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ORIGINAL REPORT

Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study

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ABSTRACT

Purpose

There are no approved treatments for recurrent/metastatic head and neck squamous cell carcinoma refractory to platinum and cetuximab. In the single-arm, phase II KEYNOTE-055 study, we evaluated pembrolizumab, an anti–programmed death 1 receptor antibody, in this platinum- and cetuximab-pretreated population with poor prognosis.

Methods

Eligibility stipulated disease progression within 6 months of platinum and cetuximab treatment. Patients received pembrolizumab 200 mg every 3 weeks. Imaging was performed every 6 to 9 weeks. Primary end points: overall response rate (Response Evaluation Criteria in Solid Tumors v1.1, central review) and safety. Efficacy was assessed in all dosed patients and in subgroups on the basis of programmed death ligand 1 (PD-L1) expression and human papillomavirus (HPV) status.

Results

Among 171 patients treated, 75% received two or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. At the time of analysis, 109 patients (64%) experienced a treatment-related adverse event; 26 patients (15%) experienced a grade ≥ 3 event. Seven patients (4%) discontinued treatment, and one died of treatment-related adverse events. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median progression-free survival was 2.1 months, and median overall survival was 8 months.

Conclusion

Pembrolizumab exhibited clinically meaningful antitumor activity and an acceptable safety profile in recurrent/metastatic head and neck squamous cell carcinoma previously treated with platinum and cetuximab.

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INTRODUCTION

In locally advanced head and neck squamous cell carcinoma (HNSCC), an aggressive approach that combines chemotherapy, surgery, and/or radiotherapy improves survival and reduces risk of recurrence.[1] For recurrent/metastatic (R/M) HNSCC not amenable to curative-intent treatment, palliative chemotherapy is the mainstay of therapy, but efficacy of such treatments is limited.[2] The best median overall survival for treatment in the first-line setting of R/M HNSCC (10 months) used a combination of cetuximab, platinum, and fluorouracil.[3] After progression on or after platinum and cetuximab, there are no approved treatment options.[4] Methotrexate, which is commonly prescribed in this setting, yields an overall response rate of 6% and median overall survival of 6 months.[5]

Immunotherapy targeting the programmed death 1 (PD-1) pathway is effective for a wide range of tumors.[6-9] The PD-1–programmed death ligand 1 (PD-L1) interaction is implicated in immune escape in HNSCC, with evidence of overexpression of the PD-1 ligands, PD-L1 and PD-L2, both on tumor cells and within the tumor microenvironment.[10-12] Upregulation

ASSOCIATED CONTENT

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Appendix
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Data Supplement
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of this pathway may allow the tumor to evade immune surveillance.[10,13,14]

Pembrolizumab (MK-3475) is an anti–PD-1 antibody that disrupts the interaction between PD-1 and its ligands. It has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types and is currently approved for R/M HNSCC with disease progression on or after platinum-containing chemotherapy in the United States.[9,15-18] In HNSCC, pembrolizumab was well tolerated and exhibited durable antitumor activity in patients with R/M HNSCC during the multicohort, phase Ib KEYNOTE-012 study (ClinicalTrials.gov identifier, NCT01848834).[7,19] KEYNOTE-012 had no prior therapy requirements.

KEYNOTE-055 (ClinicalTrials.gov identifier, NCT02255097) is the first study, to our knowledge, designed to evaluate efficacy and safety of pembrolizumab in patients with R/M HNSCC resistant to both platinum and cetuximab. We report here the results observed in this single-arm, phase II study.

METHODS

Patients

Eligible patients were ≥ 18 years old with confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx resistant to both platinum and cetuximab. Concurrent platinum and cetuximab treatment was not required, but patients were required to have had progressive disease or recurrence within 6 months of the last dose of each therapy. Additional eligibility criteria included measurable disease, provision of newly obtained core or excisional biopsy for PD-L1 expression analysis, Eastern Cooperative Oncology Group performance status of 0 to 1,[20] and adequate organ function. There was no limit to the number of prior systemic therapies for R/M disease. Patients were excluded if they had active CNS metastases, carcinomatous meningitis, autoimmune disorders requiring systemic treatment, noninfectious pneumonitis, known hepatitis B or C infection, additional malignancies requiring active treatment, or history of HIV infection. Previous treatment with drugs specifically targeting the PD-1 pathway was not allowed. Systemic immunosuppressive therapy had to be concluded within 7 days; chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks; and anticancer monoclonal antibody therapy within 4 weeks before first dose of pembrolizumab.

Study Oversight

The study protocol was approved by regulatory boards or ethics review committees at each study center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before study entry. Study investigators participating in the trial are listed in Appendix Table A1 (online only).

Study Design and Treatment

KEYNOTE-055 is a multicenter, phase II, single-arm study. Patients received pembrolizumab 200 mg intravenously every 3 weeks until documented progressive disease, intolerable toxicity, intercurrent illness preventing further treatment, patient or physician decision to withdraw, or completion of 24 months of treatment. In the case of radiographic progressive disease, progression was to be confirmed by repeat imaging performed ≥ 4 weeks later. If the repeat imaging assessment showed a < 20% tumor burden compared with nadir or stabilization or improvement of the lesion, progressive disease was not confirmed and the patient was allowed to remain on treatment. Patients achieving a complete response who received ≥ 24 weeks of pembrolizumab could discontinue therapy. Patients who stopped pembrolizumab after achieving a confirmed complete response or after completion of 2 years of treatment could receive up to an additional year of treatment on subsequent progression.

Study Assessments

Tumor assessments were performed by computed tomography or magnetic resonance imaging at baseline, 9 weeks after the first dose, every 6 weeks thereafter for the first year, and every 9 weeks thereafter. Primary efficacy end point of overall response rate, defined as the proportion of patients with complete or partial response, was assessed by central imaging vendor review using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Key secondary end points included progression-free survival, overall survival, and duration of response. Progression-free survival was defined as time from allocation to progressive disease according to RECIST v1.1 or death due to any cause, whichever occurred first. Overall survival was defined as time from allocation to death due to any cause. Duration of response was the interval from first RECIST v1.1–recorded response to progressive disease in patients who achieved at least a partial response.

Overall response rates in human papillomavirus (HPV) –positive and PD-L1–positive patients were prespecified secondary end points. HPV status for patients with oropharyngeal tumors was determined by local institution. Although the majority of institutions used p16 immunohistochemistry, this methodology was not protocol mandated. Patients with nonoropharyngeal disease were considered to be HPV negative. PD-L1 expression was retrospectively evaluated using an investigational version of the PD-L1 IHC 22C3 pharmDx assay (Dako North America, Carpinteria CA) that has been approved as a companion diagnostic for use in non–small-cell lung cancer in the United States.[21] The staining protocol used in this study was as described in the instructions for the commercial assay. Expression was scored using a combined positive score (CPS) and defined as the percentage of tumor and mononuclear inflammatory cells within the tumor nests and adjacent supporting stroma expressing PD-L1 at any intensity. CPS was chosen as an exploratory biomarker because of the association between PD-L1 expression on tumor and inflammatory cells and response to pembrolizumab observed during the KEYNOTE-012 trial.[19] CPS was measured on a scale from 0 to 100%. PD-L1 positivity was defined using a CPS ≥ 1% cutoff. Data were analyzed based on raw scores from the initial read for CPS ≥ 50%.

Adverse events were monitored throughout the study and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients were followed for an additional 30 days for adverse events and 90 days for serious adverse events and events of interest after discontinuing treatment. Certain events of interest were preselected based on potential immune-related etiology; these events are referred to as immune-mediated adverse events and are reported regardless of causality.

Statistical Analyses

Efficacy and safety end points were assessed in all patients who received one or more doses of pembrolizumab. Target enrollment size was 150 patients. It was assumed that at least 135 of these patients would be evaluable for the primary efficacy analysis. On the basis of this assumption, the study was designed to have approximately 85% power to demonstrate that the overall response rate is > 5%, with a type I error rate of 1.25% if true overall response rate was 13%. Success for this hypothesis required responses in at least 14 of 135 patients.

Response rates, 95% CIs, and one-sided *P* values for testing the null hypotheses were estimated using the exact binomial method. Patients with missing baseline or postbaseline data were considered nonresponders. The study was considered to have achieved its efficacy objective if the *P* value for the primary hypothesis was < .0125.

Kaplan-Meier statistics were applied for estimates of progression-free survival, overall survival, and duration of response. Patients without a postbaseline efficacy analysis or without survival data were censored at day 1. Patients with missing progression-free survival or overall survival data were censored at the date of their last assessment. Additional statistical details are provided in the Data Supplement.

RESULTS

Patients

From October 24, 2014, through September 23, 2015, 228 patients were screened; of these, 171 were enrolled and received one or more doses of pembrolizumab (Fig 1). Most common reasons for screen failure were decline in Eastern Cooperative Oncology Group performance status to > 1 (24 patients), CNS metastases and/or carcinomatous meningitis (10 patients), inadequate organ function (seven patients), and unwilling and/or unable to provide consent (seven patients). Median age was 61 years; 81% were male, 68% reported previous tobacco use, and 75% received two or more lines of prior systemic therapy (Table 1). The majority of patients (140 of 171; 82%) were PD-L1 positive using a CPS of ≥ 1%; 48 (28%) had a CPS of ≥ 50%. Thirty-seven patients (22%) were HPV positive; 131 (77%) were HPV negative. The data-cutoff date for these analyses was April 22, 2016. At that time, the median (range) follow-up duration was 7 (0 to 17) months, and 36 patients (21%) were still receiving pembrolizumab.

Adverse Events

At the time of data cutoff, patients had received pembrolizumab for a median (range) of 90 (1 to 401) days. Treatment-related adverse events of any grade were reported in 109 (64%) patients; most common were fatigue, hypothyroidism, nausea, AST increase, and diarrhea (Table 2). The majority of treatment-related adverse events were of grade 1 or 2; 26 patients (15%) experienced an event of grade 3 or higher. The only immune-mediated adverse events (any grade or treatment attribution) reported in ≥ 2% of patients were hypothyroidism (27 of 171; 16%), pneumonitis (seven of 171; 4%), and hyperthyroidism (four of 171; 2%). Seven patients (4%) discontinued because of treatment-related adverse events (Appendix Table A2, online only). One patient died of treatment-related pneumonitis.

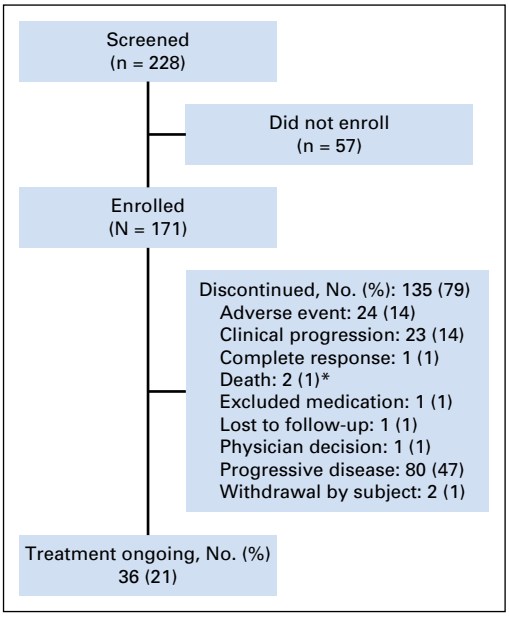

Fig 1. Patient disposition. *One patient died because of cardiac arrest (not treatment related) and one died because of pneumonitis (treatment related).

Table 1. Baseline Characteristics

Characteristic	All Patients (N = 171)
Age, years, median (range)	61 (33-90)
Male, No. (%)	138 (81)
Race, No. (%)	
White	152 (89)
Black or African American	11 (6)
Asian	7 (4)
American Indian or Alaska Native	1 (1)
ECOG performance status	
0	48 (28)
1	120 (70)
2*	3 (2)
HPV status†	
Positive	37 (22)
Negative	131 (77)
History of tobacco use	
Yes	117 (68)
No	54 (32)
History of cigarette use	
Current user	13 (8)
Past user	99 (58)
Nonuser	59 (35)
Primary tumor location	
Hypopharynx	7 (4)
Larynx	30 (18)
Nasal cavity	1 (1)
Oral cavity	28 (16)
Oropharynx	100 (58)
Pharynx	1 (1)
Other	4 (2)
Prior systemic therapies, median (range)	2 (1-6)
Prior curative treatments	
Radiation therapy and chemotherapy	153 (89)
Surgery	98 (57)
Adjuvant chemotherapy	36 (21)
Induction chemotherapy	10 (6)
Radiation alone	0 (0)
No. of previous lines for recurrent/metastatic disease	
1	39 (23)
2	68 (40)
≥ 3	61 (36)
Prior concurrent platinum and cetuximab therapy	84 (49)
Prior platinum and subsequent cetuximab therapy	116 (68)
Received another chemotherapy after platinum and/or cetuximab therapy and before trial initiation	102 (60)
Disease progressed within 6 months of completing primary treatment	49 (29)
Disease progressed within 6 months of cetuximab with concurrent radiation‡	13 (8)
Disease progressed within 6 months of cetuximab with concurrent platinum-based chemotherapy‡	44 (26)
Disease progressed within 6 months of cetuximab monotherapy‡	71 (42)
PD-L1 status§	
CPS ≥ 1%	140 (82)
CPS < 1%	26 (15)
CPS ≥ 50%	48 (28)
CPS < 50%	118 (69)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PD-L1, programmed death ligand 1.
*Three patients with an ECOG performance status of 2 were enrolled despite entry criteria violations.
†HPV status unknown for three patients.
‡Twenty patients had a missing end date for radiation therapy, 53 patients had a missing end date for platinum-based chemotherapy, and 37 patients had a missing end date for cetuximab treatment or a missing start date for disease progression. Patients with missing data were excluded from these analyses.
§CPS unknown for five patients.

Table 2. Treatment-Related Adverse Events in All Treated Patients (N = 171)

Adverse Event	Any Grade	Grade 3-5
Any	109 (64)	26 (15)
Fatigue	30 (18)	1 (1)
Hypothyroidism	16 (9)	0 (0)
Nausea	11 (6)	0 (0)
AST increase	11 (6)	4 (2)
Diarrhea	10 (6)	1 (1)
Appetite decrease	9 (5)	0 (0)
Rash	9 (5)	0 (0)
Pruritus	8 (5)	0 (0)
ALT increase	7 (4)	0 (0)
Anemia	6 (4)	3 (2)
Pneumonitis	6 (4)	2 (1)
Weight decrease	6 (4)	0 (0)
Arthralgia	6 (4)	0 (0)
Bilirubin increase	5 (3)	0 (0)
Myalgia	5 (3)	0 (0)
Peripheral neuropathy	5 (3)	0 (0)
Cough	5 (3)	0 (0)
Alkaline phosphatase increase	4 (2)	2 (1)
Hyponatremia	4 (2)	1 (1)
Dizziness	4 (2)	0 (0)
Maculopapular rash	4 (2)	1 (1)

NOTE. Data presented as No. (%). Each patient is counted once for a specific adverse event. Only the highest grade of a given adverse event is reported for each patient. Listed are events of any grade reported in at least 2% of patients.

Clinical Activity

Overall response rate was 16% (95% CI, 11% to 23%; $P < .001$; Table 3). One patient achieved complete response, 27 patients (16%) achieved partial response, and 33 patients (19%) and 87 patients (51%) experienced stable and progressive disease, respectively. Response rates were similar regardless of HPV status, with rates of 16% in HPV-positive patients and 15% in HPV-negative patients (Table 3). Overall, 50% (70 of 141) of evaluable patients experienced reduction from baseline in target lesion size (Fig 2A).

At data cutoff, median (range) time to response was 2 (2 to 5) months. Median (range) follow-up time for responders was 9 (7 to 17) months. Median (range) response durations were 8 (2+ to 12+) months in all responders (Appendix Fig A1, online only), not reached (3+ to 12+ months) in HPV-positive responders, and 7 (2+ to 10+) months in HPV-negative responders. At the data cutoff, 21 patients (75% of responders) had an ongoing response, and eight responses had lasted ≥ 6 months (Fig 2B).

Median progression-free survival was 2.1 months (95% CI, 2.1 to 2.1) in all patients and did not differ based on HPV status (Fig 2C). The 6-month progression-free survival rate was 23% in all patients, 25% in HPV-positive patients, and 21% in HPV-negative patients. Median overall survival was 8 months (95% CI, 6 to 11 months) in all patients, with similar survival observed regardless of HPV status (Fig 2D). Overall survival at 6 months was 59% in all patients, 72% in HPV-positive subgroups, and 55% in HPV-negative subgroups.

Clinical Activity by PD-L1 Status

Overall response rates (95% CI) by PD-L1 expression status using a CPS cutoff of 1% were 18% (12% to 25%) in PD-L1–positive patients (CPS ≥ 1%) and 12% (2% to 30%) in PD-L1–negative patients (CPS < 1%; Table 4). When the CPS was analyzed to 50% on the basis of raw scores, rates (95% CI) were 27% (15% to 42%) in patients with CPS ≥ 50% and 13% (7% to 20%) in patients with CPS < 50%. The one complete response achieved during the study was observed in a patient with a CPS of ≥ 50%. Six-month progression-free survival rates in PD-L1–positive patients were 24% (CPS ≥ 1%) and 31% (CPS ≥ 50%); rates were 20% and 20% in patients with CPS < 1% and CPS < 50%, respectively. Overall survival at 6 months in PD-L1–positive patients was 59% (CPS ≥ 1%) and 60% (CPS ≥ 50%); rates were 56% and 58% in patients with CPS < 1% and CPS < 50%, respectively. Kaplan-Meier estimates of progression-free survival and overall survival are outlined in Appendix Figure A2 (online only).

DISCUSSION

We have demonstrated that pembrolizumab exhibited clinically significant antitumor activity and a manageable safety profile in patients with HNSCC whose disease progressed on both platinum and cetuximab. The primary objective of this study was met; 16% of patients achieved confirmed response by central review, and responses were durable, with some > 12 months at the time of this

Table 3. Antitumor Activity of Pembrolizumab

	All Patients* (N = 171)		HPV Positive† (n = 37)		HPV Negative† (n = 131)	
Response Evaluation	No.	% (95% CI)‡	No.	% (95% CI)‡	No.	% (95% CI)‡
Overall response rate	28	16 (11 to 23)	6	16 (6 to 32)	20	15 (10 to 23)
Complete response	1	1 (0 to 3)	0	0 (0 to 10)	1	1 (0 to 4)
Partial response	27	16 (11 to 22)	6	16 (6 to 32)	19	15 (9 to 22)
Stable disease	33	19 (14 to 26)	6	16 (6 to 32)	26	20 (13 to 28)
Progressive disease	87	51 (43 to 59)	21	57 (40 to 73)	66	50 (42 to 59)
Nonevaluable§	4	2 (1 to 6)	0	0 (0 to 10)	4	3 (1 to 8)
Data unavailable‖	19	11 (7 to 17)	4	11 (3 to 25)	15	12 (7 to 18)

NOTE. Confirmed responses per Response Evaluation Criteria in Solid Tumors, version 1.1, per central imaging vendor review.
Abbreviation: HPV, human papillomavirus.
*Patients who received one or more doses of pembrolizumab.
†HPV status determined using p16 immunohistochemistry for tumors of the oropharynx. Nonoropharyngeal tumors were considered HPV negative.
‡On the basis of binomial exact confidence interval method.
§Images were not evaluable.
‖Data were unavailable because of death or withdrawal from the study before the first scheduled scan.

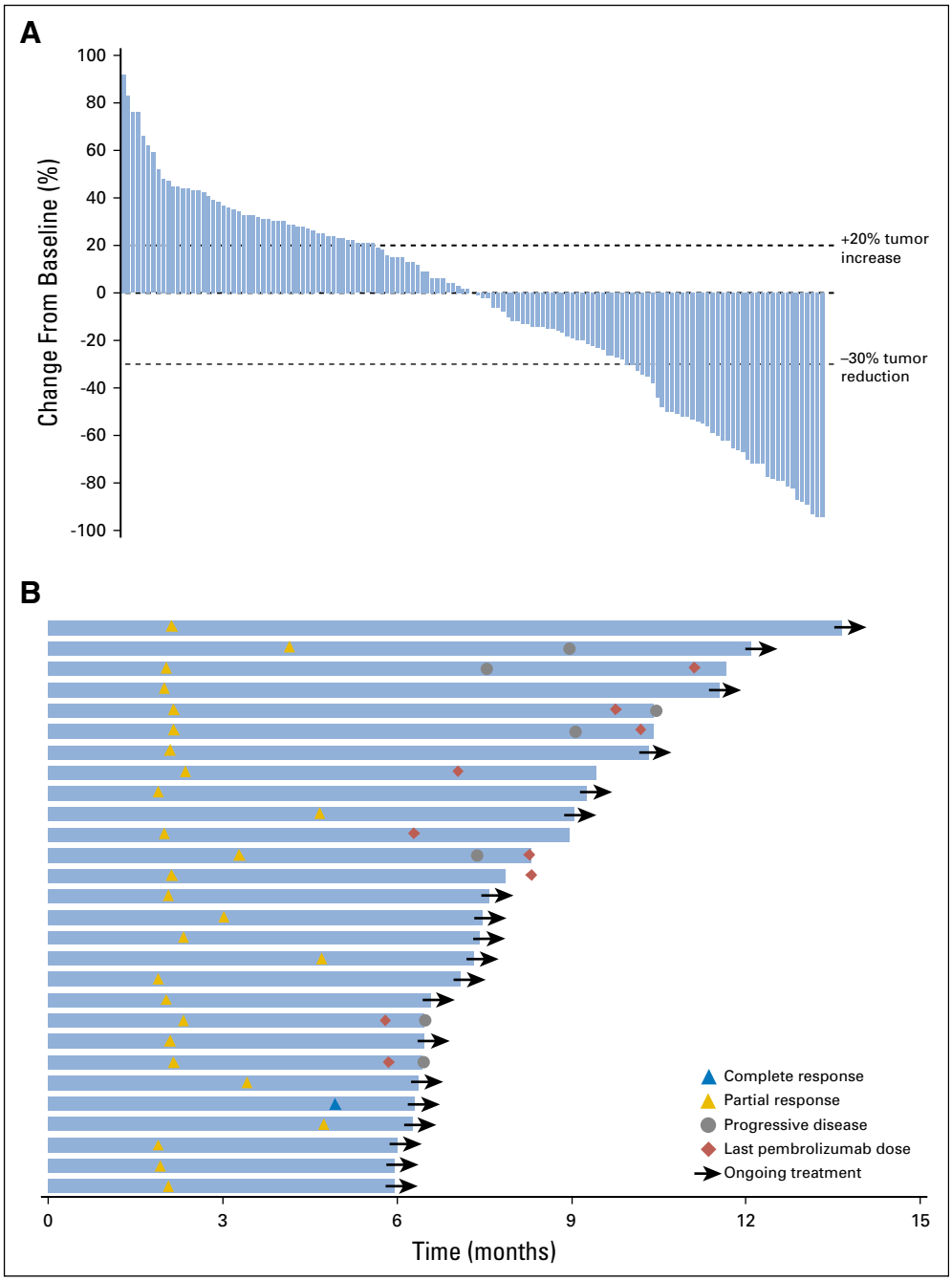

Fig 2. Efficacy of pembrolizumab. (A) The best percentage change from baseline in target lesions (ie, difference in size of target lesions between baseline and post-baseline assessments divided by baseline target lesion size times 100) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by central imaging vendor review (n = 141). (B) Treatment exposure and response duration in patients with a confirmed complete or partial response per RECIST v1.1 by central imaging vendor review (n = 28). (C) Kaplan-Meier estimate of progression-free survival per RECIST v1.1 by central imaging vendor review. (D) Kaplan-Meier estimate of overall survival. HPV, human papillomavirus.

publication. These results are consistent with those reported previously for the KEYNOTE-012 study, in which 18% of patients with R/M HNSCC responded to pembrolizumab. No specific prior treatments were mandated in KEYNOTE-012.[7,19] In both studies, patients responded to pembrolizumab regardless of HPV status. In addition, given the median overall survival of 8 months reported in the current study and in the R/M HNSCC cohorts of KEYNOTE-012,[7,19] survival with pembrolizumab in R/M HNSCC is encouraging, especially when considered in conjunction with the toxicity profile and in comparison with historical reference populations.[3-5] It is particularly notable that patients in KEYNOTE-055 had prolonged responses, given that increasing lines of therapy are generally associated with worse outcomes in oncology. Pembrolizumab may therefore lead to significant improvements in outcomes for some patients regardless of prior treatment with platinum and cetuximab.

To our knowledge, our study is the first and largest report of data from a phase II trial investigating PD-1 inhibition in patients with R/M HNSCC refractory to both platinum and cetuximab, a patient population with poor outcome and no approved treatment options. Patients in this study were heavily pretreated, with 75% receiving two or more prior lines of systemic therapy. There is a paucity of efficacy data in the literature for patients with R/M HNSCC refractory to both platinum and cetuximab with which to compare these results. Nonetheless, overall response and survival rates reported with pembrolizumab seem favorable even when compared with other treatments in patients with fewer prior

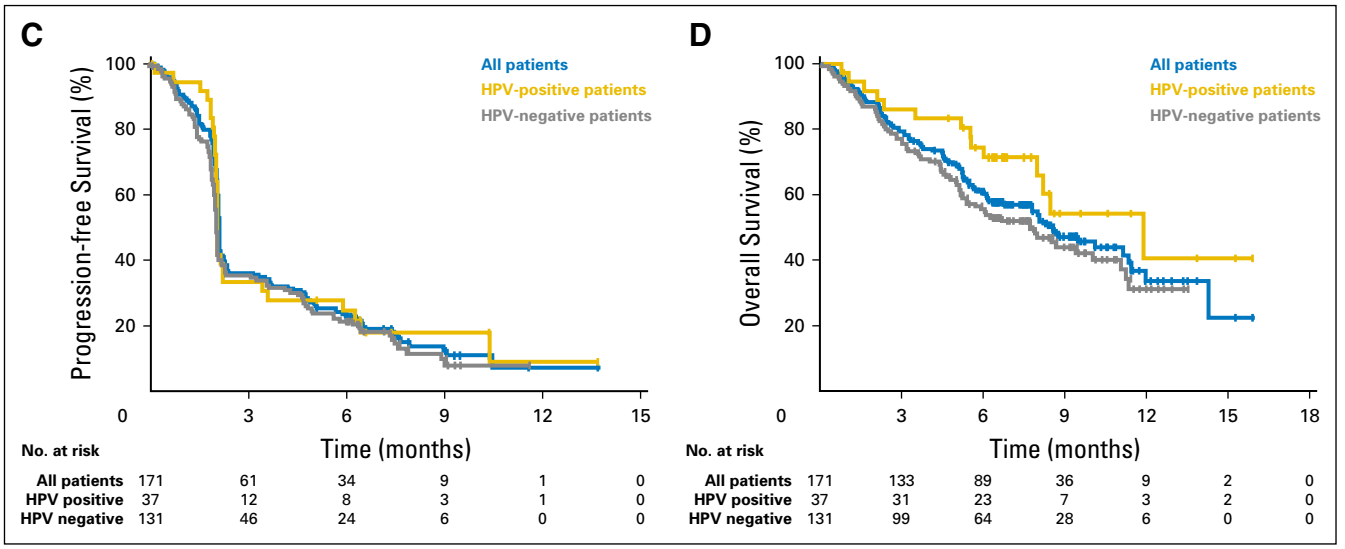

Fig 2. (Continued).

therapies. For example, response rates to single-agent cetuximab, afatinib, and methotrexate in patients with R/M HNSCC who progressed after treatment with platinum were 10%, 10%, and 6%, respectively.[5,22] In addition, median overall survival seen with pembrolizumab in the current study was encouraging compared with that seen with afatinib (7 months) and methotrexate (6 months) in previously treated R/M disease.[5] Results were similar to those from the phase III CheckMate-141 trial in which nivolumab, another anti–PD-1 antibody, resulted in improvement in overall survival (8 months) compared with investigator's choice standard of care (5 months) in patients with platinum-refractory R/M HNSCC.[23] Consistent with prior studies of immunotherapy in cancer, overall survival in KEYNOTE-055 was encouraging despite no apparent improvement in progression-free survival. This consistent finding across multiple studies implies that progression-free survival may not be the best outcome of interest for immunotherapy trials.

Importantly, pembrolizumab was well tolerated in a patient population that has already endured aggressive, toxic chemotherapy regimens; 64% of patients experienced a treatment-related adverse event, the majority of which were grade 1 to 2. Few patients, however, were removed from treatment because of toxicity. The safety profile of pembrolizumab seen in this study was consistent with the profile previously reported in R/M HNSCC and similar to that observed with PD-1 inhibition using nivolumab.[7,9,15-18,23]

Results reported here add to a growing body of evidence that patients whose tumors express PD-L1 may be more likely to respond to PD-1 pathway inhibition.[7,19,23] In CheckMate-141, 17% of patients with PD-L1 expression of $\geq$ 1% of tumor cells responded to treatment with nivolumab.[23] Similarly, in the current study, 18% of patients with $\geq$ 1% PD-L1 expression responded to pembrolizumab compared with 12% of patients with $<$ 1% expression. It should be noted that our study included a small number of patients with CPS $<$ 1% (n = 26); these findings should be interpreted with this limitation in mind. In both CheckMate-141 and KEYNOTE-055, higher response rates were noted in patients with higher PD-L1 expression. One difference between these two analyses is consideration of PD-L1 expression, not only on tumor cells but also on tumor-associated inflammatory cells. Findings from KEYNOTE-012 demonstrated the importance of PD-L1 expression on inflammatory cells, because a difference in response rate was not seen when measuring expression on tumor cells alone.[19] Thus, inflammatory cells were incorporated into the scoring system used in the current study. Nonetheless, even

Table 4. Antitumor Activity on the Basis of PD-L1 Expression Status

	CPS $\geq$ 1% (n = 140)		CPS $<$ 1% (n = 26)		CPS $\geq$ 50% (n = 48)		CPS $<$ 50% (n = 118)	
Response Evaluation	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*
Overall response rate	25	18 (12 to 25)	3	12 (2 to 30)	13	27 (15 to 42)	15	13 (7 to 20)
Complete response	1	1 (0 to 4)	0	0 (0 to 13)	1	2 (0 to 11)	0	0 (0 to 3)
Partial response	24	17 (11 to 24)	3	12 (2 to 30)	12	25 (14 to 40)	15	13 (7 to 20)
Stable disease	23	16 (11 to 24)	7	27 (12 to 48)	7	15 (6 to 28)	23	20 (13 to 28)
Progressive disease	73	52 (44 to 61)	13	50 (30 to 70)	18	38 (24 to 53)	68	58 (48 to 67)
Nonevaluable	2	1 (0 to 5)	2	8 (1 to 25)	0	0 (0 to 7)	4	3 (1 to 9)
Data unavailable	17	12 (7 to 19)	1	4 (0 to 20)	10	21 (11 to 35)	8	7 (3 to 13)

NOTE. Confirmed responses per Response Evaluation Criteria in Solid Tumors, version 1.1, per central imaging vendor review.
Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.
*On the basis of binomial exact confidence interval method.

PD-L1–negative patients responded to pembrolizumab at a rate that is clinically meaningful; 6- and 12-month progression-free survival and overall survival rates were relatively similar between PD-L1–negative and PD-L1–positive patients. These data suggest that therapeutic benefit of pembrolizumab is not limited to patients with PD-L1–positive tumors. In light of these results, we are not currently advocating for the use of CPS as a clinical decision method for whether patients should receive pembrolizumab. The investigation of additional biomarkers to aid in appropriate patient selection for PD-1 inhibitors, which have shown activity in a wide range of malignancies, continues to be an important area of study. Identifying a biomarker with adequate negative predictive value would have significant value for this patient population.

In conclusion, pembrolizumab exhibited clinically significant antitumor activity and an acceptable safety profile in heavily pretreated R/M HNSCC regardless of HPV status. Results from this study indicate that pembrolizumab is an active agent for a patient population with limited options. The robust clinical activity demonstrated in this trial confirms the activity of this class of agents and supports ongoing immunotherapy studies in head and neck cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Appendix

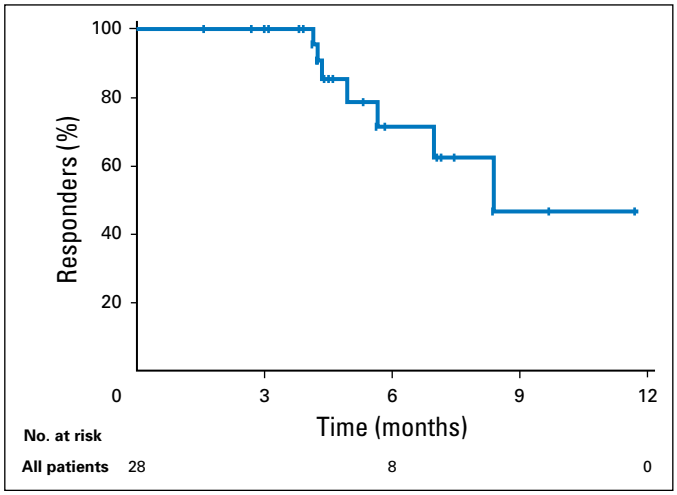

Fig A1. Duration of response in patients with confirmed response per Response Evaluation Criteria in Solid Tumors, version 1.1, by central imaging vendor review (n = 28).

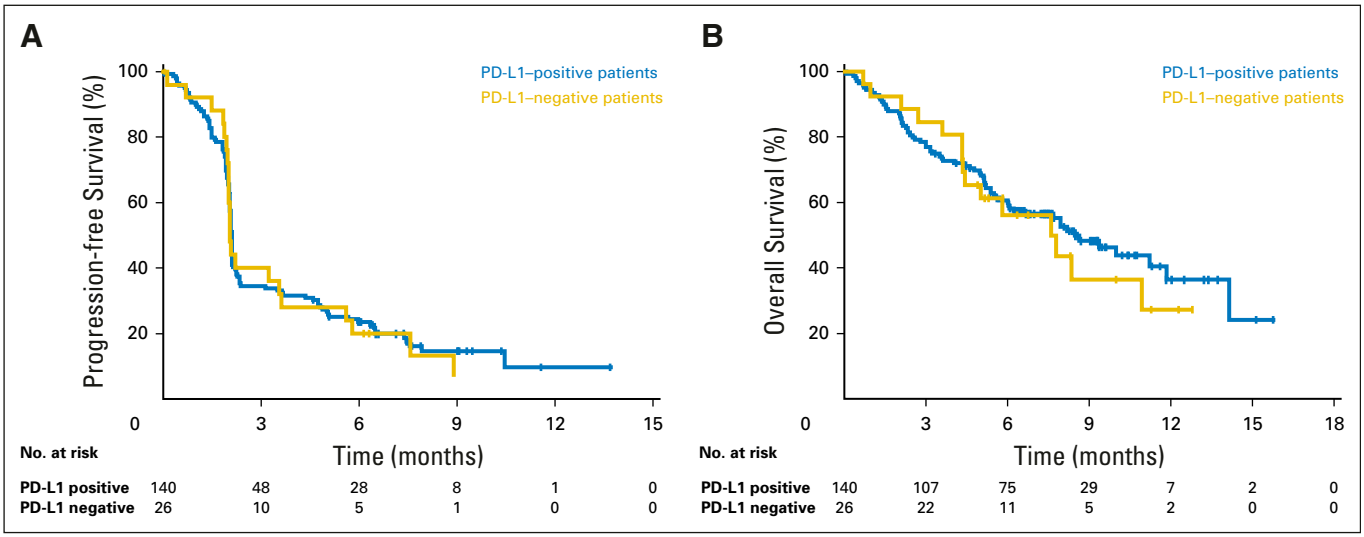

Fig A2. Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival by programmed death ligand 1 (PD-L1) status.

Table A1. Investigators Participating in the Trial

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Table A2. Discontinuations Because of Treatment-Related Adverse Events

Patient Age (years/sex)	Event	Study Day
62/M	Grade 2 fatigue	109
71/M	Grade 3 pneumonitis	344
73/F	Grade 3 AST increase	63
63/M	Grade 3 hepatitis	158
58/M	Grade 3 AST increase	3
	Grade 3 alkaline phosphatase increase	3
68/F	Grade 4 diabetic ketoacidosis	149
72/M	Grade 4 AST increase	61
59/M	Grade 5 pneumonitis	26