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

Kevin J. Harrington[1], Anthony Kong[2,3], Nicolas Mach[4], Jason A. Chesney[5], Beatriz Castelo Fernandez[6], Danny Rischin[7], Ezra E.W. Cohen[8], Hoi-Shen Radcliffe[9], Burak Gumuscu[10], Jonathan Cheng[10], Wendy Snyder[11], and Lillian L. Siu[12]

ABSTRACT

Purpose: 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.

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

Results: Thirty-six patients were enrolled into the phase Ib study. The data cut-off 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 (AE) 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% confidence interval (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 III part of this study was not further pursued (ClinicalTrials.gov Identifier: NCT02626000).

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 health care 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 on 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 III 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

[1]The Institute of Cancer Research, Royal Marsden Hospital, London, United Kingdom. [2]Institute of Cancer and Genomic Science, University of Birmingham, Birmingham, United Kingdom. [3]Comprehensive Cancer Centre, King's College London, United Kingdom. [4]Department of Oncology, University Hospital of Geneva, Geneva, Switzerland. [5]James Graham Brown Cancer Center, University of Louisville, Louisville, Kentucky. [6]Medical Oncology Department, University Hospital La Paz, Madrid, Spain. [7]Peter MacCallum Cancer Centre, Melbourne, Australia. [8]Moores Cancer Center UC San Diego Health, La Jolla, California. [9]Amgen Limited, Uxbridge, United Kingdom. [10]Merck & Co., Inc., Kenilworth, New Jersey. [11]Amgen, Inc., Thousand Oaks, California. [12]Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

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K.J. Harrington and A. Kong contributed equally to this article.

Corresponding Author: Kevin J. Harrington, The Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, United Kingdom. Phone: 207-153-5030; Fax: 207-808-2235; E-mail: Kevin.Harrington@icr.ac.uk

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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 Ib study, we tested a novel combination of talimogene laherparepvec, a genetically modified herpes simplex virus-1–based oncolytic immunotherapy, and pembrolizumab, a humanized mAb 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 with 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.

total population, 23% in the population with PD-L1 CPS of ≥20, and 19% in the population with PD-L1 CPS of ≥1. Pembrolizumab alone or with chemotherapy improved OS versus cetuximab with chemotherapy in the CPS of ≥20 and CPS of ≥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% confidence interval (CI), 0.63–0.93); $P = 0{\cdot}0034$; ref. 6]. In the phase II KEYNOTE-055 and phase III 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% CI, 6.4–9.4 vs. 6.9 months; 95% CI, 5.9–8.0; HR = 0.80; 0.65–0.98; nominal $P = 0.0161$; ref. 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 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 I/II 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 Ib 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 IFNγ were observed in tumors from responders (16). Another randomized, phase II 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%, $P = 0.002$; ref. 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.

Patients and Methods

Patients

Eligible patients had an age of 18 years or older; 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: (i) 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 (ii) 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 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 Ib/III, multicenter trial. In the phase Ib 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 (±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 (±3 days). Treatment continued until CR, no injectable lesions, confirmed progressive disease per immune-related RECIST (irRECIST; ref. 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 III part of the study.

The phase III 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 III study are described below.

All patients provided written informed consent. The studies were conducted under ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines for Good Clinical Practice, which follow the principles of the Declaration of Helsinki and CIOMS (International Ethical Guidelines for Biomedical Research Involving Human Subjects). Institutional Review Board approval was obtained.

Endpoints

For the phase Ib 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 (±1 week), week 18 (±1 week), and then every 9 weeks (±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 (±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 (±28 days) for approximately 36 months after the last patient was enrolled. PD-L1 positivity used in this article was defined using a CPS ≥1 cutoff.

Data sharing

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

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 ≤10% versus the alternative hypothesis of a rate ≥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 (AE). 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 Ib 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 (**Fig. 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 1 cm 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

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* (%)[a]	
Positive	28 (77.8)
Not positive	3 (8.3)
Unknown	5 (13.9)
Number of patients reporting prior anticancer therapies – *n* (%)	36 (100.0)
Prior lines of therapy in recurrent/metastatic setting – *n* (%)	
None	17 (47.2)
1st line	9 (25.0)
2nd line	7 (19.4)
3rd line	0 (0.0)
4th line	3 (8.3)
Type of prior therapy – *n* (%)	
Chemotherapy	36 (100.0)
Curative intent, locally advanced	16 (44.4)
Palliative intent, 1st-line recurrent or metastatic	9 (25.0)
Palliative intent, 2nd-line recurrent or metastatic	7 (19.4)
Palliative intent, 3rd-line recurrent or metastatic	0 (0.0)
Palliative intent, 4th-line recurrent or metastatic	3 (8.3)
Other	1 (2.8)
Immunotherapy	3 (8.3)
Targeted biologics	6 (16.7)
Radiotherapy	33 (91.7)
Number of injected lesions – *n*[b]	57
Cutaneous – *n* (%)[c]	5 (8.8)
Face	2 (3.5)
Neck	3 (5.3)
Subcutaneous – *n* (%)[c]	15 (26.3)
Face	5 (8.8)
Neck	10 (17.5)
Nodal – *n* (%)[c]	37 (64.9)
Neck	31 (54.4)
Axilla	2 (3.5)
Submandibular	2 (3.5)
Submental	1 (1.8)
Chest	1 (1.8)

[a]PD-L1 cutoff: CPS of 1.
[b]Includes both target and nontarget lesions injected on day 1 from all patients.
[c]Calculations used "number of injected lesions" as the denominator.

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 serious AEs, 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 serious AEs 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 ≥ 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 Fig. S1).

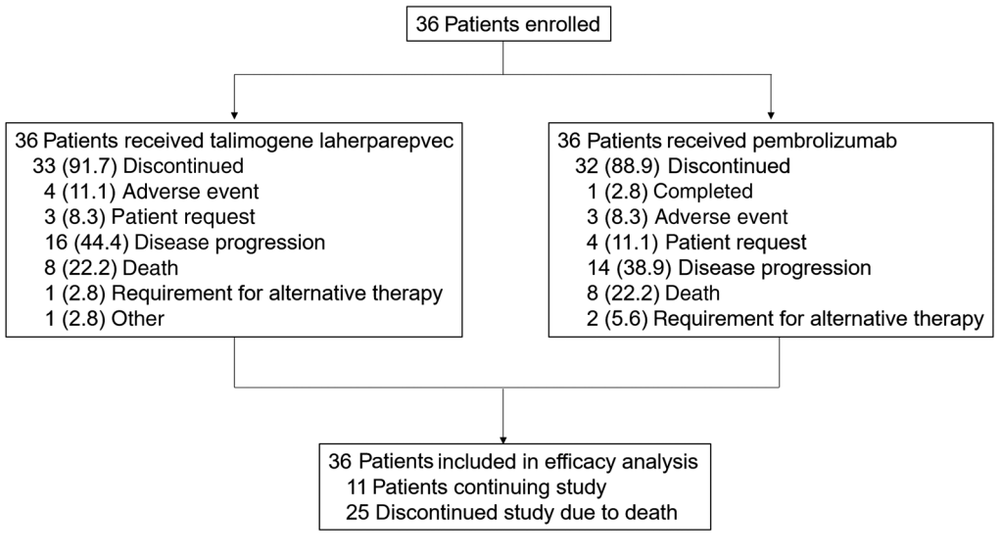

Figure 1.
Patient disposition. Values within parentheses are percentages.

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[a]	6 (16.7)	5 (17.9)	0 (0.0)
Not done[b]	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[c]			
≥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

[a]One 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.
[b]Ten patients died prior to the first tumor assessment at week 9.
[c]Percentages calculated out of number of responders.

Of the 4 HPV-negative patients with oropharyngeal cancer, 1 achieved confirmed PR, 1 progressed, 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 ≥25% reduction in tumor burden; 7 of them were PD-L1–positive at baseline (**Fig. 2A** and **B**).

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 (**Fig. 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 with baseline at week 63. The duration of response for this patient lasted 37 weeks (**Fig. 2B**). Among 5 responders, 1 progressed and died in March 2019 and 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 (**Fig. 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 Ib study evaluated for the first time the combination of T-VEC, an oncolytic virus, and pembrolizumab, an anti–PD-1 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 ≥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 Ib KEYNOTE-012 (18%, 8/45 patients), phase II KEYNOTE-055 (16%, 28/171), and phase 3 KEYNOTE-040 (14.6%, 36/247) studies (5, 10, 11). In the current 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 postbaseline 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 postbaseline assessment in this study significantly limited the comparison. In addition, the current study required patients to have injectable lesions (nonvisceral), 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–PD-1 agents, which might have included patients without locoregional recurrence and with metastatic disease only.

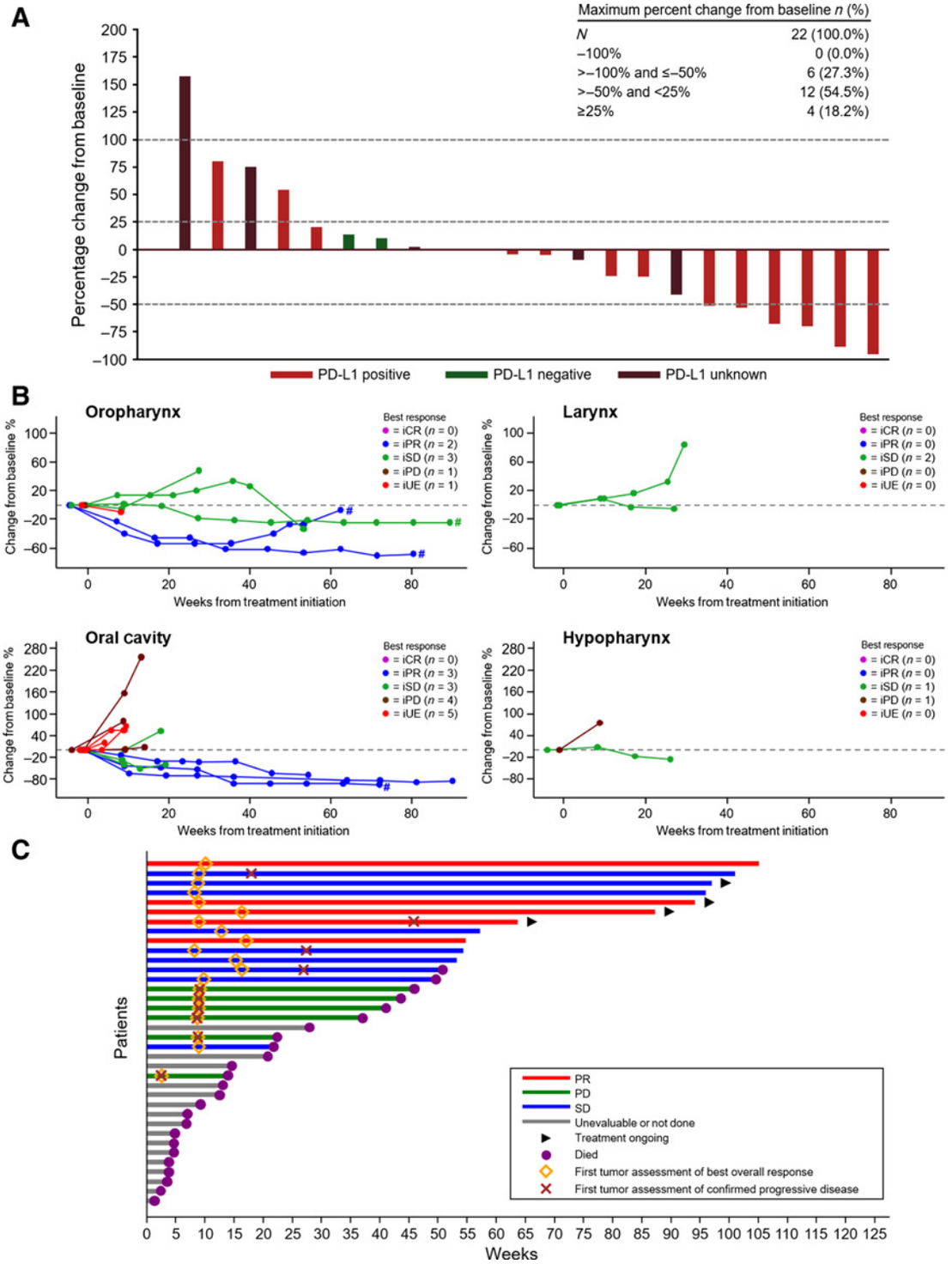

Figure 2.

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. #, treatment ongoing. **C,** Overall survival and best overall response.

Ten patients (27.8%) had received ≥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 ≥3, grade ≥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 ≥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 ≥50% reduction, and 24% had 100% reduction; ref. 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 IHC testing, which is rarely tested in nonoropharyngeal 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 ≥ 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 postbaseline 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 III 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.

Disclosure of Potential Conflicts of Interest

K.J.Harrington reports personal fees from Amgen (paid to institute) and grants and personal fees from Merck Sharp Dohme (paid to institute) during the conduct of the study; grants and personal fees from AstraZeneca (paid to institution), personal fees from Bristol-Myers Squibb (paid to institution), grants and personal fees from Boehringer-Ingelheim (paid to institution), personal fees from Merck (paid to institution) and Pfizer (paid to institution), grants and personal fees from Replimune (paid to institution), and personal fees from Vyriad (paid to institution) outside the submitted work. A. Kong reports personal fees from Amgen (advisory role) and personal fees from MSD (speakers bureau, advisory role, and travel accommodation for conferences) during the conduct of the study; personal fees from Bristol-Myers Squibb (honoraria and speakers bureau) and Centauri Therapeutics (consulting and advisory role), grants and personal fees from Puma Biotechnology (advisory role and research grant funding), personal fees from Merck & Co (honoraria, speakers bureau, and travel accommodation for conferences), and grants from AstraZeneca (research grant funding) outside the submitted work. J. Chesney reports financial support to conduct clinical trials from Amgen during the conduct of the study. D. Rischin reports grants from Amgen during the conduct of the study; grants and personal fees from MSD and GlaxoSmithKline, grants from Regeneron, Sanofi, Bristol-Myers Squibb, Roche, and Kura outside the submitted work; and is a member of advisory boards (all uncompensated) at Merck, Regeneron, Sanofi, GlaxoSmithKline, Bristol-Myers Squibb, and Amgen. E.E.W. Cohen reports personal fees from Merck, MSD, Bristol-Myers Squibb, Regeneron, AstraZeneca, and Pfizer outside the submitted work. H. Radcliffe reports employment and stock ownership from Amgen outside the submitted work. B. Gumuscu reports other from Merck & Co (employment) during the conduct of the study, as well as other from Merck & Co (employment) outside the submitted work. J. Cheng reports employment from Merck outside the submitted work. W. Snyder reports employment from Amgen during the conduct of the study, as well as stock ownership from Regeneron outside the submitted work. L.L. Siu reports institutional support for the clinical trial from Amgen during the conduct of the study; personal fees from Merck (advisory board), Pfizer (advisory board), Celgene (advisory board), AstraZeneca (advisory board), Morphosys (advisory board), Roche (advisory board), GeneSeeq (advisory board), Loxo (advisory board), Oncorus (advisory board), Symphogen (advisory board), Seattle Genetics (advisory board), GlaxoSmithKline (advisory board), Voronoi (advisory board), personal fees and other from Treadwell Therapeutics [advisory board (self); co-founder (spouse)], personal fees from Arvinas (advisory board), Tessa (advisory board), Navire (advisory board), Relay (advisory board), Rubius (advisory board), grants from Novartis (institutional support for clinical trials), Bristol-Myers Squibb (institutional support for clinical trials), Pfizer (institutional support for clinical trials), Boehringer-Ingelheim (institutional support for clinical trials), GlaxoSmithKline (institutional support for clinical trials), Roche/Genentech (institutional support for clinical trials), Karyopharm (institutional support for clinical trials), AstraZeneca (institutional support for clinical trials), Merck (institutional support for clinical trials), Astellas (institutional support for clinical trials), Bayer (institutional support for clinical trials), Abbvie (institutional support for clinical trials), Symphogen (institutional support for clinical trials), Intensity Therapeutics (institutional support for clinical trials), Mirati Therapeutics (institutional support for clinical trials), Shattucks Laboratories (institutional support for clinical trials), and Avid Therapeutics (institutional support for clinical trials) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

K.J. Harrington: Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **A. Kong:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **N. Mach:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **J.A. Chesney:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **B.C. Fernandez:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **D. Rischin:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and

editing. **E.E.W. Cohen:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **H.-S. Radcliffe:** Resources, data curation, software, formal analysis, supervision, visualization, writing-original draft, writing-review and editing. **B. Gumuscu:** Conceptualization, resources, data curation, software, formal analysis, methodology, writing-review and editing. **J. Cheng:** Conceptualization, resources, data curation, software, formal analysis, supervision, investigation, methodology, writing-original draft, writing-review and editing. **W. Snyder:** Conceptualization, resources, data curation, software, formal analysis, supervision, investigation, methodology, writing-original draft, writing-review and editing. **L.L. Siu:** Conceptualization, resources, data curation, software, formal analysis, supervision, investigation, methodology, writing-original draft, writing-review and editing.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc 2016;91:386–96.
3. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
4. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.
5. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956–65.
6. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915–28.
7. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–24.
8. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013;369:134–44.
9. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28.
10. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. J Clin Oncol 2017;35:1542–9.
11. Cohen EEW, Soulieres D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 2019;393:156–67.
12. Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Gene Ther 2003;10:292–303.
13. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33:2780–8.
14. Harrington KJ, Hingorani M, Tanay MA, Hickey J, Bhide SA, Clarke PM, et al. Phase I/II study of oncolytic HSV GM-CSF in combination with radiotherapy and cisplatin in untreated stage III/IV squamous cell cancer of the head and neck. Clin Cancer Res 2010;16:4005–15.
15. Long GV, Dummer R, Andtbacka RH, Johnson DB, Michielin O, Martin-Algarra S, et al. Follow-up analysis of MASTERKEY-265 phase 1b study of talimogene laherparepvec in combination with pembrolizumab in patients with unresectable stage IIIB–IVM1c melanoma [abstract]. In: Proceedings of the 15th International Congress by The Society for Melanoma Research; 2018 Oct 24–27; Manchester, England. Available from: https://www.societymelanomaresearch.org/meetings/past.
16. Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. Cell 2017;170:1109–19.
17. Chesney J, Puzanov I, Collichio F, Singh P, Milhem MM, Glaspy J, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. J Clin Oncol 2018;36:1658–67.
18. Andtbacka RH, Ross M, Puzanov I, Milhem M, Collichio F, Delman KA, et al. Patterns of clinical response with talimogene laherparepvec (T-VEC) in patients with melanoma treated in the OPTiM phase III clinical trial. Ann Surg Oncol 2016;23:4169–77.
19. Puzanov I, Milhem MM, Minor D, Hamid O, Li A, Chen L, et al. Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB-IV melanoma. J Clin Oncol 2016;34:2619–26.
20. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19:3936–43.
21. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol 2016;17:717–26.
22. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, Eder JP, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer 2018;119:153–9.
23. Jordan RC, Lingen MW, Perez-Ordonez B, He X, Pickard R, Koluder M, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol 2012;36:945–54.
24. Kimple RJ, Harari PM. The prognostic value of HPV in head and neck cancer patients undergoing postoperative chemoradiotherapy. Ann Transl Med 2015;3:S14.
25. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
26. Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. J Clin Oncol 2014;32:2486–95.