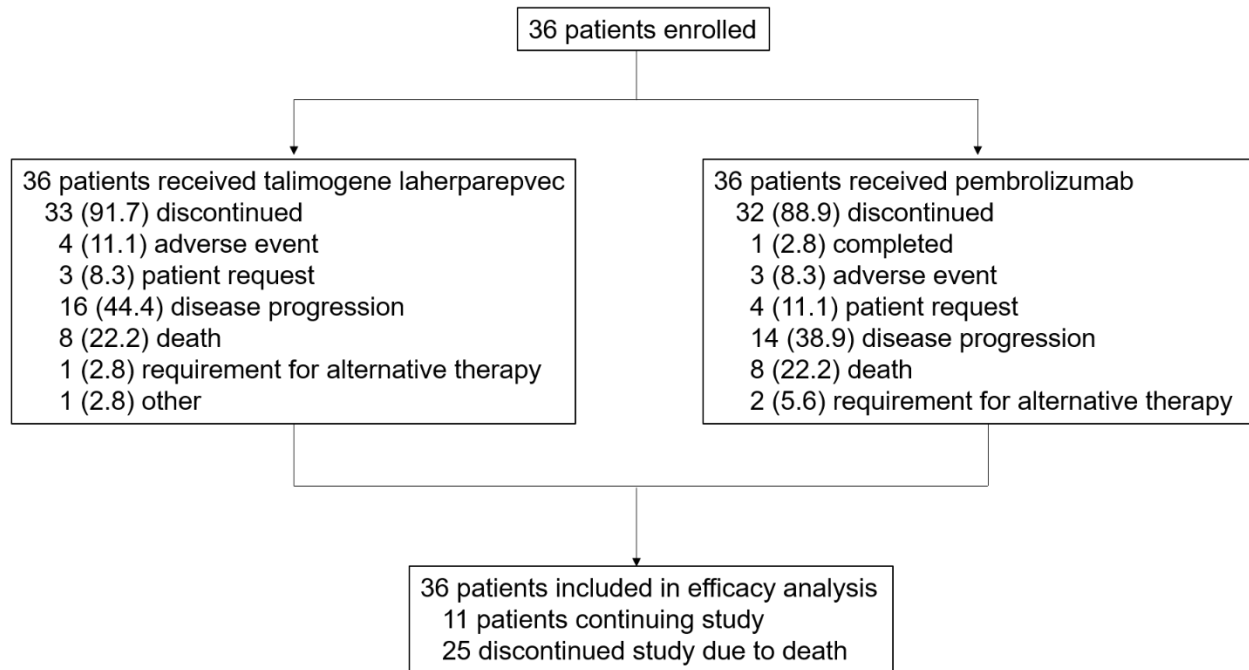
<sup>a</sup>1 patient withdrew prior to the first 9-week tumor assessment; 5 had progressive disease at 9-week assessment and died before the next confirmatory assessment.

<sup>b</sup>10 patients died prior to the first tumor assessment at week 9.

<sup>c</sup>Percentages calculated out of number of responders.

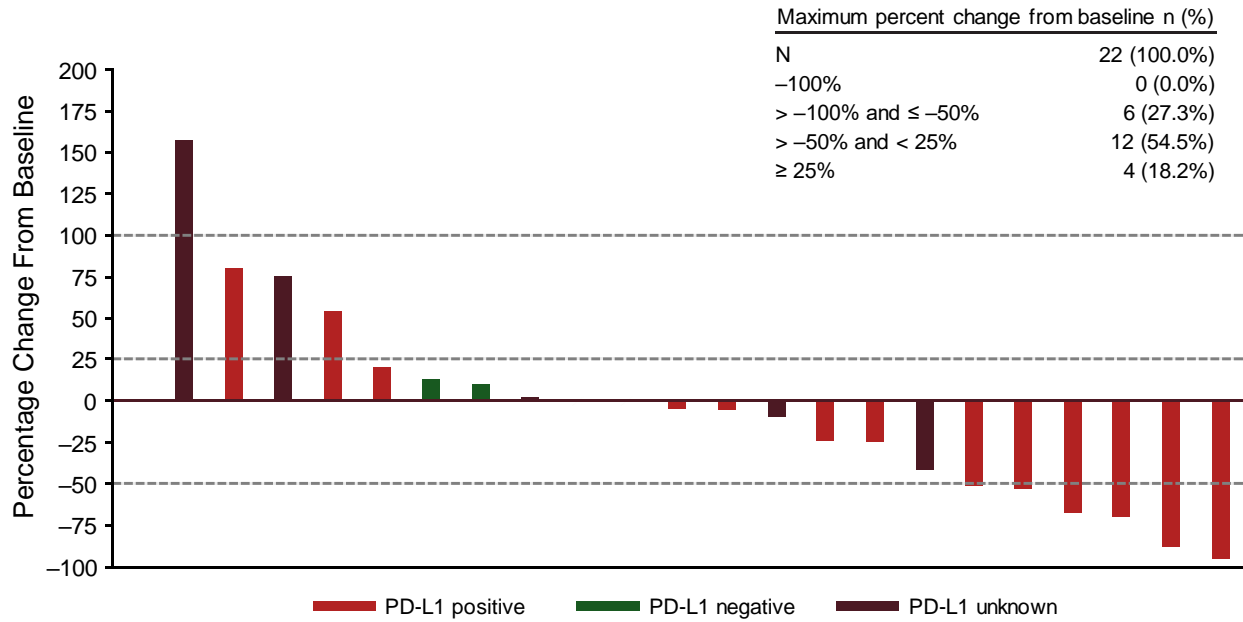
**Figures.**

**Figure 1: Patient disposition.** Values within parentheses are percentages.

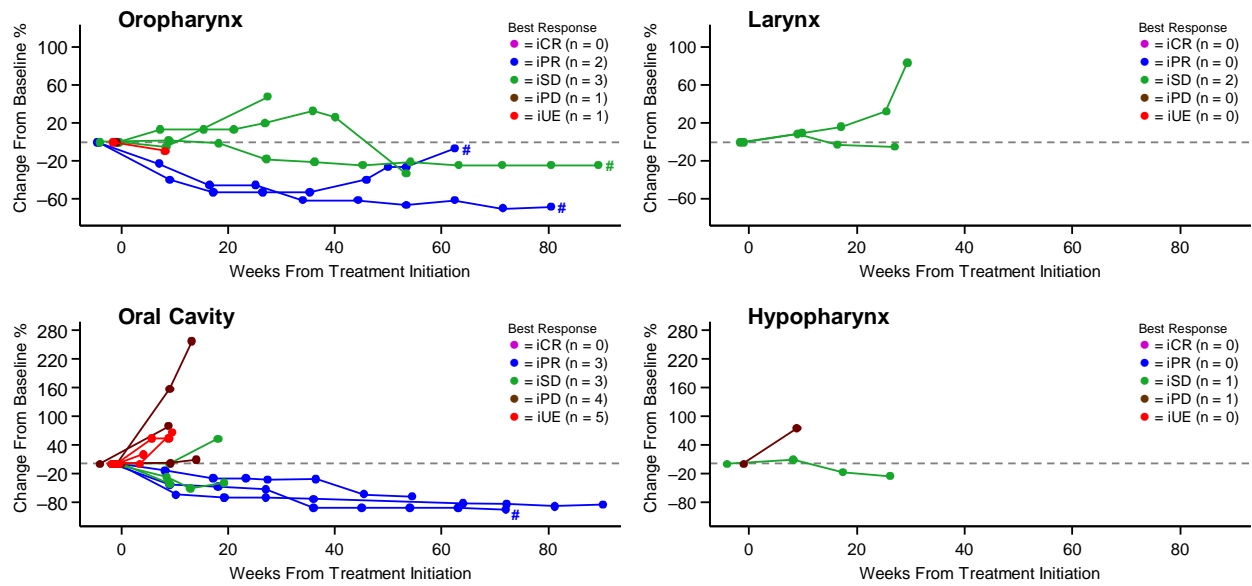


**Figure 2: Efficacy of T-VEC in combination with pembrolizumab.** (A) Maximum percent change in tumor burden by baseline PD-L1 status (N = 22). Eleven patients did not have postbaseline assessments, and 3 additional patients did not have targeted tumor measurements postbaseline to contribute to the tumor burden. (B) Tumor burden change from baseline by baseline primary tumor site. Plots are based on confirmed responses. Ten patients whose first postbaseline tumor assessment was not done due to early death are not shown. # indicates treatment ongoing. (C) Overall survival and best overall response.

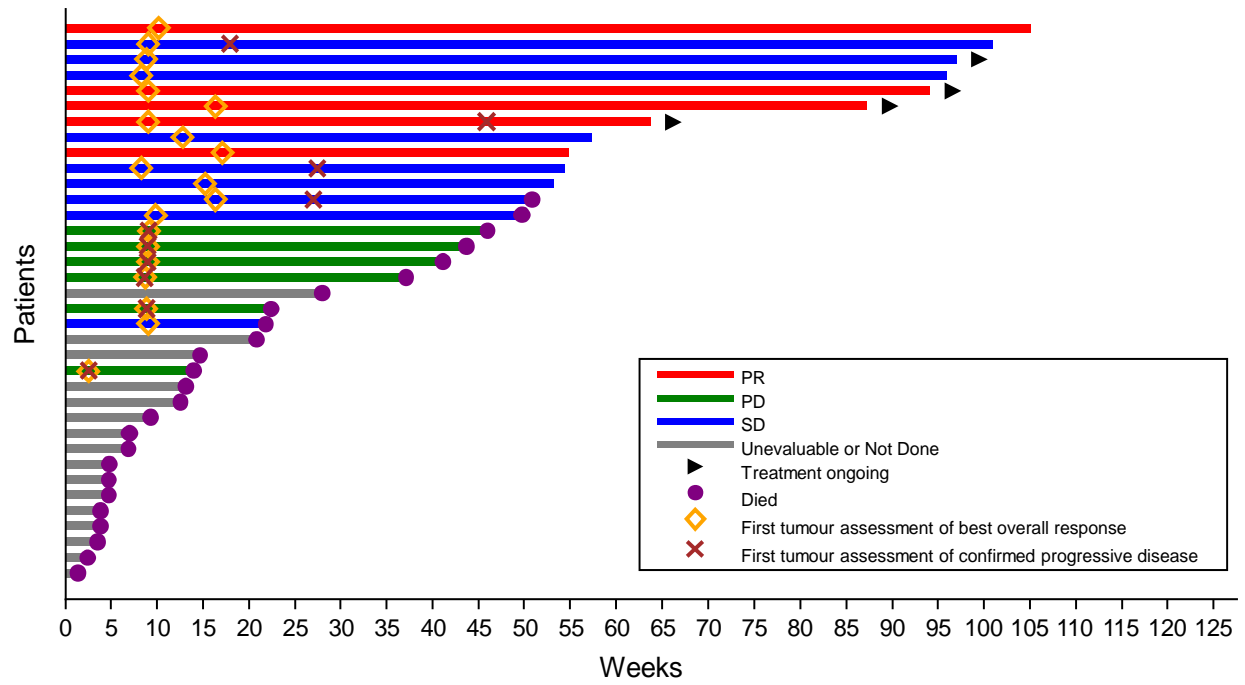
(A)



(B)



(C)





**Supplementary Table S1. Confirmed best overall response per irRECIST by baseline PD-L1 CPS of  $\geq 1$ ,  $\geq 20$ , and  $\geq 50$**

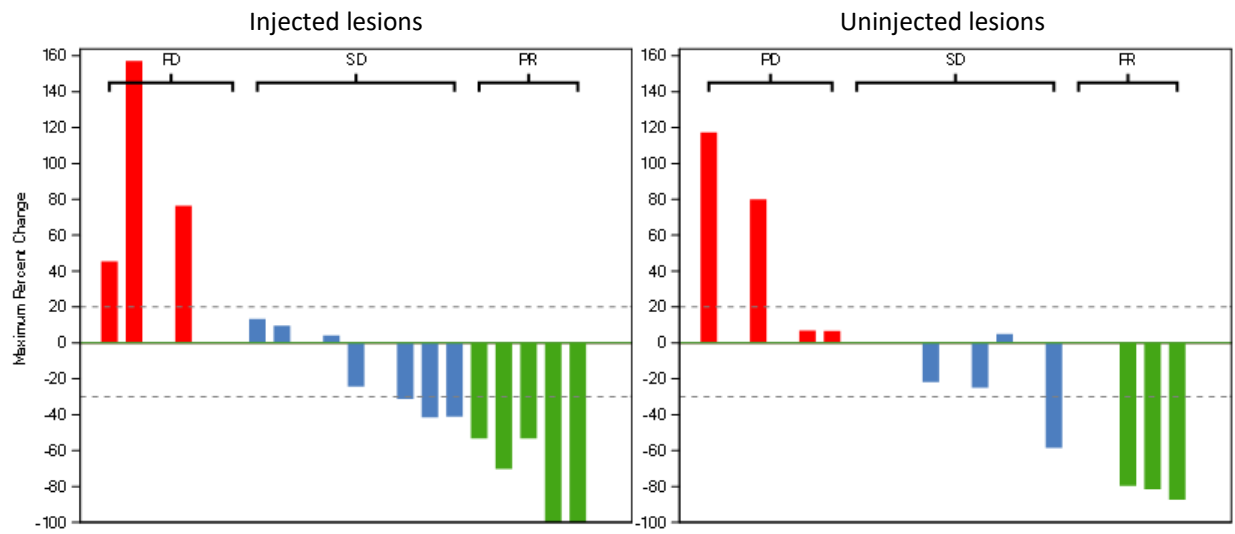
	Talimogene Laherparepvec + Pembrolizumab (N=36), n (%)	PD-L1 CPS $\geq 1$ (N=28), n (%)	PD-L1 CPS $\geq 20$ (N=15), n (%)	PD-L1 CPS $\geq 50$ (N=8), n (%)
Response assessment based on investigator - n (%)				
Complete response (iCR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (iPR)	5 (13.9)	5 (17.9)	4 (26.7)	4 (50.0)
Stable disease (iSD)	9 (25.0)	6 (21.4)	1 (6.7)	0 (0.0)
Progressive disease (iPD)	6 (16.7)	3 (10.7)	3 (20.0)	2 (25.0)
Unevaluable (iUE)	6 (16.7)	5 (17.9)	3 (20.0)	1 (12.5)
Not done	10 (27.8)	9 (32.1)	4 (26.7)	1 (12.5)

**Supplementary Table S2. Lesion-level best overall response in injected lesions vs. uninjected lesions**

	Number of injected lesions (N=33) n (%)	Number of uninjected lesions (N=40) n (%)
Response assessment based on investigator – n (%)		
Complete response	2 (6.1)	3 (7.5)
Partial response	5 (15.2)	3 (7.5)
Non-complete/partial response	26 (78.8)	34 (85.0)
Objective response rate – n (%) (95% CI)	7 (21.2) (9.0, 38.9)	6 (15.0) (5.7, 29.8)

Data were derived from target lesions in 32 patients, excluding 4 patients with locoregionally advanced disease with a recurrence less than 3 months after prior platinum-containing curatively intended multimodal therapy.

**Supplementary Figure S1.** Change from baseline in tumor burden of target lesions at patient level



Plot shows the change in tumor burden of all target lesions in patients. Each bar represents the total tumor burden change in the sum of all target lesions for each individual patient.  
PD: progressive disease; SD: stable disease; PR: partial response.