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Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: Health-related quality-of-life results from KEYNOTE-048

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ABSTRACT

Objectives: To assess health-related quality of life (HRQoL) with first-line pembrolizumab, pembrolizumab-chemotherapy, or cetuximab-chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) in the phase 3 KEYNOTE-048 trial (NCT02358031).

Materials and Methods: HRQoL was measured using the European Organisation for Research and Treatment of Cancer 30-question quality-of-life (EORTC QLQ-C30), the EORTC 35-question quality-of-life head and neck cancer–specific module (EORTC QLQ-H&N35), and the EuroQol 5-dimension 3-level instruments (EQ-5D-3L).

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Quality of life
Squamous cell carcinoma of head and neck

Secondary endpoints included mean change from baseline in EORTC QLQ-C30 global health status/quality of life (GHS/QoL) at week 15 and time to deterioration (TTD) in EORTC QLQ-C30 GHS/QoL and EORTC QLQ-H&N35 pain and swallowing.

Results: Of 882 enrolled participants, 844 received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL assessment; adherence was ≥ 79% at week 15 across treatment groups. At week 15, EORTC QLQ-C30 GHS/QoL scores remained stable; no clinically meaningful between-group differences were observed (least squares mean difference, pembrolizumab vs cetuximab-chemotherapy, 0.24; 95% CI, −3.34 to 3.82; pembrolizumab-chemotherapy vs cetuximab-chemotherapy, 0.40; 95% CI, −3.46 to 4.26). Median TTD in EORTC QLQ-C30 GHS/QoL and EORTC QLQ-H&N35 pain and swallowing scores was not reached over 51 weeks across groups, showing stable HRQoL. TTD was similar between groups for EORTC QLQ-C30 GHS/QoL (pembrolizumab vs cetuximab-chemotherapy: HR, 1.38; 95% CI, 0.95–2.00; pembrolizumab-chemotherapy vs cetuximab-chemotherapy: HR, 1.37; 95% CI, 0.94–2.00), as was TTD in EORTC QLQ-H&N35 pain and swallowing scores.

Conclusions: Pembrolizumab monotherapy and pembrolizumab-chemotherapy extended OS while maintaining HRQoL, further supporting first-line use for R/M HNSCC.

Introduction

Patients with head and neck squamous cell carcinoma (HNSCC) are at high risk of poor health-related quality of life (HRQoL) [1]. The tumor itself or treatments such as surgical resection or chemoradiotherapy can cause facial disfigurement, damage to anatomic structures, and deterioration in physical functioning, which can compound common cancer symptoms of pain and fatigue, and result in diminished HRQoL [1–3].

For the past decade, the standard first-line treatment for unresectable HNSCC has been cetuximab plus platinum and 5-fluorouracil (5-FU) [4]. This treatment combination results in median overall survival (OS) of approximately 10 months but is associated with substantial toxicity [4]. Recently, immune checkpoint inhibitors have demonstrated robust antitumor activity and manageable safety in HNSCC [5–9]. The PD-1 inhibitors nivolumab and pembrolizumab prolong OS while maintaining HRQoL in patients with recurrent or metastatic (R/M) HNSCC that progressed during or after platinum-based chemotherapy [3,5,8]. Pembrolizumab monotherapy and pembrolizumab with chemotherapy have also demonstrated antitumor activity as first-line treatments. In the phase 3 KEYNOTE-048 study, pembrolizumab monotherapy improved OS compared with cetuximab-chemotherapy in participants with R/M HNSCC and PD-L1 combined positive score (CPS) of ≥ 20 and CPS of ≥ 1, and pembrolizumab-chemotherapy improved OS compared with cetuximab-chemotherapy in the total population and in the CPS ≥ 20 and CPS ≥ 1 populations [10]. Pembrolizumab monotherapy also demonstrated favorable safety compared with cetuximab-chemotherapy, and pembrolizumab-chemotherapy showed comparable safety with cetuximab-chemotherapy [10]. The clinical benefit of pembrolizumab shown in the KEYNOTE-048 study has resulted in global regulatory approvals, including from the US Food and Drug Administration [11] and the European Medicines Agency [12].

Response to therapy, symptom burden, and treatment toxicity can impact the HRQoL of patients with HNSCC. Therefore, it is important to study the effect of pembrolizumab and pembrolizumab-chemotherapy on HRQoL relative to cetuximab-chemotherapy. Prespecified HRQoL analyses from KEYNOTE-048 are presented.

Methods

Study design

The design of the KEYNOTE-048 (NCT02358031) randomized, open-label, phase 3 study has been reported [10]. Eligible participants had pathologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and not curable by local therapy. Participants were randomly assigned in a 1:1:1 ratio to receive pembrolizumab alone (pembrolizumab 200 mg every 3 weeks [Q3W]), pembrolizumab-chemotherapy (pembrolizumab 200 mg Q3W plus cisplatin 100 mg/m^2 Q3W or carboplatin area under the curve 5 mg/m^2 [AUC 5] Q3W, and 5-FU 1000 mg/m^2/day continuous from day 1 to day 4 Q3W), or cetuximab-chemotherapy (cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly plus cisplatin 100 mg/m^2 Q3W or carboplatin AUC 5 Q3W, and 5-FU 1000 mg/m^2/day continuous from day 1 to day 4 Q3W). Until disease progression, unacceptable toxicity, or participant or investigator decision to withdraw, participants received pembrolizumab intravenously for ≤ 35 cycles or cetuximab intravenously. Neither participants nor investigators were masked to treatment assignment. Randomization occurred centrally using an interactive voice response system/integrated web response system and was stratified according to the percentage of PD-L1–expressing tumor cells, known as the tumor proportion score (the percentage of tumor cells with membranous PD-L1 expression; ≥50% vs < 50%), p16 status for oropharyngeal cancers (positive vs negative; participants with nonoropharyngeal tumors were considered p16 negative), and Eastern Cooperative Oncology Group performance status (ECOG PS; 0 vs 1).

The study protocol and all amendments were approved by the appropriate ethics committee and Institutional Review Board at each center. The study was conducted in accordance with the protocol, its amendments, the Declaration of Helsinki, and the standards of Good Clinical Practice. All participants provided written informed consent.

Outcomes

The primary efficacy endpoints in KEYNOTE-048 (OS and progression-free survival) and secondary safety and tolerability data (adverse events) have been reported [10]. The HRQoL outcomes reported here were the prespecified secondary and exploratory endpoints. All HRQoL endpoints were evaluated for pembrolizumab compared with cetuximab-chemotherapy and for pembrolizumab-chemotherapy compared with cetuximab-chemotherapy in the total population. Prespecified subgroup analysis in participants with PD-L1 CPS of ≥ 1 and PD-L1 CPS of ≥ 20 was also performed.

HRQoL data were collected at baseline; at weeks 3, 6, and 9; every 6 weeks thereafter up to 1 year (51 weeks) or end of treatment (whichever came first); and at the 30-day safety follow-up visit (online Supplemental Table S1). At each scheduled visit, three HRQoL instruments were administered on an electronic tablet before other study procedures: EuroQol 5-dimension 3-level questionnaire (EQ-5D-3L) [13], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [14], and EORTC 35-question head and neck cancer–specific module (EORTC QLQ-H&N35) [15]. The EORTC QLQ-C30 is a widely used cancer-specific HRQoL instrument, covering global health status and quality of life, important functional domains, and generalized symptoms associated with cancer such as fatigue, general pain, and nausea [14]. The EORTC QLQ-H&N35 is a head and neck cancer–specific module designed to be used in conjunction with the EORTC QLQ-C30 that considers disease- and treatment-related symptoms of particular importance to patients with head and neck cancer, such as site-specific pain and the ability to swallow [15]. Both

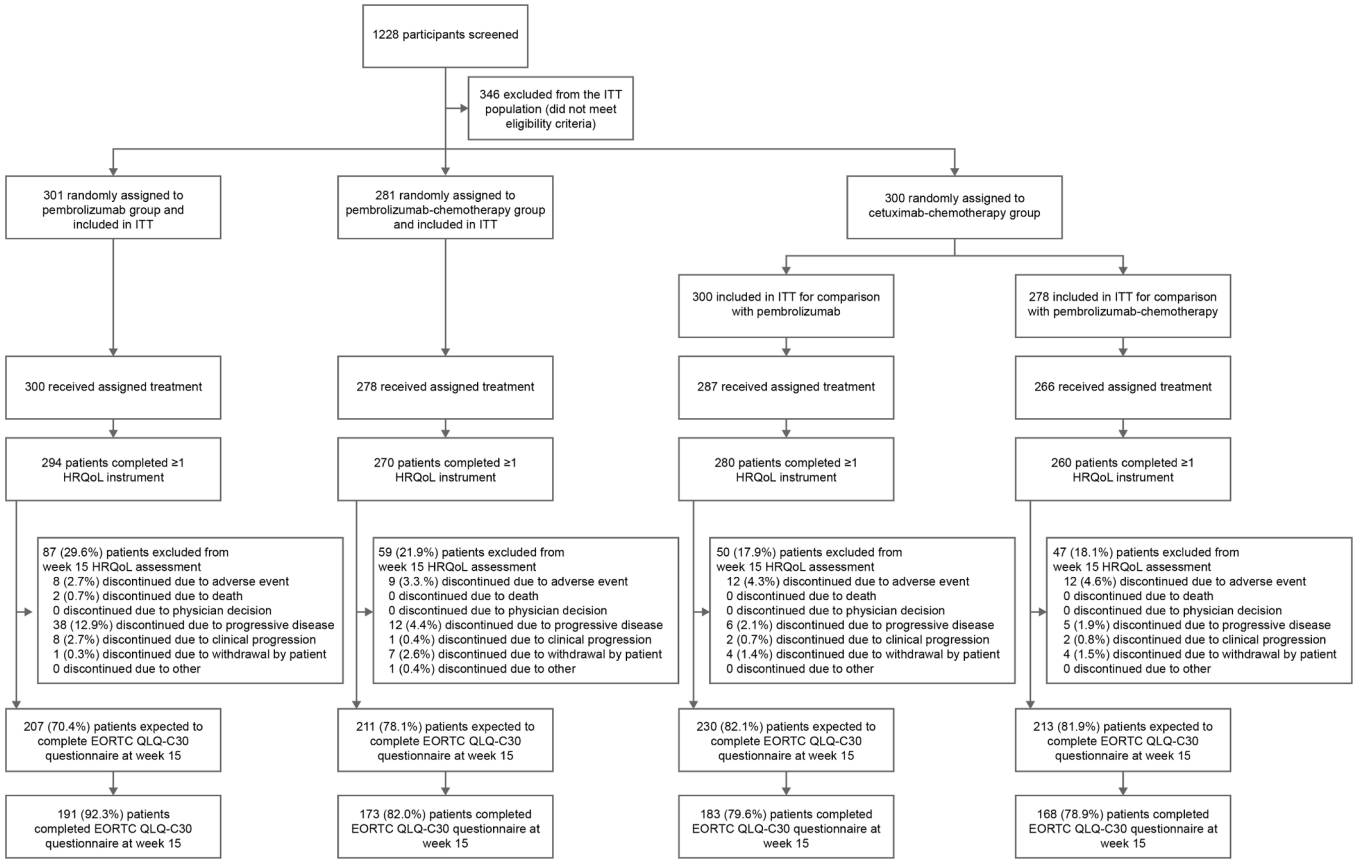


Fig. 1. Consort diagram. ITT: intention to treat.

the EORTC QLQ-C30 and the EORTC QLQ-H&N35 have been psychometrically and clinically validated for use in patients with HNSCC [14,15]. The EQ-5D-3L is a standardized instrument used as a measure of general health status [13]. Additional details on the HRQoL instruments and scoring are provided in the online supplemental material.

Responses for each of the global health status (GHS)/QoL, functioning, and symptom scales of the EORTC QLQ-C30 and the QLQ-H&N35 were aggregated and linearly transformed to a scale of 0 to 100 according to the procedures defined in the EORTC scoring manual [16]. To simplify presentation within this report, symptom scales for which higher scores represented higher symptom burden were reverse scored, such that a higher score for each of the GHS/QoL, functioning, and symptom scales represents better HRQoL. EQ-5D-3L responses were weighted and aggregated into utility scores based on the European algorithm, with scores ranging from 0 (equivalent to death) to 1 (equivalent to full health) [17]. Responses to the EuroQol visual analog scale (EQ VAS) were scored from 0 (worst imaginable) to 100 (best imaginable).

Secondary endpoints included mean change from baseline in the GHS/QoL score of the EORTC QLQ-C30, time to deterioration (TTD) in the GHS/QoL score of the EORTC QLQ-C30, and pain and swallowing scores of the EORTC QLQ-H&N35. Exploratory HRQoL endpoints included mean change from baseline in the functioning and symptom scores of the EORTC QLQ-C30 and QLQ-H&N35 and health status from the EQ-5D-3L questionnaire. Mean change from baseline in the EORTC QLQ-C30, QLQ-H&N35, and EQ-5D-3L scores were evaluated primarily at week 15; this time point was selected because completion rates were expected to be low after 15 weeks in the cetuximab-chemotherapy group given the anticipated disease progression.

Deterioration of $\geq$ 10 points was considered a clinically meaningful change in GHS/QoL, functioning, and symptom scores [18]. TTD was defined as the time to first onset of deterioration of $\geq$ 10 points from baseline for each of the GHS/QoL, pain, and swallowing endpoints and was confirmed by a second adjacent deterioration of $\geq$ 10 points from baseline. Consistent with current recommendations [3,19], deaths were not included as events, and participants who did not have documented HRQoL deterioration or who discontinued from the study were censored at the time of last HRQoL assessment. For the EQ-5D-3L, deterioration was defined as a $\geq$ 0.08 decline from baseline in EQ-5D-3L utility index and a $\geq$ 7-point decline from baseline on the EQ VAS based on clinically meaningful differences reported for these measures [20].

Statistical analysis

No formal power calculations were performed for the HRQoL outcomes. The HRQoL analysis population included all participants who received $\geq$ 1 dose of study drug and who completed $\geq$ 1 HRQoL assessment. Adherence and completion rates were summarized by treatment group and visit. Adherence was defined as proportion of participants who completed an HRQoL assessment among those expected to complete the instruments at each visit (excluding participants who discontinued study treatment). Completion was defined as the proportion of participants who completed an HRQoL assessment among the total HRQoL analysis population. Change in least squares mean (LSM) score from baseline to week 15 was assessed using a constrained longitudinal data analysis model, with HRQoL score as the response variable and treatment by study visit interaction and randomization stratification factors as covariates [21,22]. Additional details are provided in the online supplemental material.

Descriptive analyses of mean score and mean score changes from baseline (and 95% CI) in the GHS/QoL score of the EORTC QLQ-C30 were summarized for participants who were on study and completed questionnaires at each time point through week 51. Additional post hoc analyses of LSM change from baseline in GHS/QoL scores in participants

Table 1
Baseline characteristics in the overall HRQoL population.[a]

Characteristic	Pembrolizumab vs cetuximab-chemotherapy		Pembrolizumab-chemotherapy vs cetuximab-chemotherapy	
	Pembrolizumab n = 294	Cetuximab-chemotherapy n = 280	Pembrolizumab-chemotherapy n = 270	Cetuximab-chemotherapy n = 260[b]
Age, median (IQR), years	62 (56–68)	61 (55–68)	61 (55–68)	61 (55–68)
Male sex, n (%)	244 (83)	243 (87)	215 (80)	226 (87)
Region of enrollment, n (%)				
Europe	83 (28)	101 (36)	87 (32)	90 (35)
North America	73 (25)	55 (20)	58 (21)	53 (20)
Rest of world	138 (47)	124 (44)	125 (46)	117 (45)
ECOG PS, n (%)				
0	116 (39)	110 (39)	109 (40)	102 (39)
1	178 (61)	170 (61)	161 (60)	158 (61)
Smoking status, n (%)				
Current or former	234 (80)	219 (78)	218 (81)	201 (77)
Never	60 (20)	60 (21)	52 (19)	58 (22)
Unknown	0	1 (0)	0	1 (0)
Oropharyngeal p16 positive, n (%)	63 (21)	61 (22)	58 (21)	56 (22)
Tumor cells with PD-L1 expression, n (%)				
≥50%	64 (22)	63 (23)	62 (23)	59 (23)
<50%	230 (78)	217 (78)	208 (77)	201 (77)
PD-L1 CPS, n (%)				
≥1	252 (86)	238 (85)	231 (86)	220 (85)
≥20	129 (44)	112 (40)	120 (45)	101 (39)
Disease status, n (%)				
Metastatic	210 (71)	188 (67)	192 (71)	173 (67)
Recurrent only[c]	81 (28)	89 (32)	74 (27)	84 (32)
Newly diagnosed, nonmetastatic	3 (1)	3 (1)	4 (1)	3 (1)
Primary tumor location, n (%)				
Hypopharynx	37 (13)	39 (14)	44 (16)	36 (14)
Larynx	72 (24)	57 (20)	41 (15)	52 (20)
Oral cavity	79 (27)	85 (30)	79 (29)	79 (30)
Oropharynx	112 (38)	104 (37)	110 (41)	98 (38)
Investigator's choice of platinum for study treatment,[d] n (%)				
Carboplatin	176 (60)	160 (57)	151 (56)	147 (57)
Cisplatin	118 (40)	120 (43)	119 (44)	113 (43)

CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 GHS/QoL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 global health score/quality of life; HRQoL: health-related quality of life; IQR: interquartile range; PD-L1: programmed death ligand 1.

[a] The overall HRQoL analysis population included all patients who received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL assessment.

[b] Includes only participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrollment.

[c] Recurrent includes only participants with locally recurrent disease and disease that spread to cervical lymph nodes.

[d] Investigators were required to choose which platinum would be administered before participants were randomly assigned to study treatment.

Table 2
Difference in LSM change from baseline in the EORTC QLQ-C30 GHS/QoL score by treatment for participants who remained on study at week 15.

Treatment	Baseline,[a] mean (SD)	Week 15,[a] mean (SD)	Change from baseline to week 15,[b] LSM (95% CI)[c]	Difference in LSM (95% CI)
Pembrolizumab vs cetuximab-chemotherapy				
Pembrolizumab	n = 280 61.31 (21.60)	n = 191 64.66 (20.55)	n = 294 0.85 (−1.90 to 3.59)	0.24 (−3.34 to 3.82)
Cetuximab-chemotherapy	n = 262 59.70 (21.48)	n = 182 62.59 (18.80)	n = 279 0.60 (−2.19 to 3.40)	
Pembrolizumab-chemotherapy vs cetuximab-chemotherapy				
Pembrolizumab-chemotherapy[d]	n = 255 62.19 (21.18)	n = 173 64.60 (21.10)	n = 268 1.17 (−1.79 to 4.12)	0.40 (−3.46 to 4.26)
Cetuximab-chemotherapy[d]	n = 244 59.97 (21.86)	n = 167 63.27 (18.73)	n = 259 0.77 (−2.22 to 3.76)	

ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HPV: human papillomavirus; HRQoL: health-related quality of life; LSM: least squares mean; PD-L1: programmed death ligand 1.

[a] n is the number of participants in each treatment group who completed the EORTC QLQ-C30 questionnaire at that time point.

[b] n is the number of participants in the total HRQoL analysis population.

[c] Based on a constrained longitudinal data analysis model with HRQoL scores as the response variable and with treatment by study visit interaction, stratification factors (ECOG PS [0 vs 1], HPV status [positive vs negative], and PD-L1 status [strongly positive vs not strongly positive]) as covariates.

[d] Includes only participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrollment.

with progressive disease and those without progressive disease at week 15 were evaluated and compared between groups to assess the association between response to therapy and GHS/QoL. The Kaplan-Meier method was used to estimate the TTD survival curve for each of the GHS/QoL, pain, and swallowing endpoints in each treatment group. A Cox proportional hazards model with the Efron method of handling ties was used to assess the magnitude of treatment differences stratified using the randomization stratification factors. Median TTD hazard ratio and 95% CI were reported.

All stratified analyses for HRQoL endpoints followed the same principle as that used for the efficacy endpoints. Randomization stratification factors were used for the current analyses in all participants and all participants with PD-L1 CPS of ≥ 1. For analyses in the PD-L1 CPS ≥ 20 subgroup, p16 status and ECOG PS were used as stratification factors.

Results

A total of 882 participants were enrolled from 200 sites in 37 countries in KEYNOTE-048 between April 20, 2015, and January 17, 2017 [10]. The HRQoL analysis population included 844 participants who received treatment and completed ≥ 1 HRQoL assessment by the final analysis (February 25, 2019) (Fig. 1). The HRQoL analysis population for the evaluation of pembrolizumab versus cetuximab-chemotherapy included 294 participants in the pembrolizumab group and 280 participants in the cetuximab-chemotherapy group. As described [10], participants randomly assigned to receive cetuximab-chemotherapy during the enrollment hold for pembrolizumab-chemotherapy were excluded from comparisons of pembrolizumab-chemotherapy versus cetuximab-chemotherapy. As a result, the HRQoL analysis population for the evaluation of pembrolizumab-chemotherapy versus cetuximab-chemotherapy included all 270 participants in the pembrolizumab-chemotherapy group and 260 of 280 participants in the cetuximab-chemotherapy group. Median (interquartile range) follow-up for participants in the total population [10], defined as the time from randomization to death or data cutoff, whichever occurred first, was 11.5 months (5.1–25.7) in the pembrolizumab group, 13.0 months (6.4–26.6) in the pembrolizumab-chemotherapy group, and 10.7 months (6.6–19.7) in the cetuximab-chemotherapy group.

Among participants in the HRQoL analysis population, adherence rates for the EORTC QLQ-C30 questionnaire were $\geq 94\%$ at baseline and $\geq 79\%$ in all treatment groups at week 15 (Supplemental Tables S2 and S3). Completion rates decreased over time based on treatment discontinuation as a result of disease progression, intolerable toxicity, physician/participant decision to withdraw, or death; however, rates remained at $\geq 64\%$ in all treatment groups at week 15 (Fig. 1; Supplemental Tables S2 and S3). Between weeks 33 and 51, relative completion rates for EORTC QLQ-C30 decreased more sharply (from 27% to 8%) for cetuximab-chemotherapy than for pembrolizumab-chemotherapy (39% to 20%); this decrease reflects the reduced number of patients able to complete the questionnaire in the cetuximab-chemotherapy group, which was primarily because of disease progression, adverse events, or death. Adherence and completion rates for the EORTC QLQ-H&N35 and EQ-5D-3L questionnaires were similar to those observed for EORTC QLQ-C30 (Supplemental Tables S2 and S3).

Baseline demographics and disease characteristics of the total trial population were as expected and similar between groups [10]; baseline demographics and disease characteristics of the HRQoL population followed the same trend (Table 1). Among the subgroup of participants who remained on study at week 15, baseline characteristics were also generally well balanced between treatment groups and similar to the overall HRQoL population, suggesting no systematic differences in the characteristics of participants able to complete the HRQoL assessments at week 15 (Supplemental Table S4; Table 1). Baseline EORTC QLQ-C30 GHS QoL scores in the overall HRQoL population were well balanced across treatment comparisons (Table 2). At baseline, mean EORTC QLQ-C30 GHS/QoL scores (standard deviation [SD]) with pembrolizumab were 61.31 (21.60) versus 59.70 (21.48) with cetuximab-chemotherapy and with pembrolizumab-chemotherapy were 62.19 (21.18) versus 59.97 (21.86) with cetuximab-chemotherapy. Among the subgroup of participants who remained on study at week 15, mean EORTC QLQ-C30 GHS/QoL scores at baseline were also well balanced between treatment groups and similar to those of the overall HRQoL population, further suggesting no systematic differences in the characteristics of participants able to complete the HRQoL assessments at week 15 (Supplemental Table S4).

For participants who remained on study at week 15, EORTC QLQ-C30 GHS/QoL scores remained stable relative to baseline in each treatment group (Table 2). No clinically meaningful between-group differences in LSM scores were observed when comparing pembrolizumab with cetuximab-chemotherapy (LSM difference, 0.24 points; 95% CI, –3.34 to 3.82) and pembrolizumab-chemotherapy versus cetuximab-chemotherapy (LSM difference, 0.40 points; 95% CI, –3.46 to 4.26). Descriptive analyses of mean change from baseline revealed that EORTC QLQ-C30 GHS/QoL scores were stable relative to baseline at each time point through week 51 across all treatment groups for those who were on study and able to complete questionnaires at later time points (Fig. 2). Similar trends in EORTC QLQ-C30 GHS/QoL score at week 15 and over time through week 51 were observed in the CPS ≥ 1 and CPS ≥ 20 populations (Supplemental Table S5; Fig. S1).

Descriptive analyses of mean change from baseline according to disease progression status identified stable EORTC QLQ-C30 GHS/QoL scores for participants with and without progressive disease at week 15 across all treatment groups, with no meaningful differences observed across treatment comparisons (Table 3). The difference in LSM for participants without progressive disease was 2.89 points (95% CI, −1.42 to 7.21) for pembrolizumab versus cetuximab-chemotherapy and 1.05

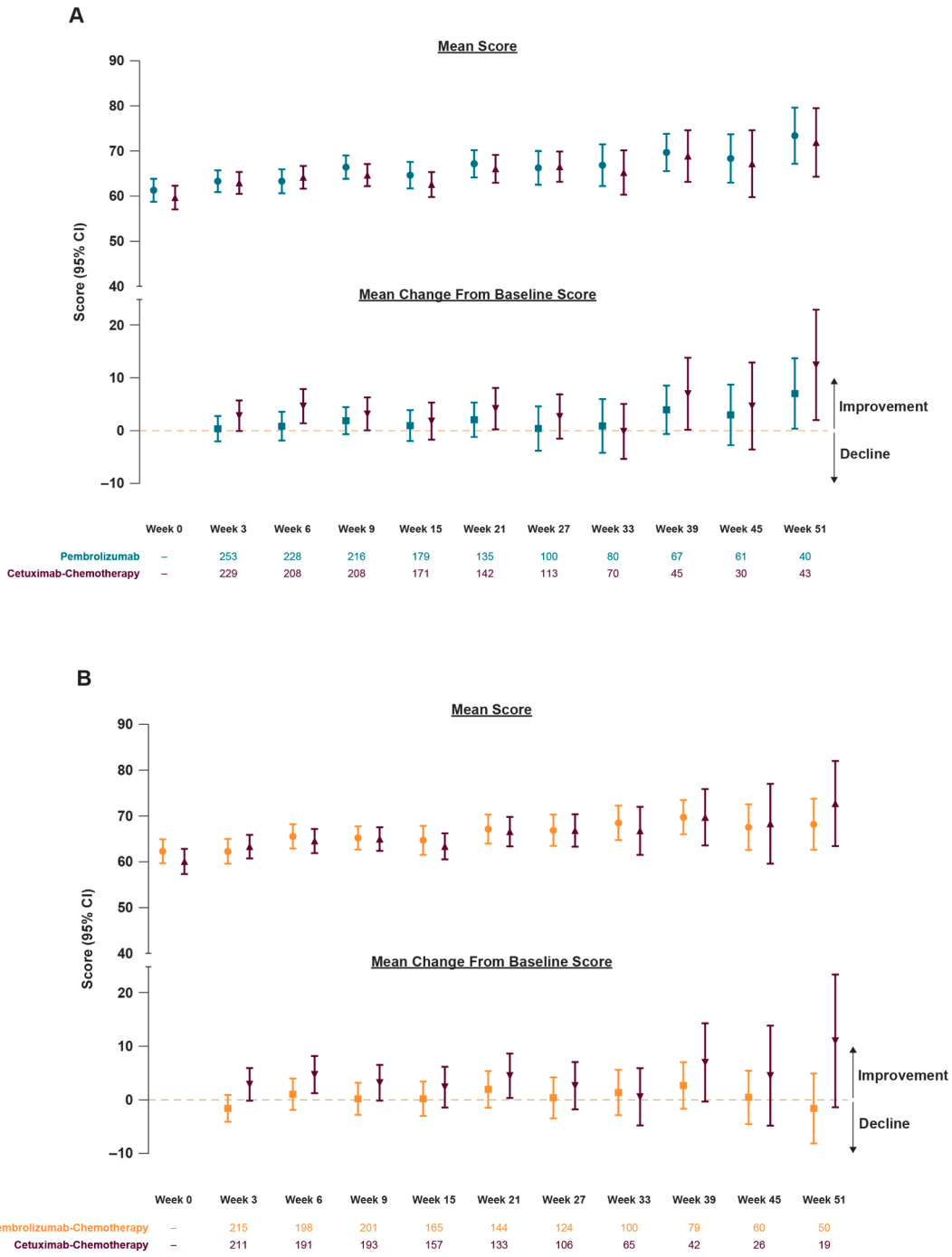


Fig. 2. Change from baseline in EORTC QLQ-C30 GHS/QoL score over time for participants on study at each time point. **(A)** pembrolizumab versus cetuximab-chemotherapy and **(B)** pembrolizumab-chemotherapy versus cetuximab-chemotherapy.[a] EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL: global health status/quality of life. [a]Includes only participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrollment. The mean score change from baseline over time was calculated among participants with available GHS/QoL scores at baseline and at each time point.

points (95% CI, −3.18 to 5.29) for pembrolizumab-chemotherapy versus cetuximab-chemotherapy. The difference in LSM for participants with progressive disease was 0.24 points (95% CI, −5.45 to 5.93) for pembrolizumab versus cetuximab-chemotherapy and −1.84 points (95% CI, −8.84 to 5.16) for pembrolizumab-chemotherapy versus cetuximab-chemotherapy.

Median TTD in the EORTC QLQ-C30 GHS/QoL score and EORTC QLQ-H&N35 pain and swallowing scores were not reached over 51 weeks of follow-up, and few deterioration events occurred across all treatment groups in participants who remained on study, further underscoring the stable HRQoL results observed (Fig. 3A and Fig. 4A). The TTD in EORTC QLQ-C30 GHS/QoL score was similar for participants receiving pembrolizumab and those receiving cetuximab-chemotherapy (HR, 1.38; 95% CI, 0.95–2.00) (Fig. 3A) as it was for participants receiving pembrolizumab-chemotherapy and those receiving cetuximab-chemotherapy (HR, 1.37; 95% CI, 0.94–2.00) (Fig. 4A). Similar results of TTD in EORTC QLQ-H&N35 pain and swallowing scores were observed for both treatment comparisons (Fig. 3B and 3C, Fig. 4B and 4C). Similar TTD results were observed in the CPS $\geq$ 1 and CPS $\geq$ 20 populations (Supplemental Tables S6 and S7).

Table 3
Difference in LSM change from baseline in EORTC QLQ-C30 GHS/QoL by treatment and progressive disease status for participants who remained on study at week 15.

Treatment	Without progressive disease LSM (95% CI)[a,b]	With progressive disease[c] LSM (95% CI)[a,b]	Difference by progressive disease status LSM (95% CI)[a,b]
Pembrolizumab	4.76 (1.26 to 8.26)	−2.64 (−6.00 to 0.71)	7.41 (3.19 to 11.63)
Cetuximab-chemotherapy	1.87 (−1.11 to 4.85)	−2.89 (−7.74 to 1.97)	4.76 (−0.41 to 9.92)
Difference in LSM between groups (95% CI)	2.89 (−1.42 to 7.21)	0.24 (−5.45 to 5.93)	
Pembrolizumab-chemotherapy[d]	2.91 (−0.31 to 6.13)	−3.84 (−8.79 to 1.12)	6.75 (1.43 to 12.07)
Cetuximab-chemotherapy[d]	1.86 (−1.37 to 5.09)	−2.00 (−7.23 to 3.24)	3.85 (−1.70 to 9.41)
Difference in LSM between groups (95% CI)	1.05 (−3.18 to 5.29)	−1.84 (−8.84 to 5.16)	

ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL: global health status/quality of life; HPV: human papillomavirus; HRQoL: health-related quality of life; LSM: least squares mean; PD-L1: programmed death ligand 1; SOC: standard of care.

[a] Based on a constrained longitudinal data analysis model with HRQoL score as the response variable and with 3-way interaction term for treatment by study visit by progressive disease status, stratification factors (ECOG PS [0 vs 1], HPV infection status [positive vs negative], and PD-L1 expression status [strongly positive vs not strongly positive]), as covariates.

[b] Positive GHS/QoL score indicates improvement, whereas negative score indicates decline. A mean difference of 5–10 points was defined as a small but clinically meaningful change in GHS/QoL score.

[c] Patients who experienced progressive disease and whose last HRQoL assessments occurred before week 15 were not captured in the analysis. In the pembrolizumab group, 13% of patients (38/294) with progressive disease and 3% (8/294) with clinical progression were excluded from the week 15 HRQoL assessment. In the pembrolizumab-chemotherapy group, 4% of patients (12/270) with progressive disease and < 1% of patients (1/270) with clinical progression were excluded from the week 15 HRQoL assessment. In the cetuximab-chemotherapy group, 2% of patients (6/280) compared with the pembrolizumab group and 2% of patients (5/260) compared with pembrolizumab-chemotherapy group with progressive disease and < 1% of patients (4/280 and 4/260) with clinical progression were excluded from the week 15 HRQoL assessment.

[d] Includes only participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrollment.

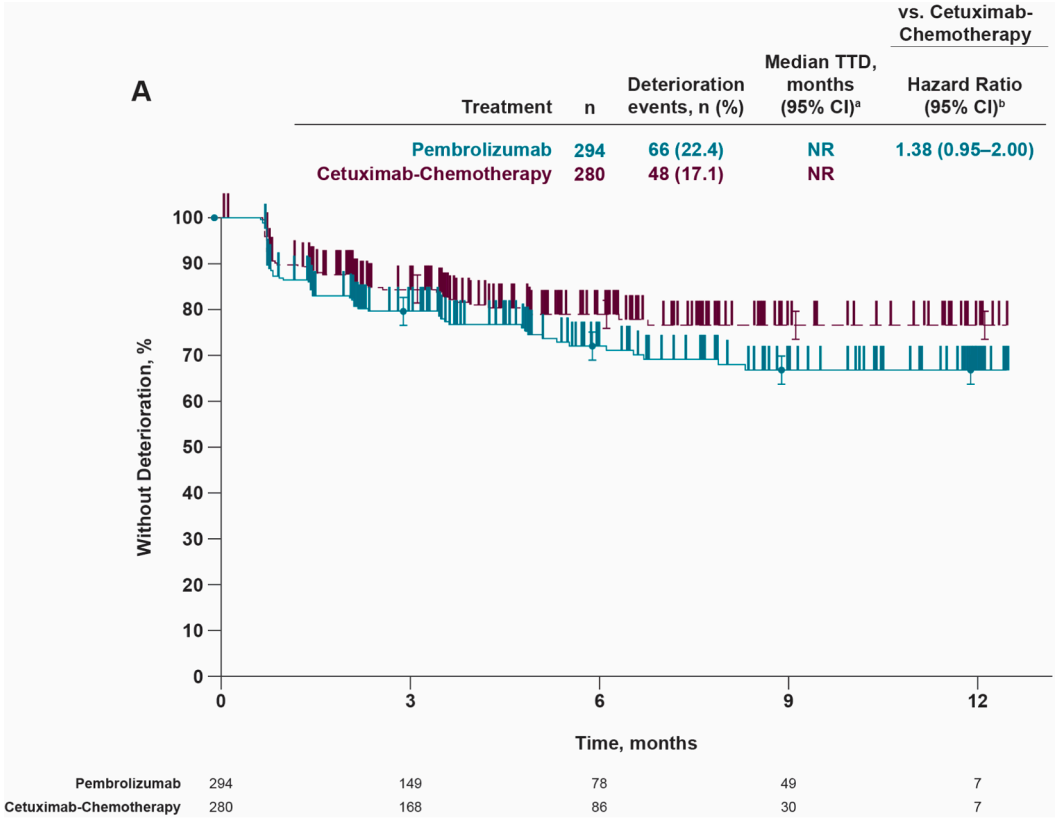
Participants in all treatment groups who remained on study at week 15 generally exhibited stable EORTC QLQ-C30 GHS/QoL and stable functioning and symptom scores; no clinically meaningful differences between treatment groups were observed (Supplemental Figs. S2 and S3). A trend toward improvement of weight loss scores (participants not losing as much weight) (Supplemental Fig. S2C) was observed at week 15 in participants receiving pembrolizumab and cetuximab-chemotherapy. A trend toward improvement in the range of < 10 points in the pain (less pain) (Supplemental Fig. S3B), insomnia (less insomnia) (Supplemental Fig. S3B), pain medication use (less use) (Supplemental Fig. S3C), and weight loss (participants not losing as much weight) (Supplemental Fig. S3C) scores was observed at week 15 in participants receiving pembrolizumab-chemotherapy and cetuximab-chemotherapy. Moderate declines in the range of < 10 points were observed in the physical functioning (Supplemental Figs. S2A and S3A), fatigue (Supplemental Figs. S2B and S3B), and weight gain (Supplemental Figs. S2C and S3C) scores in all treatment groups; moderate declines in the nausea/vomiting (Supplemental Fig. S2B) and dyspnea (Supplemental Fig. S2B) scores were observed in the cetuximab-chemotherapy group. Similar results were observed in the CPS ≥ 1 and CPS ≥ 20 populations (Supplemental Figs. S4–S7). Participants in all treatment groups who remained on study at week 15 exhibited stable EQ-5D-3L VAS and utility scores; similar results were observed in the CPS ≥ 1 and CPS ≥ 20 populations (Supplemental Tables S8 and S9).

Discussion

Treatment regimens that prolong survival while maintaining HRQoL are needed for R/M HNSCC. The KEYNOTE-048 study results showed statistically significant and clinically meaningful improvements in OS in the CPS ≥ 1 and CPS ≥ 20 populations treated with pembrolizumab monotherapy and in the overall, CPS ≥ 1, and CPS ≥ 20 populations treated with pembrolizumab-chemotherapy in comparison with populations treated with cetuximab-chemotherapy [10]. The safety profile was favorable for pembrolizumab monotherapy compared with cetuximab-chemotherapy and similar in the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups. In KEYNOTE-048, participants who received first-line pembrolizumab monotherapy or pembrolizumab-chemotherapy and remained on study at week 15 maintained stable HRQoL. Pembrolizumab or pembrolizumab-chemotherapy versus cetuximab-chemotherapy led to no clinically meaningful difference in EORTC QLQ-C30 GHS/QoL, functioning, and symptom scores. These HRQoL results are particularly significant when considered with the improved toxicity profile of first-line pembrolizumab compared with cetuximab-chemotherapy in KEYNOTE-048. The favorable tolerability profile of pembrolizumab and the added survival benefit with maintained HRQoL are particularly advantageous in this patient population predisposed to significant disease-associated morbidity.

Furthermore, the descriptive trend in stable EORTC QLQ-C30 GHS/QoL scores extended for as long as 51 weeks. Median TTD in EORTC QLQ-C30 GHS/QoL score and EORTC QLQ-H&N35 pain and swallowing scores were not reached over 51 weeks of follow-up and were similar across treatment comparisons, further illustrating the stability of HRQoL. Although no clinically meaningful differences in HRQoL scores or TTD were observed in any treatment group, the relative completion rate for the HRQoL questionnaires toward the end of the study decreased substantially in the cetuximab-chemotherapy arm because of the greater proportion of patients discontinuing treatment. Therefore, analysis at later time points includes only patients well enough to continue treatment, which may have contributed to the maintenance of HRQoL observed in the cetuximab-chemotherapy arm. Subgroup analysis revealed that HRQoL was maintained in pembrolizumab-treated participants with and without disease progression, and consistent results were observed in the PD-L1 CPS ≥ 1 and CPS ≥ 20 populations.

PD-1 inhibitors provide antitumor activity and manageable safety while maintaining or improving HRQoL in various cancers [23,24]. In R/M HNSCC, HRQoL benefits with pembrolizumab and nivolumab have been observed in patients whose disease progressed during or after platinum-based chemotherapy [3,5,8,25]. In KEYNOTE-040, patients treated with pembrolizumab who remained on study at week 15 had stable EORTC QLQ-C30 GHS/QoL, whereas patients treated with chemotherapy experienced a small but clinically meaningful decline [25]. In the CheckMate-141 study, patients treated with nivolumab exhibited stable HRQoL scores from baseline to weeks 9 and 15, whereas chemotherapy led to clinically meaningful deterioration in HRQoL [3]. The current analysis of KEYNOTE-048 shows that pembrolizumab monotherapy and pembrolizumab-chemotherapy maintain HRQoL in the first-line setting. In this analysis, stable EORTC QLQ-C30 GHS/QoL scores extended for as long as 51 weeks in pembrolizumab-treated participants and HRQoL was maintained in pembrolizumab-treated participants regardless of disease progression or PD-L1 status. The findings in this analysis are consistent with those of the KEYNOTE-040 and CheckMate-141 studies, which also showed that PD-L1 status had



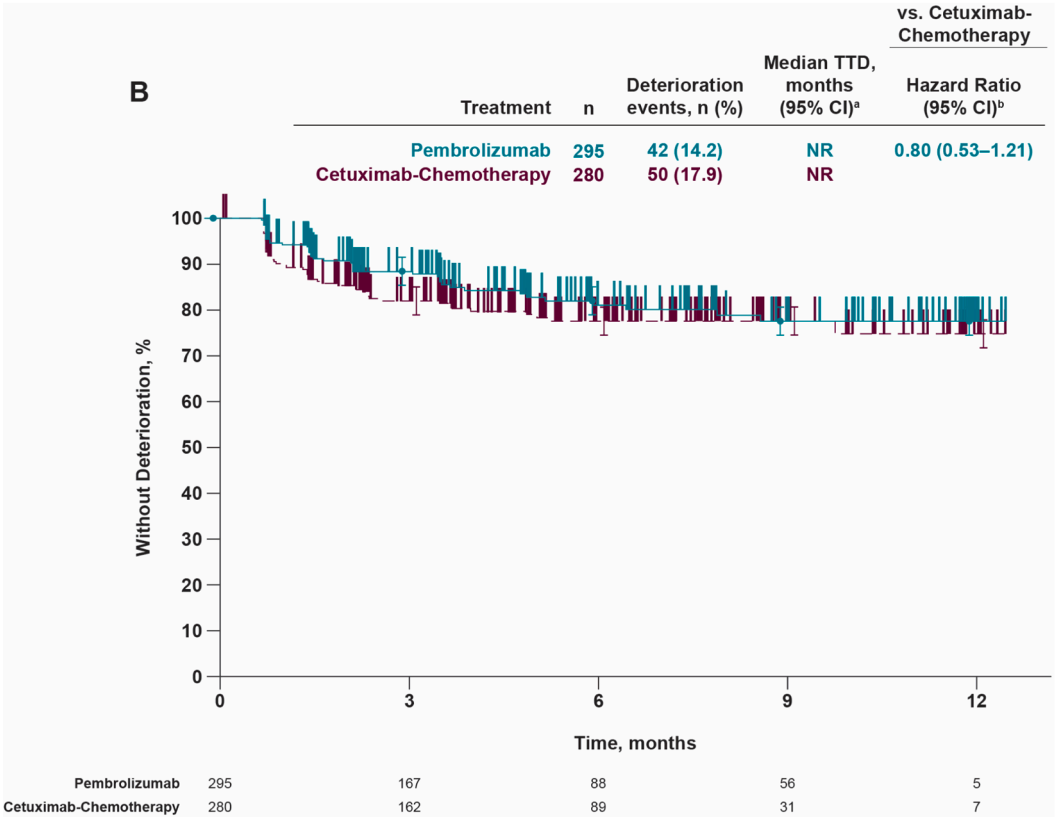


Fig. 3. Kaplan-Meier estimates of time to deterioration by treatment (pembrolizumab vs cetuximab-chemotherapy) in **(A)** the EORTC QLQ-C30 GHS/QoL score and the EORTC QLQ-H&N35 **(B)** pain and **(C)** swallowing scores. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 35-question head and neck cancer–specific module; GHS/QoL: global health status/quality of life; HPV: human papillomavirus; NR: not reached; PD-L1: programmed death ligand 1. [a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with the Efron method of handling ties with treatment as a covariate stratified by ECOG PS (0 vs 1), HPV status (positive vs negative), and PD-L1 status (strongly positive vs not strongly positive).

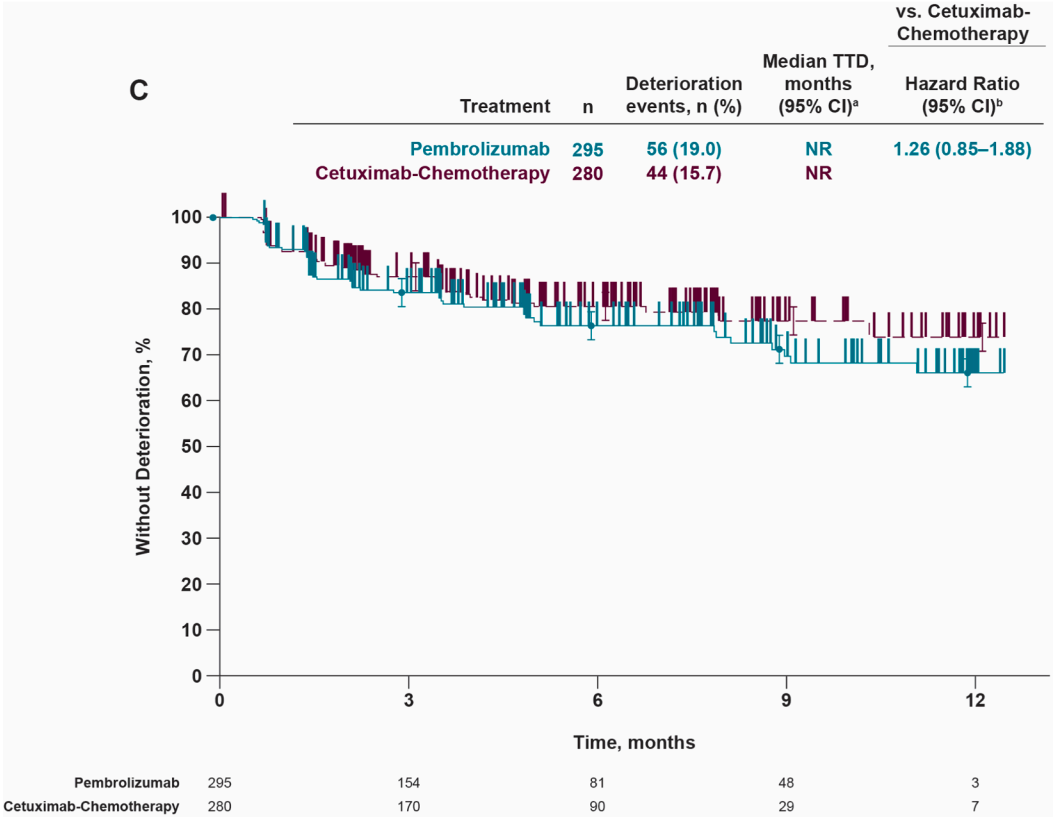


Fig. 3. (*continued*).

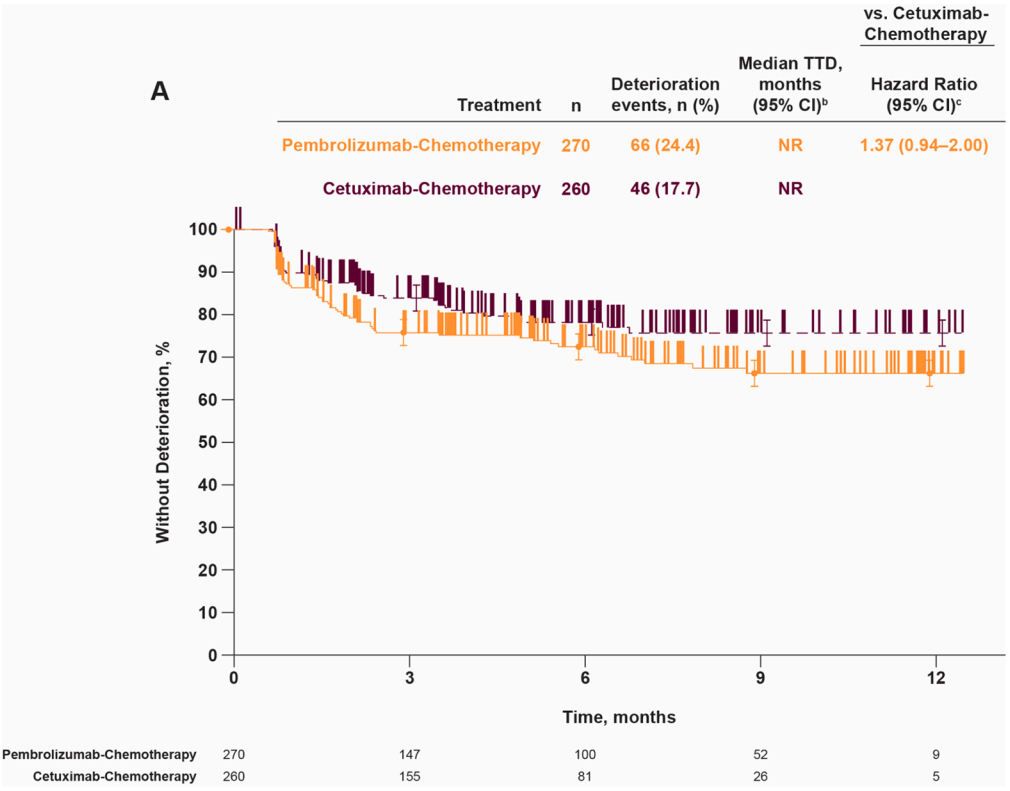
no impact on HRQoL [25].

Limitations of this analysis include the open-label design of the study, which may have impacted participant response to HRQoL questions. However, baseline completion rates and mean EORTC QLQ-C30 GHS/QoL scores were similar among treatment groups, suggesting patients' awareness of treatment allocation did not influence HRQoL reporting at trial initiation. Furthermore, EORTC QLQ-C30 GHS/QoL scores for participants treated with pembrolizumab were stable (rather than improved) from baseline to week 15 and were similar among treatment groups, suggesting there was little evidence of influence at later time points. Second, the primary analysis was conducted at week 15 to ensure sufficient completion rates. However, general trends in HRQoL scores at week 15 remained consistent through week 51. HRQoL data were also collected only while participants were still receiving study treatment and up to 30 days thereafter. Thus, the current analysis could not adequately capture and evaluate HRQoL outcomes from patients with progressive disease who discontinued study treatment, which is a common limitation of HRQoL analyses. Last, the EORTC QLQ-H&N35 questionnaire was validated in patients with newly diagnosed disease [26]. However, the current analysis included patients with locally recurrent or metastatic HNSCC who may have received prior treatment for localized disease and that treatment may have impacted their experience of local effects such as pain or swallowing. The EORTC QLQ-H&N35 has since been updated to the EORTC QLQ-H&N43 to incorporate additional issues of importance, including the impact of multimodal and targeted treatment. However, the EORTC QLQ-H&N43 was not available at the time the KEYNOTE-048 study was designed [27].

The HRQoL results from KEYNOTE-048 add to the body of evidence demonstrating clinically meaningful benefit of pembrolizumab in patients with R/M HNSCC. Treatment with pembrolizumab, as monotherapy or in combination with chemotherapy, prolongs OS in comparison with cetuximab-chemotherapy while maintaining HRQoL, further supporting its use for first-line treatment of patients with R/M HNSCC.

CRediT authorship contribution statement

Danny Rischin: Resources, Formal analysis, Investigation, Writing – review & editing. **Kevin J. Harrington:** Conceptualization, Resources, Formal analysis, Investigation, Methodology, Writing – review & editing. **Richard Greil:** Resources, Formal analysis, Investigation, Writing – review & editing. **Denis Soulières:** Conceptualization, Resources, Formal analysis, Investigation, Methodology, Writing – review & editing. **Makoto Tahara:** Resources, Formal analysis, Investigation, Writing – review & editing. **Gilberto de Castro Jr:** Resources, Formal analysis, Investigation, Writing – review & editing. **Amanda Psyrri:** Formal analysis, Writing – review & editing. **Irene Braña:** Resources, Formal analysis, Investigation, Writing – review & editing. **Prakash Neupane:** Resources, Investigation, Writing – review & editing. **Åse Bratland:** Conceptualization, Resources, Investigation, Methodology, Writing – review & editing. **Thorsten Fuereder:** Resources, Formal analysis, Investigation, Writing – review & editing. **Brett G.M. Hughes:** Resources, Formal analysis, Investigation, Writing – review & editing. **Ricard Mesía:** Conceptualization, Resources, Investigation, Methodology, Writing – review & editing. **Nuttapong Ngamphaiboon:** Resources, Investigation, Writing – review & editing. **Tamara Rordorf:** Resources, Investigation, Writing – review & editing. **Wan Zamaniah Wan Ishak:** Writing – review & editing. **Ruey-Long Hong:** Resources, Investigation, Writing – review & editing. **René Gonzalez Mendoza:** Formal analysis, Writing – review & editing. **Liyi Jia:** Formal analysis, Writing – review & editing. **Diana Chirovsky:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Josephine Norquist:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Fan Jin:** Conceptualization, Methodology, Writing – review & editing. **Barbara Burtness:** Conceptualization, Resources,



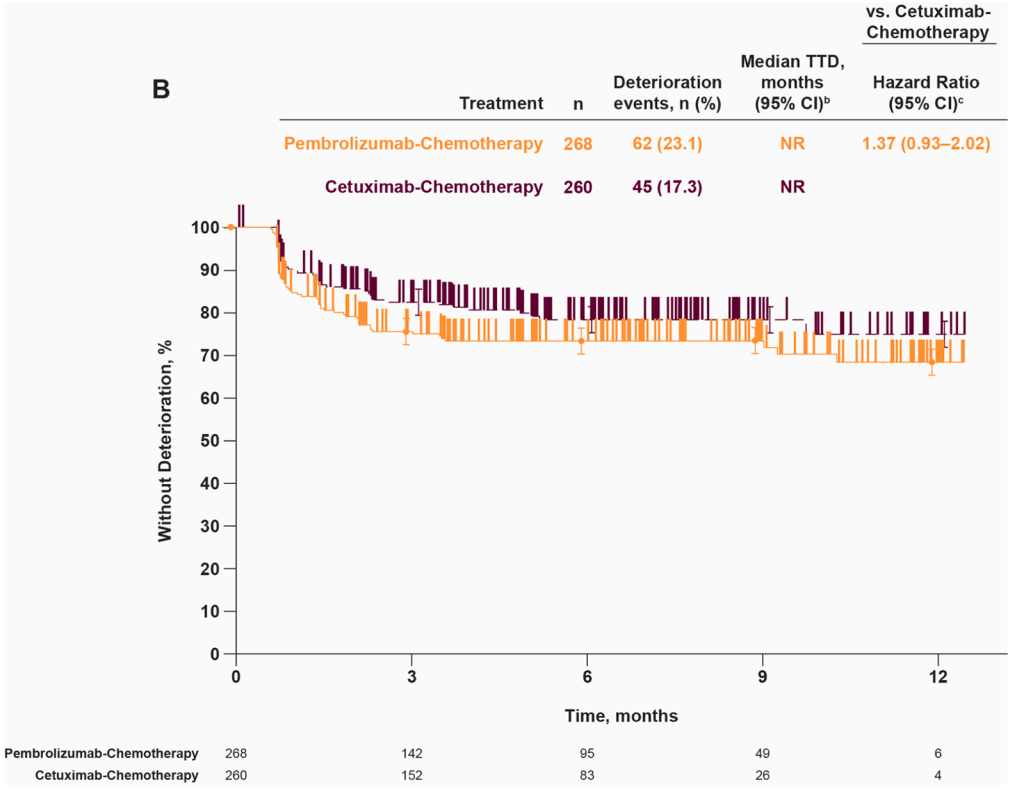


Fig. 4. Kaplan-Meier estimates of time to deterioration by treatment (pembrolizumab-chemotherapy vs cetuximab-chemotherapy[a]) in **(A)** the EORTC QLQ-C30 GHS/QoL score and EORTC QLQ-H&N35 **(B)** pain and **(C)** swallowing score. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-H&N35: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 35-question head and neck cancer–specific module; GHS/QoL: global health status/quality of life; HPV: human papillomavirus; NR: not reached; PD-L1: programmed death ligand 1. [a]Includes only participants randomly allocated to the cetuximab-chemotherapy group while the pembrolizumab-chemotherapy group was open for enrollment. [b]From product-limit (Kaplan-Meier) method for censored data. [c]Based on Cox regression model with the Efron method of handling ties with treatment as a covariate stratified by ECOG PS (0 vs 1), HPV status (positive vs negative), and PD-L1 status (strongly positive vs not strongly positive).

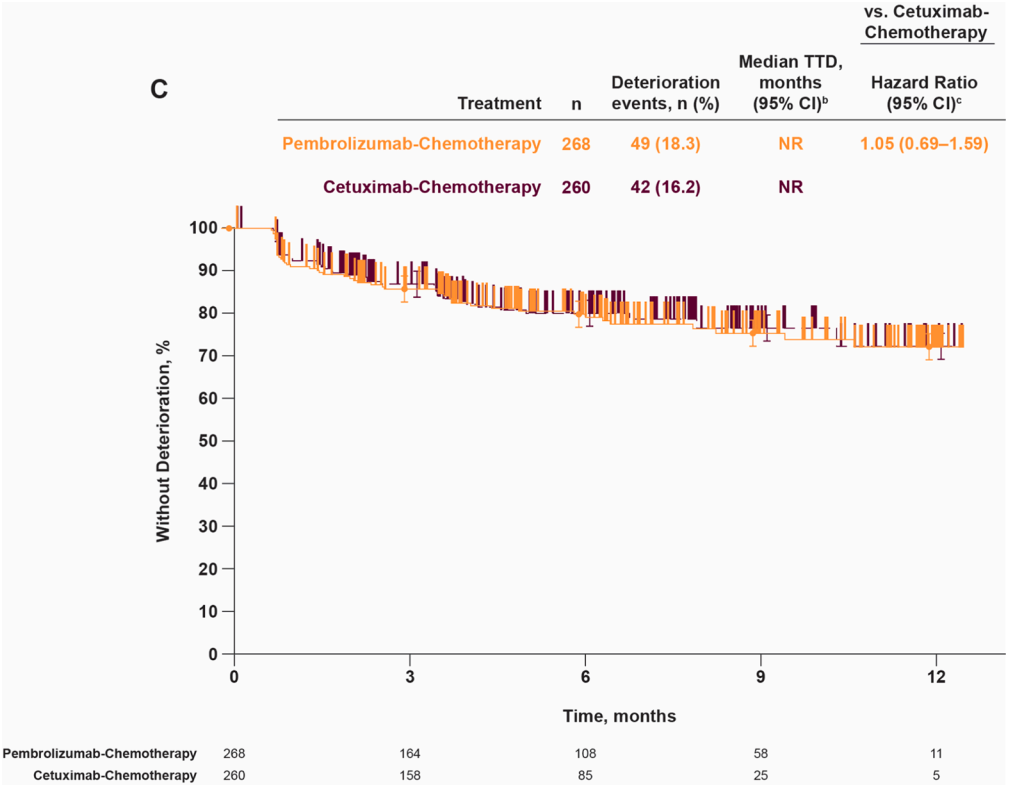


Fig. 4. (*continued*).

Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D. Rischin reports institutional research funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD); research funding from MSD, Regeneron, GlaxoSmithKline, Sanofi, Roche, and Bristol Myers Squibb; and nonfinancial support from MSD. K. Harrington reports personal fees to institution from AstraZeneca, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, MSD, Merck Serono, Pfizer, and Replimune; research funding to institution from AstraZeneca, Boehringer Ingelheim, MSD, and Replimune. R. Greil reports honoraria, travel expenses, consulting fees, and research funding from Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, MSD, Sandoz, AbbVie, Gilead, Daiichi Sankyo, and Janssen. D. Soulières reports institutional research funding and honoraria from MSD. M. Tahara reports research funding from MSD, Bayer, AstraZeneca, Eisai, Bristol Myers Squibb, Ono Pharmaceutical, Pfizer, Rakuten Medical, and Novartis; and personal fees from MSD, Bayer, AstraZeneca, Merck Serono, Eisai, Bristol Myers Squibb, Ono Pharmaceutical, Pfizer, Rakuten Medical, Celgene, and Amgen. G. de Castro reports honoraria, consulting fees, speakers bureau fees, travel expenses, and institutional research funding from Bristol Myers Squibb, MSD, AstraZeneca, and Merck Serono. A. Psyrri reports advisory board fees and honoraria from MSD; advisory board fees, honoraria, and research funding from Bristol Myers Squibb, AstraZeneca, and Merck Serono. I. Braña reports research funding from MSD, Bristol Myers Squibb, AstraZeneca, Regeneron, Novartis, GlaxoSmithKline, Kura, Pfizer, Orion Pharma, Merck Serono, Celgene, Roche, Incyte, Shattuck Labs, Rakuten Aspyrian, VCN Biosciences, and Instituto Salud Carlos III Research funding: personal grant—Rio Hortega Contract—CM15/00255. P. Neupane and A. Bratland declare no disclosures. T. Fuereder reports honoraria from MSD, Bristol Myers Squibb/Celgene, Roche, Merck KGaA, Pfizer, Boehringer Ingelheim, and Amgen; consulting or advisory roles with Merck KGaA, MSD, Amgen, Boehringer Ingelheim, and Janssen; travel, accomodations, and expenses from MSD, Bristol Myers Squibb/Celgene, and Merck KGaA; and institutional research funding from MSD, Merck KGaA, Bristol Myers Squibb/Celgene, and Kura Oncology. Hughes reports consulting fees from MSD, Bristol Myers Squibb, Roche, AstraZeneca, Pfizer, Eisai, and Boehringer Ingelheim. R. Mesía reports advisory fees from Merck KGaA, MSD, Bristol Myers Squibb, Bayer, Nanobiotix, Pfizer, Seattle Genetics, Roche, AstraZeneca, and Rakuten Pharma; and lecture fees from Merck KGaA, MSD, and Bristol Myers Squibb. N. Ngamphaiboon reports institutional research funding from MSD, Roche, Pfizer, RAPT Therapeutics, and Exelixis; and personal fees and nonfinancial support from MSD, Roche, AstraZeneca, Amgen, Novartis, Bristol Myers Squibb, Claris, Eli-Lilly, and Bayer. T. Rordorf reports consulting fees from MSD and Bristol Myers Squibb. W.Z.W. Ishak reports research funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Roche, and AstraZeneca; honoraria from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Ipsen Malaysia, Roche, Eisai Malaysia, AstraZeneca, and Eli Lilly; and advisory board fees from Celgene Singapore. R.L. Hong and R. Gonzalez Mendoza declare no disclosures. J. Norquist and F. Jin report employment with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. L. Jia and D. Chirovsky report employment with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and stock ownership in Merck & Co., Inc., Kenilworth, NJ, USA. B. Burtness reports institutional research funding from Merck, Bristol Myers Squibb, Aduro, and GlaxoSmithKline; advisory board fees from Bristol Myers Squibb, IDDI, Maverick, and GlaxoSmithKline; and steering committee fees from Aduro.

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Consent for Publication

Not applicable.

Availability of Data and Material

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. The company is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php). Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing the requested data.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.105815.

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