original reports

Safety and Efficacy of Pembrolizumab With Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Phase IB Study

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abstract

PURPOSE Pembrolizumab is a humanized monoclonal antibody that blocks interaction between programmed death receptor-1 (PD-1) and its ligands (PD-L1, PD-L2). Although pembrolizumab is approved for recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), its role in the management of locally advanced (LA) disease is not defined. We report a phase IB study evaluating the safety and efficacy of adding pembrolizumab to cisplatin-based chemoradiotherapy in patients with LA HNSCC.

PATIENTS AND METHODS Eligible patients included those with oral cavity (excluding lip), oropharyngeal, hypopharyngeal, or laryngeal stage III to IVB HNSCC (according to American Joint Committee on Cancer, 7th edition, staging system) eligible for cisplatin-based, standard-dose (70 Gy) chemoradiotherapy. Pembrolizumab was administered concurrently with and after chemoradiotherapy with weekly cisplatin. Safety was the primary end point and was determined by incidence of chemoradiotherapy adverse events (AEs) and immune-related AEs (irAEs). Efficacy was defined as complete response (CR) rate on end-of-treatment (EOT) imaging or with pathologic confirmation at 100 days postradiotherapy completion. Key secondary end points included overall (OS) and progression-free survival (PFS).

RESULTS The study accrued 59 patients (human papillomavirus [HPV] positive, n = 34; HPV negative, n = 25) from November 2015 to October 2018. Five patients (8.8%) required discontinuation of pembrolizumab because of irAEs, all of which occurred during concurrent chemoradiotherapy; 98.3% of patients completed the full planned treatment dose (70 Gy) of radiotherapy without any delays ≥ 5 days; 88.1% of patients completed the goal cisplatin dose of ≥ 200 mg/m^2. EOT CR rates were 85.3% and 78.3% for those with HPV-positive and -negative HNSCC, respectively.

CONCLUSION Pembrolizumab in combination with weekly cisplatin-based chemoradiotherapy is safe and does not impair delivery of curative radiotherapy or chemotherapy in HNSCC. Early efficacy data support further investigation of this approach.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

Patients with locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) have a 5-year survival of only 50% with the current standard treatment of concurrent chemoradiotherapy.[1] Although those with human papillomavirus (HPV)–associated HNSCC have better outcomes, patients with significant tobacco use or advanced tumor or nodal stage still have 3-year survival rates of 70%.[2] Strategies to improve survival with intensified therapy for patients with high-risk disease have been limited by excessive toxicity.[3,4] Recent understanding of the immune response during chemoradiotherapy has offered new therapeutic possibilities.

The interaction between programmed death receptor-1 (PD-1) and its ligands (PD-L1, PD-L2) may contribute to immune escape in HNSCC.[5] PD-L1 upregulation and resulting immune exhaustion have been seen in preclinical models with both radiotherapy[6,7] and cisplatin.[8] Analysis of circulating immune cells during concurrent chemoradiotherapy in HNSCC demonstrated an exhausted immunophenotype, in part because of increased PD-1 expression on CD4+ T cells.[9]

Pembrolizumab is a high-affinity immunoglobulin G4 monoclonal antibody against the interaction between PD-1 and PD-L1/PD-L2. It was granted accelerated approval for platinum-refractory, recurrent/metastatic

(R/M) HNSCC on August 5, 2016, based on response and survival data from KEYNOTE-012 and supported by KEYNOTE-040 trials.[10,11] In these studies, 13% to 17% of patients experienced grade ≥ 3 treatment-related adverse events (AEs), a majority of which required discontinuation of monotherapy. KEYNOTE-048 evaluated pembrolizumab in combination with platinum and fluorouracil chemotherapy for first-line treatment of R/M HNSCC; however, the all-cause grade ≥ 3 toxicity rate was 85.1%.[12] Because the acute grade ≥ 3 toxicity rates already exceed 77% for standard concurrent chemoradiotherapy in HNSCC, the safety of adding pembrolizumab warrants prudent investigation.[13,14]

With these data in mind, we performed a clinical trial adding pembrolizumab to definitive chemoradiotherapy in LA HNSCC to explore safety and efficacy. We used weekly cisplatin at a dose of 40 mg/m^2 rather than standard high-dose cisplatin (100 mg/m^2 every 3 weeks) as our chemotherapy backbone because of its decreased potential for causing severe (grade 3-4) myelosuppression[15,16] and its improved tolerability in other studies.[17,18] This was combined with radiotherapy at a total dose of 70 Gy.

PATIENTS AND METHODS

Study Design and Participants

This phase IB study took place at 3 National Cancer Institute (NCI) Community Oncology Research Program Centers (Sanford Health) and an NCI Comprehensive Cancer Center (UCSD). The study enrolled an initial lead-in cohort to evaluate safety and efficacy regardless of HPV status. After a planned interim analysis, the study expanded into 2 cohorts, evaluating efficacy in HPV-positive and -negative disease. Enrolled patients were age ≥ 18 years with TNM clinical stage III, IVA, or IVB (by American Joint Committee on Cancer, 7th edition, staging system) histologically confirmed HNSCC of the oral cavity (excluding lip), oropharynx, hypopharynx, or larynx who were candidates for curative, definitive chemoradiotherapy. Participants were required to have adequate organ function and performance status (Eastern Cooperative Oncology Group performance status 0 or 1) to receive cisplatin-based chemoradiotherapy. Measurable disease by RECIST (version 1.1) using computed tomography (CT) or magnetic resonance imaging was required.[19] HPV status by p16 immunohistochemistry or HPV16 in situ hybridization (ISH) was required for enrollment regardless of disease site.[20] Exclusion criteria included prior radiotherapy or systemic cancer therapy, known immunosuppression, active autoimmune disease, prior noninfectious pneumonitis, or any condition that could interfere with trial participation. The study was approved by the institutional review board at each participating institution, and all patients provided written informed consent.

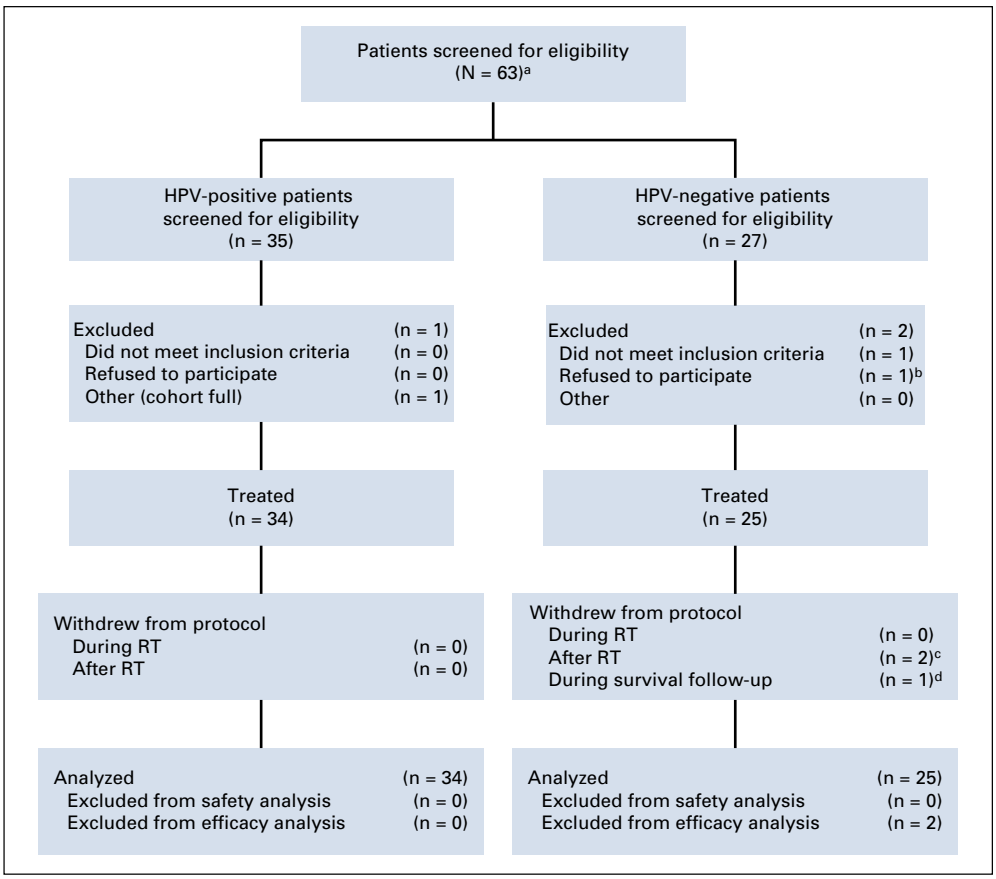

FIG 1. Patient screening and disposition. RT, radiotherapy. (a) One screening failure before determination of human papillomavirus (HPV) status. (b) Was enrolled but withdrew before any study treatment because of insurance reasons. (c) Two patients withdrew before day-150 efficacy analysis and replaced per the protocol replacement strategy. (d) One patient was withdrawn after day 150 at physician's discretion because of incarceration and was not replaced.

TABLE 1. Patient Demographic and Clinical Characteristics

Characteristic	No. (%)		
	HPV Positive (n = 34)	HPV Negative (n = 25)	All Patients (N = 59)
Age, years			
Median	59	60.9	59.8
Range	36-81	47-77	36-81
Sex			
Male	32 (94.1)	18 (72.0)	50 (84.8)
Female	2 (5.9)	7 (28.0)	9 (15.2)
ECOG PS			
0	24 (70.6)	15 (60.0)	39 (66.1)
1	10 (29.4)	10 (40.0)	20 (33.9)
Race			
White, non-Hispanic	33 (97.0)	23 (92.0)	56 (94.9)
White, Hispanic	1 (3.0)	0	1 (1.8)
Black, non-Hispanic	0	1 (4.3)	1 (1.8)
Native American, non-Hispanic	0	1 (4.3)	1 (1.8)
Primary site			
Oropharynx	31 (91.2)	9 (36.0)	40 (67.8)
Larynx	2 (5.9)	11 (44.0)	13 (22.0)
Hypopharynx	1 (2.9)	5 (22.0)	6 (10.5)
TNM stage (AJCC 7th edition)			
III	3 (8.8)	6 (24.0)	9 (15.3)
IVA	30 (88.2)	17 (68.0)	47 (79.7)
IVB	1 (2.9)	2 (8.0)	3 (5.1)
T0-1[a]	8 (23.5)	3 (13.0)	11 (19.3)
T2	8 (23.5)	5 (21.8)	13 (22.8)
T3	7 (20.6)	11 (47.8)	18 (31.6)
T4	11 (32.4)	4 (17.4)	15 (26.3)
N0-N1	7 (20.6)	4 (16.0)	11 (18.6)
N2A,B	17 (50.0)	12 (48.0)	29 (49.2)
N2C	9 (26.5)	8 (32.0)	17 (28.8)
N3	1 (2.9)	1 (4.0)	2 (3.4)
p16 status			
IHC positive	34	—	—
IHC negative	—	24	—
ISH negative	—	1[b]	—
Smoking status			
Never-smoker	8 (23.5)	1 (4.0)	9 (15.2)
Pipe or cigar smoker only	2 (5.9)	0 (0)	2 (3.4)
Cigarette smoker, pack-years			
< 10	6 (17.7)	2 (8.0)	8 (13.5)
≥ 10	18 (52.9)	22 (88)	40 (67.8)

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Study Treatment

Treatment included a loading dose of pembrolizumab 200 mg administered intravenously (IV) 7 days before chemoradiotherapy (day −7), 2 additional doses on days 15 and 36 during chemoradiotherapy (concurrent), and after completion (consolidation) every 3 weeks on days 57, 78, 99, 120, and 141. PD-1 blockade was used during both these periods based on previously reported circulating immunophenotype findings,[9] high rates of viable nodal disease on neck dissection after radiotherapy,[21] and positive survival data with consolidation PD-L1 blockade for non–small-cell lung cancer.[22] Chemoradiotherapy was started on day 1 with cisplatin 40 mg/m^2 IV weekly for a total of 6 planned doses (240 mg/m^2 maximum) with concomitant head and neck irradiation (intensity-modulated radiotherapy) at 70 Gy fractionated at 2 Gy once daily over 35 fractions. Corticosteroid antinausea prophylaxis was allowed but not required.

Safety Evaluation During Treatment and Response Assessment

Participants were seen weekly for adverse event (AE) assessment and laboratory studies during chemoradiotherapy treatment (days −7 to 50). During consolidation treatment (starting day 57), participants were seen every 3 weeks for AE assessment and laboratory studies. Safety follow-up with examinations, laboratory studies, and AE assessments then continued every 3 months for the first year, every 6 months for the second year, and then annually through year 5.

Response was determined using a composite end point of overall end-of-treatment (EOT) complete response (CR) at day 150 (approximately 12 weeks after completion of chemoradiotherapy) by using CT of the neck. Optional positron emission tomography (PET) imaging was allowed rather than neck dissection if CT could not confirm CR.[23] Complete metabolic response was assessed using Hopkins score of 1, 2, or 3 on PET imaging.[24] Assessments were performed by a radiology subinvestigator at each center and confirmed by the site principal investigator. For those without an imaging CR, pathologic confirmation was recommend (but not required) by selective neck dissection and/or directed biopsy of the suspected active disease site. If pathologic evaluation of the potential disease site confirmed no residual invasive or in situ cancer, the patient was determined to have a pathologic CR. In cases with both an imaging CR and pathologic response assessment, the pathologic response defined final overall response. Therefore, patients with a final EOT CR included those with either an imaging (CT or PET) or pathologic CR. Recurrence assessment with CT scan of the neck occurred every 3 months for year 1, every 6 months for year 2, and then annually until year 5. Key secondary efficacy end points included progression-free (PFS) and overall survival (OS).

TABLE 1. Patient Demographic and Clinical Characteristics (continued)

Characteristic	No. (%)		
	HPV Positive (n = 34)	HPV Negative (n = 25)	All Patients (N = 59)
Alcohol history			
None	4 (11.8)	6 (24.0)	10 (16.9)
< 1 drink per month	8 (23.5)	1 (4.0)	9 (15.2)
1-10 drinks per week	11 (32.4)	11 (44.0)	22 (37.3)
11-20 drinks per week	10 (29.4)	7 (28.0)	17 (28.8)
Unknown	1 (2.9)	0 (0)	1 (1.8)
Intermediate-risk disease[c]	27 (79)	—	—

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in situ hybridization.

[a]One patient with no identifiable primary tumor.

[b]One patient with questionable p16 results had HPV ISH testing performed.

[c]T4N0-N3/T1-3N3 disease regardless of smoking history or tobacco use of > 10 pack-years or T1-2N2b-N3/T3-4N0-3 disease.

Tumor Assessments

HPV status was determined based on immunohistochemical (IHC) staining for p16. Positivity was based on > 70% of tumor cell staining positive for p16 expression. For cases in which p16 testing could not be accurately performed, HPV positivity could be evaluated by high-risk HPV DNA ISH testing as previously described.[20]

Retrospective analysis of PD-L1 expression was performed on all accessible baseline tumor specimens after completion of enrollment. Testing was performed centrally by QualTek Laboratories (Santa Barbara, CA) using the PD-L1 IHC 22C3 pharmDx (Dako North America, Carpinteria, CA) IHC assay as previously described.[25] PD-L1 evaluation was performed using the combined proportional score (CPS). This includes the tumor cells and any tumor-infiltrating mononuclear inflammatory cells with adjacent supporting stroma, which demonstrate membrane staining PD-L1 > 1+ intensity divided by the total number of tumor cells × 100 (range, 0-100).

Statistical Analysis

The primary objective of this trial was to characterize the safety and tolerability of pembrolizumab in combination with chemoradiotherapy in patients with LA HNSCC. Safety was assessed by reported AEs and serious AEs (SAEs) using Common Terminology Criteria for Adverse Events (version 4.0). Immune-related adverse events (irAEs) were collected, and serious irAEs were designated as events of clinical interest (ECIs).[26] Toxicities and treatment compliance to chemotherapy and radiotherapy were assessed. After an initial safety lead-in of 8 patients, ECIs and SAEs were reviewed and compared with data from a prior study in this setting[27] by a data safety monitoring board (DSMB) as part of a planned analysis. If deemed safe, 27 total patients would then be enrolled for interim efficacy analysis. Treatment would be determined futile if ≤ 13 overall CRs were seen in the 27 patients. After this analysis, the study moved to expansion cohorts to estimate efficacy in patients with HPV-positive or -negative disease. The primary efficacy end point was EOT CR rate. Sample size calculations for the expansion cohorts were based on EOT response data from a similar study using standard high-dose cisplatin in the same treatment groups.[27] Sample size calculations were based on a 1-arm binomial design with a type I error rate of 5% and power of 80%. For the HPV-positive cohort, 34 patients were required to show an improvement in EOT CR rate from 74% to 90%. For the HPV-negative cohort, 23 patients were required to show an improvement in EOT CR rate from 50% to 75%.

Safety and tolerability were assessed by clinical review of all relevant parameters, including AEs, laboratory tests, treatment compliance, and vital signs. Survival outcomes were estimated by the Kaplan-Meier method. Patients with missing PFS or OS data were censored to the time of their last visit. Treatment group comparisons of mean radiotherapy and chemotherapy doses were evaluated by Welch's *t* test. Pembrolizumab discontinuation because of irAEs and completion of all doses were compared using Barnard's and χ^2 tests, respectively.

RESULTS

Patient Characteristics

Patients were enrolled from November 2015 to October 2018. The DSMB reviewed safety lead-in data on March 8, 2016, and determined that there were no SAEs or grade ≥ 3 irAEs and the study could continue enrollment to 27 patients. The study was paused on August 23, 2016, for planned efficacy analysis.[28] Expansion cohorts reopened on January 12, 2017, and concluded enrollment in October 2018. Of 63 total patients screened, 59 were evaluable (HPV positive, n = 34; HPV negative, n = 23) for the primary safety end point and 57 were evaluable for the efficacy end points. As outlined in Figure 1, 4 participants were excluded before treatment and 2 withdrew during active treatment and were replaced per study protocol criteria. Demographic and baseline disease characteristics of the evaluable patients are listed in Table 1. PD-L1 status was high in both groups based on both the CPS ≥ 1 and ≥ 20 cutoffs, as summarized in Appendix Table A1 (online only).

Treatment Delivery and Compliance

Detailed treatment compliance and toxicity events are listed in Table 2. A total of 59 patients started study therapy; 2 withdrew consent before treatment completion (both patients declined consolidation treatment because of travel concerns and inability to comply with protocol requirements). As a result, 59 patients were evaluated for safety, and 57 were included for response assessments; 76% of participants completed all 8 of the planned pembrolizumab doses. Pembrolizumab discontinuation

TABLE 2. Protocol Treatment Compliance

Treatment	No. (%)		
	HPV Positive (n = 34)	HPV Negative (n = 25)	All Patients (N = 59)
Pembrolizumab (8 planned doses)			
≤ 3 doses (RT)	1 (3.0)	6 (24.0)	7 (11.9)[a]
> 3 but < 8 doses (post-RT)	3 (8.8)	4 (16.0)	7 (11.9)
All 8 doses	30 (88.2)	15 (60.0)	45 (76.0)
Cisplatin (40 mg/m^2 × 6 weekly doses)			
Dose reduction	4 (11.8)	3 (12.0)	7 (11.9)[b]
Dose omission	9 (26.5)	7 (28.0)	16 (27.1)[b]
Completed ≥ 200 mg/m^2	30 (88.2)	22 (88.0)	52 (88.1)
Cumulative dose, mg/m^2			
Mean	226.6	221.1	224.3
Standard deviation	23.4	35.1	28.8
RT (35 fractions, 70 Gy planned)			
Treatment delay, days			
> 5	0 (0)	0 (0)	0 (0)
≤ 5	2 (5.9)	1 (4.0)	3 (3.5)[c]
70 Gy of RT completed	34 (100)	24 (96.0)[d]	58 (98.3)
Duration, days			
Mean	49.4	49.3	49.4
Range	46-57	46-54	46-57

Abbreviations: HPV, human papillomavirus; RT, radiotherapy.

[a]Five patients discontinued because of immune-related adverse events (irAEs; HPV-positive cohort, n = 1; HPV-negative cohort, n = 4), which included increased AST (grade 3), colitis (grade 3), adrenal insufficiency (grade 4), hyponatremia (grade 4), and peripheral motor neuropathy (grade 2). Two patients (HPV-negative group) discontinued because of withdrawal of consent (n = 1) and nursing home placement (n = 1).

[b]Dose reductions because of neutropenia (n = 4), thrombocytopenia (n = 1), elevated creatinine (n = 2), and dose omissions as a result of neutropenia (n = 10), thrombocytopenia (n = 1), elevated creatinine (n = 2), hyponatremia (n = 2), and possible allergic reaction (n = 1).

[c]Delays because of equipment malfunction (n = 2) and recovery from AE (n = 1; grade 3 aspiration event).

[d]One patient refused final 3 fractions (6 Gy) of radiotherapy.

because of irAEs during chemoradiotherapy occurred in 5 patients (8.8%). Discontinuation because of irAEs was higher in the HPV-negative cohort (16%) compared with the HPV-positive cohort (2.9%), but this was not statistically significant (P = .0841). These irAEs were reversible with drug discontinuation and corticosteroid therapy, if indicated. One patient discontinued before starting consolidation treatment because of nursing home placement and did not continue therapy per protocol. Another patient discontinued because of withdrawal of consent. After chemoradiotherapy, 11.9% of patients discontinued therapy. None of these discontinuations were because of irAEs; rather, they were related to nonprotocol-related procedures (early neck dissection, n = 2; prolonged hospitalization, n = 1; acute kidney injury, n = 1; patient declined, n = 1; withdrawal of consent, n = 1); however, in 1 patient, pembrolizumab was held at the investigator's discretion because of concern for worsening postradiotherapy Lhermitte syndrome–like symptoms.

Cisplatin dose reductions and omissions predominantly resulting from myelosuppression and elevated creatinine. All but 1 of the participants received the full planned dose of radiotherapy, without any treatment delays > 5 days. Evaluating treatment compliance between the HPV-negative and -positive groups, the only significant difference was in those completing all 8 doses of pembrolizumab (HPV positive, 88.2% *v* HPV negative, 60%; P = .0118).

Toxicity

Pooled treatment-related (irAEs and any treatment-related AEs) and all-cause toxicities are listed in Table 3 and Appendix Table A2 (online only), respectively. No significant difference in toxicity was seen between the 2 cohorts. There was 1 patient death resulting from cardiac arrest without prior progression in the HPV-negative cohort before response assessment but after completion of chemoradiotherapy. This was felt to be unrelated to study therapy; the patient had discontinued pembrolizumab after 2 doses because of increased AST (grade 3), which had resolved

TABLE 3. Selected Treatment-Related AEs

AE	No. (%)		
	All Grade	Grade 3	Grade 4
Immune related			
Pruritus	8 (14)	0 (0)	0 (0)
Hyponatremia	3 (5)	1 (2)	2 (3)
Lymphocyte count decreased	3 (5)	1 (2)	1 (2)
Hypothyroidism	3 (5)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders (other, specify)[a]	3 (5)	0 (0)	0 (0)
Colitis	2 (3)	2 (3)	0 (0)
Diarrhea	2 (3)	1 (2)	0 (0)
Chills	2 (3)	0 (0)	0 (0)
Neck edema	2 (3)	0 (0)	0 (0)
Adrenal insufficiency	1 (2)	0 (0)	1 (2)
Sepsis	1 (2)	0 (0)	1 (2)
AST increased	1 (2)	1 (2)	0 (0)
Autoimmune disorder[b]	1 (2)	0 (0)	0 (0)
Cough	1 (2)	0 (0)	0 (0)
Cytokine release syndrome	1 (2)	0 (0)	0 (0)
Fatigue	1 (2)	0 (0)	0 (0)
Fever	1 (2)	0 (0)	0 (0)
Flu-like symptoms	1 (2)	0 (0)	0 (0)
Hot flashes	1 (2)	0 (0)	0 (0)
Hyperglycemia	1 (2)	0 (0)	0 (0)
Hyperthyroidism	1 (2)	0 (0)	0 (0)
Lymphedema	1 (2)	0 (0)	0 (0)
Oral pain	1 (2)	0 (0)	0 (0)
Paresthesia	1 (2)	0 (0)	0 (0)
Peripheral motor neuropathy	1 (2)	0 (0)	0 (0)
Peripheral sensory neuropathy	1 (2)	0 (0)	0 (0)
Pharyngolaryngeal pain	1 (2)	0 (0)	0 (0)
Proteinuria	1 (2)	0 (0)	0 (0)
Rash acneiform	1 (2)	0 (0)	0 (0)
Rash maculopapular	1 (2)	0 (0)	0 (0)
Vascular disorder (other, specify)[c]	1 (2)	0 (0)	0 (0)
WBC decreased	1 (2)	0 (0)	0 (0)
Treatment related			
Lymphocyte count decreased	58 (98)	29 (49)	23 (39)
Anemia	56 (95)	11 (19)	1 (2)
WBC decreased	55 (93)	30 (51)	2 (3)
Dermatitis radiation	52 (88)	5 (8)	0 (0)
Dysphagia	51 (86)	28 (47)	0 (0)
Fatigue	51 (86)	1 (2)	0 (0)
Weight loss	50 (85)	19 (32)	0 (0)
Dry mouth	50 (85)	0 (0)	0 (0)

(continued on following page)

TABLE 3. Selected Treatment-Related AEs (continued)

AE	No. (%)		
	All Grade	Grade 3	Grade 4
Nausea	48 (81)	4 (7)	0 (0)
Mucositis oral	48 (81)	17 (29)	0 (0)
Dysgeusia	47 (80)	0 (0)	0 (0)
Hyponatremia	45 (76)	10 (17)	3 (5)
Constipation	41 (69)	1 (2)	0 (0)
Salivary duct inflammation	41 (69)	1 (2)	0 (0)
Neutrophil count decreased	39 (66)	11 (19)	6 (10)
Hypomagnesemia	36 (61)	1 (2)	0 (0)
Vomiting	35 (59)	2 (3)	0 (0)
Platelet count decreased	34 (58)	3 (5)	0 (0)
Anorexia	34 (58)	2 (3)	0 (0)
Sore throat	33 (56)	6 (10)	0 (0)
Dehydration	29 (49)	9 (15)	0 (0)
Diarrhea	29 (49)	2 (3)	0 (0)
Lymphedema	25 (42)	0 (0)	0 (0)
Hypoalbuminemia	23 (39)	0 (0)	0 (0)
Pruritus	23 (39)	0 (0)	0 (0)
Hypokalemia	21 (36)	2 (3)	1 (2)
Hypothyroidism	21 (36)	0 (0)	0 (0)
Proteinuria	21 (36)	0 (0)	0 (0)
Pain	19 (32)	1 (2)	0 (0)
Mucosal infection	19 (32)	0 (0)	0 (0)
Tinnitus	19 (32)	0 (0)	0 (0)

NOTE. Treatment related occurring in ≥ 30% of participants.
Abbreviation: AE, adverse event.
[a]Skin and subcutaneous tissue disorders (other, specify) includes: worsening rosacea, vitiligo, and redness around gastrostomy tube site.
[b]Autoimmune disorder: sarcoidosis.
[c]Vascular disorders (other, specify): Raynaud's phenomenon.

with corticosteroid treatment 15 weeks before death. Hematologic and electrolyte abnormalities were the only grade 4 toxicities experienced. Beyond these, common grade 3 chemoradiotherapy-related toxicities occurring at least once included dysphagia, weight loss, oral mucositis, dehydration, sore throat, radiation dermatitis, nausea, vomiting, and anorexia.

Response

Of the 57 per-protocol population, all were evaluable except for the patient who died during study treatment. Detailed response data for the HPV-positive and -negative cohorts are listed in Table 4. In the HPV-positive group, 19 (55.9%) achieved a CR based on RECIST (version 1.1) criteria. Of the 12 (35.3%) with a RECIST (version 1.1) partial response (PR), an additional 8 patients (23.5%) were determined to have a CR based on PET Hopkins criteria. Of the remaining patients without an imaging CR, an additional 2 (5.9%) were determined to have a pathologic CR (neck dissection, n = 1; biopsy of distant site, n = 1). As a result, the final overall CR rate for the HPV-positive group at EOT was 85.3%. Two additional patients with an imaging PR did not undergo confirmatory surgery or biopsy, because there was no apparent clinical disease to biopsy. These patients both achieved a CR on 12-month imaging. In the HPV-negative cohort, 12 (52.2%) achieved a CR based on RECIST (version 1.1) criteria. Of the 9 (39.1%) with a RECIST (version 1.1) PR, an additional 5 (21.7%) were determined to have a CR based on PET Hopkins criteria. One additional patient (4.3%) with an imaging PR underwent neck dissection confirming pathologic CR. As a result, the final CR rate for the HPV-negative cohort at EOT was 78.3%.

Survival

Median follow-up time was 28.4 months (range, 9.5-40.1 months) and 17.5 months (range, 5.3-38.5 months) for the

TABLE 4. Response Assessment at EOT (day 150)

Response	No. (%)	
	HPV Positive (n = 34)	HPV Negative (n = 23)
RECIST (version 1.1)		
CR	19 (55.9)	12 (52.2)
PR	12 (35.3)	9 (39.1)
SD	—	—
PD	3 (8.8)	1 (4.3)
UE[a]	—	1 (4.3)
Hopkins		
Negative	26 (76.5)	14 (60.8)
Positive	7 (20.6)	8 (34.8)
UE	1 (2.9)[b]	1 (4.3)[b]
Pathologic		
No pathologic confirmation	27 (79.4)	19 (82.6)
Neck dissection pCR	2 (5.9)	2 (8.6)
Directed biopsy pCR	2 (5.9)	1 (4.3)
Non-CR	3 (8.8)	1 (4.3)
Final		
CR	29 (85.3)	18 (78.3)
PR	4 (11.8)	3 (13.0)
SD	—	—
PD	1 (2.9)	1 (4.3)
UE[a]	—	1 (4.3)

Abbreviations: CR, complete response; EOT, end of treatment; HPV, human papillomavirus; pCR, pathologic complete response; PD, progressive disease; PR, partial response; SD, stable disease; UE, unevaluable.

[a]One patient died before day 150 (HPV negative).

[b]One patient's insurance denied positive emission tomography (HPV positive), tone patient died before day 150 (HPV negative).

HPV-positive and -negative cohorts, respectively. In addition to 1 patient death (HPV-negative cohort) during study treatment, 8 deaths occurred during survival follow-up (HPV positive, n = 2; HPV negative, n = 6), with 4 resulting from disease recurrence and 4 from other causes (2nd primary cancer, motor vehicle accident, GI bleed, respiratory failure resulting from pneumonia). On the basis of current follow-up, 1- and 2-year OS and PFS estimates for both cohorts are shown in Figure 2. For the HPV-positive cohort, 2-year OS was 97.1% (95% CI, 80.9% to 99.6%) and PFS was 92.8% (95% CI, 73.7% to 98.2%). In the HPV-positive cohort, 1 patient experienced distant failure, 2 had persistent locoregional disease, and 1 had late locoregional relapse. Follow-up time limited estimation of 2-year OS and PFS for the HPV-negative cohort, but 1-year OS was 86.5% (95% CI, 63.8% to 95.5%) and PFS was 72.6% (95% CI, 48.7% to 86.7%). In this group, 2 patients experienced distant failure and 3 experienced locoregional failure (persistent disease, n = 1; recurrent disease, n = 2). Detailed information on patterns of first failure by HPV status is listed in Table 5.

DISCUSSION

This prospective phase IB study combining pembrolizumab with standard chemoradiotherapy demonstrates that this approach is safe in LA HNSCC. Pembrolizumab discontinuations because of irAEs were in line with monotherapy, and no new safety signals were identified.[10,26] Furthermore, the addition of pembrolizumab did not impair delivery of curative doses of standard therapy. Although optimal cisplatin dosing during definitive chemoradiotherapy is not clearly defined, cumulative doses ≥ 200 mg/m^2 are generally recommended.[16,29] In pivotal studies using high-dose cisplatin, 84% to 93% of patients have achieved this dose.[13,30] In our study, 88.1% of patients achieved this target dose, with dose reductions and omissions as a result of anticipated toxicities. Radiotherapy delivery was also not compromised, with related toxicities (mucositis, radiation dermatitis, and dysphagia) limited to grade 3 and comparable to those in large randomized trials in this setting.[4] In addition to an acceptable safety profile, early efficacy data are promising.

Despite not meeting the final EOT response end point in the HPV-positive group, the 2-year OS rate of 97.1% was encouraging, because 79% of participants had intermediate-risk disease. Only 1 distant failure occurred in this group; however, follow-up was limited, and late recurrences can occur in HPV-positive disease. For the HPV-negative cohort, although the follow-up period was too short to draw major conclusions, the EOT CR rate exceeded the primary end point goal, and 1-year survival data are supportive of further investigation. Treatment failures did occur in both groups; however, recurrence rates were consistent with historical disease control rates.

Although other chemoradiotherapy combination trials have used response end points,[31] our use of a PET imaging end point posed a challenge in this study. Despite not being widely evaluated in large, prospective trials, we chose this modality because of increasing clinical use and supporting data demonstrating a strong concordance of EOT PET response with recurrence and survival.[32,33] In this study, use of PET led to a high false-positive rate, which in turn may have contributed to the failure to meet the final efficacy end point for the HPV-positive group. However, with surgical confirmation and continued imaging surveillance, CR was confirmed in an additional 4 patients (11.8%). Variability in PET imaging and interpretation across centers could pose challenges in accurate response assessment despite the use of established scoring criteria. This highlights the importance of confirmation of response as this treatment approach moves forward.

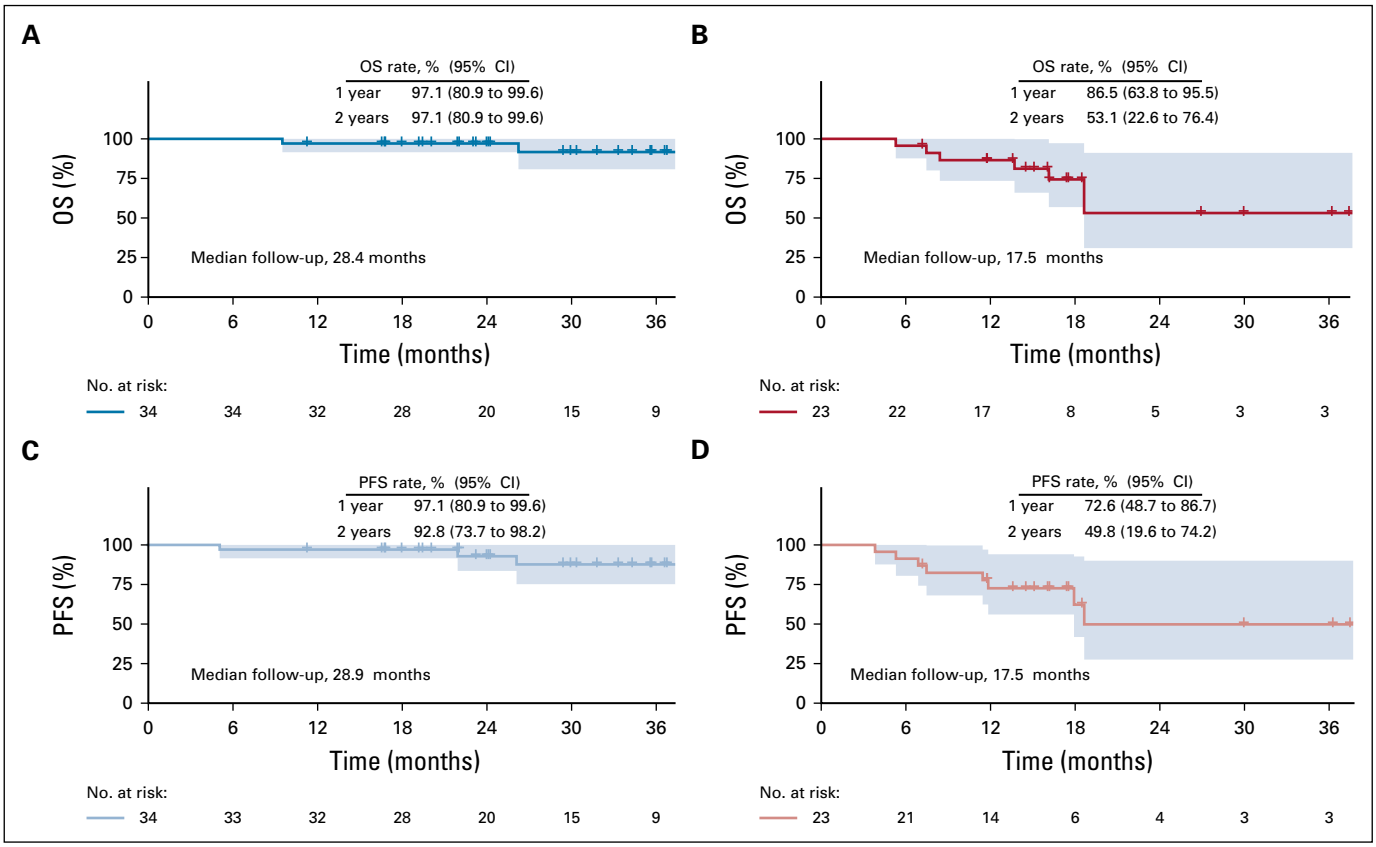

FIG 2. Kaplan-Meier estimates of survival. Overall survival (OS) for (A) human papillomavirus (HPV)–positive and (B) HPV-negative cohorts. Progression-free survival (PFS) for (C) HPV-positive and (D) HPV-negative cohorts.

It is also important to note that although our overall compliance rates were similar to those seen with other combinations,[34] significantly fewer HPV-negative participants were able to complete all planned pembrolizumab doses compared with HPV-positive participants (60% *v* 88.2%; $P = .0118$). Although there was a nonsignificant increase in irAEs leading to pembrolizumab discontinuation in the HPV-negative group, a majority did not result directly from drug toxicity. This is important to consider, because this group historically has a higher rate of comorbidities and overall mortality.[35] Despite these discontinuations, chemoradiotherapy delivery was similar between the groups.

Our study has several limitations. First, on the basis of the single-arm design, we cannot make direct toxicity comparisons with standard-of-care chemoradiotherapy. Second, follow-up time was limited, so we cannot draw any conclusions

TABLE 5. Pattern of First Treatment Failure

Patient	T Stage	N Stage	HPV Status	Time to First Failure (days)	Site of Failure	RECIST Response	Hopkins Response
1	T3	N2b	Negative	55	Local, nodal[a]	PR	Positive
2	T4	N3	Positive	93	Local, nodal[a]	PR	Negative
3	T3	N2c	Negative	116	Distant	PD	Positive
4	T0	N2b	Positive	158	Distant	PD	Positive
5	T3	N2b	Positive	173	Local, primary[b]	PD	Negative
6	T3	N2c	Negative	348	Local, nodal	CR	Positive
7	T3	N0	Negative	360	Local, primary	CR	Positive
8	T3	N2b	Negative	545	Distant	CR	Negative
9	T4	N1	Positive	671	Local, primary and nodal	PR	Positive

Abbreviations: CR, complete response; HPV, human papillomavirus; PD, progressive disease; PR, partial response.
[a]Early nodal dissection after radiotherapy with persistent disease.
[b]Surgical resection performed because of conflicting imaging findings with persistent disease at the primary site.

about late toxicities or long-term survival at this point. The small sample size limits the use of PD-L1 as a predictive biomarker and additional subgroup analyses. Despite these limitations, early toxicity and outcome data from this study have been provocative enough to support the development of several phase III trials using a similar approach.[36,37]

In conclusion, this study demonstrates an acceptable safety profile and efficacy signal from the addition of pembrolizumab to definitive chemoradiotherapy in HNSCC. Confirmation of the safety and efficacy of this approach awaits the completion of larger randomized studies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Efficacy of Pembrolizumab With Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Phase IB Study

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APPENDIX

TABLE A1. PD-L1 Expression by HPV Status

	No. (%)		
CPS	**HPV Positive (n = 34)**	**HPV Negative (n = 23)**	**All Patients (N = 57)**
Evaluable for CPS PD-L1	27 (79.4)	16 (69.6)	43 (75.4)
< 1	1 (3.7)	0 (0)	1 (2.3)
≥ 1	26 (96.3)	16 (100)	42 (97.7)
< 20	9 (33.3)	3 (18.8)	12 (27.9)
≥ 20	18 (66.7)	13 (81.2)	31 (72.1)

Abbreviations: CPS, combined positivity score; HPV, human papillomavirus; PD-L1, programmed death-1 ligand.

TABLE A2. Detailed All-Cause AEs

AE Toxicity	All Grade (%)	Grades 3-4 (%)
Lymphocyte count decreased	98	88
Anemia	98	20
WBC decreased	93	54
Dysphagia	90	49
Weight loss	88	32
Dermatitis radiation	88	8
Dry mouth	88	0
Fatigue	86	2
Nausea	85	7
Mucositis oral	81	29
Dysgeusia	80	0
Hyponatremia	78	25
Constipation	78	2
Salivary duct inflammation	69	2
Neutrophil count decreased	66	29
Vomiting	61	5
Hypomagnesemia	61	2
Anorexia	59	3
Platelet count decreased	58	5
Sore throat	56	10
Diarrhea	54	3
Dehydration	49	15
Hypoalbuminemia	42	0
Lymphedema	42	0
Pruritus	42	0
Pain	41	3
Proteinuria	39	0
Hypokalemia	37	7
Hypothyroidism	36	0
Mucosal infection	34	2
Cough	32	0
Dizziness	32	0
Insomnia	32	0
Tinnitus	32	0
Hypophosphatemia	31	8
Oral pain	27	3
Headache	27	0
ALT increased	25	0
Alopecia	25	0
Peripheral sensory neuropathy	25	0
Hyperuricemia	24	2
Hypocalcemia	24	2
Hypotension	24	0

(continued in next column)

TABLE A2. Detailed All-Cause AEs (continued)

AE Toxicity	All Grade (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders (other, specify)[a]	24	0
Chills	22	0
Depression	22	0
Dyspnea	20	3
Dyspepsia	20	0
Hematuria	20	0
Neck pain	20	0

Abbreviation: AE, adverse event.

NOTE. Definitely, probably, or possibly related to study drug or standard treatment occurring in at least 20% of participants.

[a]Skin and subcutaneous tissue disorders (other) includes: mild skin rashes, dermatitis, peeling skin, abrasions, redness around gastronomy tube, basal cell carcinoma, skin nodules, and pityriasis rubra pilaris.