Quality of Life With Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-040

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Abstract (249 words; maximum, 250)

Background: Head and neck squamous cell carcinoma (HNSCC) affects health-related quality of life (HRQoL); few treatments have demonstrated clinically meaningful HRQoL benefit. KEYNOTE-040 evaluated pembrolizumab versus standard of care (SOC) in patients with recurrent/metastatic (R/M) HNSCC whose disease recurred/progressed after platinum-containing regimen.

Methods: Patients received pembrolizumab 200 mg or SOC (methotrexate, docetaxel, or cetuximab). Exploratory HRQoL analyses used European Organisation for Research and Treatment of Cancer (EORTC) 30 quality-of-life, EORTC 35-question quality-of-life head and neck cancer-specific module, and EuroQoL 5-dimensions questionnaires.

Results: The HRQoL population comprised 469 patients (pembrolizumab=241, SOC=228). HRQoL compliance for patients on study at week 15 was 75.3% (116/154) for pembrolizumab and 74.6% (85/114) for SOC. Median time to deterioration in global health status (GHS)/QoL score was 4.8 months with pembrolizumab and 2.8 months with SOC (HR, 0.79; 95% CI: 0.59, 1.05). For patients on study at week 15, GHS/QoL scores were stable for pembrolizumab (least squares mean [LSM], 0.39; 95% CI: –3.00, 3.78) but worsened for SOC (LSM, –5.86; 95% CI: –9.68, –2.04); LSM between-group difference was 6.25 points (95% CI: 1.32, 11.18; nominal 2-sided *P*=.013). Greater difference in LSM score for GHS/QoL was observed with pembrolizumab versus docetaxel (10.23) compared with pembrolizumab versus methotrexate (6.21) or pembrolizumab versus cetuximab (–1.44).,–Pembrolizumab-treated patients had stable functioning and symptoms at week 15, with no notable differences from SOC.

Conclusions: GHS/QoL was stable with pembrolizumab but declined with SOC in patients on study at week 15, supporting the clinically meaningful benefit of pembrolizumab in R/M HNSCC.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT02252042

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Key Words: Pembrolizumab; Chemotherapy; Standard of care; HNSCC; HRQoL

Health-related quality of life (HRQoL) is a critical component of measuring patients' overall health status (1). Head and neck squamous cell carcinoma (HNSCC), occurring in structurally complex and functionally important areas, can profoundly affect patients' social interactions and psychological well-being—compounding their common cancer symptoms of pain and fatigue—resulting in diminished HRQoL (2,3). Additionally, prognosis is poor for patients with recurrent and/or metastatic (R/M) HNSCC. Until recently, systemic treatment options for platinum-refractory R/M HNSCC were limited to single-agent chemotherapy or cetuximab, with a median overall survival (OS) of ≤6 months (4-9). Although HRQoL is an independent prognostic factor of OS in R/M HNSCC, it has been assessed in few clinical trials in this population, and few treatments have demonstrated clinically meaningful HRQoL benefit (9-14). Thus, therapies that prolong OS while preserving HRQoL in patients with R/M HNSCC are needed (12,15).

Targeting programmed death 1 (PD-1) receptor and programmed death ligand 1 (PD-L1) has demonstrated significant benefit in patients with R/M HNSCC (16-18). The PD-1 inhibitor nivolumab prolonged OS over investigator's choice of standard of care (SOC) therapy while maintaining HRQoL from baseline to weeks 9 and 15 in platinum-refractory R/M HNSCC; however, low compliance at later time points limited HRQoL analyses beyond week 15 (16,19).

In KEYNOTE-040 (22), the PD-1 inhibitor pembrolizumab prolonged OS versus investigator's choice of SOC (hazard ratio [HR], 0.80; 95% CI: 0.65, 0.98; nominal 1-sided P = .0161), while resulting in fewer treatment-related adverse events in patients with platinum-refractory R/M HNSCC. Results of prespecified exploratory HRQoL analyses of KEYNOTE-040 are presented.

Methods

Study Design and Treatment

KEYNOTE-040 (ClinicalTrials.gov, NCT02252042) is a randomized phase 3 trial evaluating pembrolizumab versus SOC in patients with R/M HNSCC that progressed during or after platinum-containing treatment (22). In brief, patients were randomly allocated (1:1) to receive pembrolizumab or SOC of methotrexate, docetaxel, or cetuximab. Investigators chose one of these three drugs based on product characteristics and in accordance with local guidelines before patients were randomly assigned to receive pembrolizumab or SOC. Study protocol and amendments were approved by appropriate ethics review committees, and the study was conducted in accordance with the ethical principles in the Declaration of Helsinki.

Patients

Detailed eligibility criteria for the KEYNOTE-040 trial are published (22). Patients with R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx who had platinum-refractory disease were eligible. All patients provided written informed consent.

HRQoL Assessments

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. At each visit, three validated HRQoL instruments were administered before all other study procedures: three-level version of the EuroQoL 5-dimensions questionnaire (EQ-5D-3L), European Organisation for Research and Treatment of Cancer core 30 quality-of-life questionnaire (EORTC

QLQ-C30), and EORTC 35-question head and neck cancer-specific module (EORTC QLQ-H&N35) (23-25). Additional details on HRQoL instruments and scoring are provided in the supplement.

Key HRQoL analyses assessed time to deterioration (TTD) and mean change from baseline in individual scores of EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D. Deterioration in all scales of both EORTC questionnaires was defined as a ≥10-point decline from baseline in HRQoL scores (24,26-28). Changes from baseline in EORTC QLQ-C30 scores were interpreted according to recent subscale-specific guidelines, which indicate that clinically meaningful differences vary by scale; mean difference of 5 to 10 points was defined as a small but clinically meaningful change in global health status (GHS)/QoL score (26,29,30). For the EQ-5D, deterioration was defined as a decline from baseline of ≥0.08 in the utility index and a decline from baseline of ≥7 on the EQ-5D visual analog scale (31).

Statistical Analysis

No formal power calculations were performed for these exploratory outcomes. The overall HRQoL analysis population included all patients who received ≥1 dose of study therapy and completed ≥1 HRQoL assessment. Compliance was defined as the proportion who completed ≥1 HRQoL assessment among those expected to complete the instruments at each visit (excluding patients who discontinued study treatment). Completion was defined as the proportion who completed ≥1 HRQoL assessment among the overall HRQoL analysis population.

Median TTD of individual EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D scores was estimated using Kaplan-Meier analysis. HRs were estimated using a stratified (by Eastern Cooperative Oncology Group performance status [ECOG PS],

human papillomavirus infection status, and PD-L1 expression status) Cox proportional hazards model. Consistent with current recommendations (19,32), deterioration was applied at the individual patient level; confirmation was not required at a subsequent visit, deaths were not included as events, and patients ongoing or discontinued from the study without deterioration were censored at the last assessment.

Treatment effect of change from baseline in the EORTC QLQ-C30, QLQ-H&N35, and EQ-5D scores was evaluated primarily at week 15, selected because a low completion rate based on disease progression was expected after week 15 for the SOC group. Change in least squares mean (LSM) score from baseline to week 15 was assessed using a constrained longitudinal data analysis (cLDA) model, with HRQoL score as the response variable and treatment-by-time interaction and trial stratification factors as covariates (33,34). The cLDA model implicitly treats missing data as missing-at-random, although they could be missing-not-at-random given that increased patient attrition occurs because of disease progression or death. Therefore, to compare the estimated treatment differences for the EORTC QLQ-C30 GHS/QoL score with the cLDA model results, five sensitivity analyses using more conservative assumptions on missing data were performed according to the control-based mean imputation method (35) and two rank-based nonparametric methods (Wilcoxon rank-sum test and aligned rank test), with two imputation strategies for missing data (36,37). Details on the cLDA methodology and each of the sensitivity analysis methods are provided in the supplement.

To further analyze trends observed at week 15, descriptive analyses of mean change from baseline (and 95% CIs) in GHF/QoL were summarized for patients who remained on study and completed questionnaires at each time point through week

51. Additionally, LSM change from baseline in GHS/QoL scores according to progressive disease status was evaluated for patients on study at week 15 and compared between groups to assess the association of response to therapy on GHS/QoL. Subgroup analyses of LSM change from baseline according to investigator's choice of SOC therapy (methotrexate, cetuximab, or docetaxel) and PD-L1 biomarker expression (combined positive score [CPS] ≥1 vs CPS <1 and tumor proportion score [TPS] ≥50% vs TPS <50%) in EORTC QLQ-C30, QLQ-H&N35, and EQ-5D scores were performed to further assess potential factors associated with HRQoL outcomes.

Descriptive analyses of postbaseline EORTC QLQ-C30 and EORTC QLQ-H&N35 scores at week 15 were classified as improved, stable, or deteriorated based on a ≥10-point change relative to baseline and were summarized using numbers and proportions. Proportions were calculated based on multiply imputed datasets assuming missing-at-random, then synthesized based on Rubin's rule.

Data cutoff date was May 15, 2017 (final analysis).

Results

HRQoL Instrument Completion and Compliance

Of 495 patients enrolled, the overall HRQoL population included 469 patients (94.7%) who received treatment and completed ≥1 HRQoL assessment (pembrolizumab, N = 241; SOC, N = 228). (Figure 1). Median duration of follow-up was 7.5 months (interquartile range, 3.4-13.3) (22). EORTC QLQ-C30 compliance rates were >94% at baseline and >74% for patients on study at week 15 for both treatment groups (Table S1). Completion rates decreased at week 15 based on treatment discontinuation because of disease progression, intolerable toxicity,

physician/patient decision to withdraw, or death (Figure 1). At week 15, the EORTC QLQ-C30 completion rate was 48.1% with pembrolizumab and 37.3% with SOC (Table S1). EORTC QLQ-H&N35 and EQ-5D compliance and completion rates were similar to those observed for EORTC QLQ-C30.

Baseline Characteristics of the HRQoL Population

Baseline characteristics of the total population were generally balanced between treatment groups (22); baseline characteristics of the HRQoL population followed the same trend overall and at week 15 with certain exceptions (Table 1). At week 15, imbalances across treatment groups in the distribution of investigator's choice of methotrexate and cetuximab were seen because of the proportionately higher dropout for patients on methotrexate in the SOC group. In contrast, the proportion of patients assigned to SOC of docetaxel remain balanced at week 15. Relative to the overall HRQoL population, a slightly higher proportion of patients at week 15 had PD-L1 TPS ≥50% and CPS ≥1 status in the pembrolizumab group and ECOG PS of 0 in both groups; between-group comparisons of the HRQoL scores incorporated stratification for PD-L1 and ECOG PS to address these imbalances.

Baseline (mean [SD]) GHS/QoL scores of EORTC QLQ-C30 were similar with pembrolizumab (56.0 [21.2]) and SOC (55.8 [21.6]) in the overall HRQoL population. For the HRQoL population at week 15, baseline mean GHS/QoL scores appeared slightly higher for pembrolizumab (62.03 [20.66]) than for SOC (59.18 [19.59]) and the overall HRQoL population. Thus, sensitivity analyses in the between-group comparisons of the GHS/QoL scores were applied to vary assumptions on the missing GHS/QoL scores at week 15 (Table S2).

TTD in HRQoL Scores

Median TTD in the GHS/QoL score was 4.8 months with pembrolizumab and 2.8 months with SOC (Figure 2), resulting in a trend toward prolonged TTD with pembrolizumab versus SOC (HR, 0.79; 95% CI: 0.6, 1.1; nominal 2-sided *P* = .096). Although few clinically meaningful differences occurred in TTD across individual EORTC QLQ-C30, QLQ-H&N35, and EQ-5D scales, with few exceptions trends in longer TTD tended to favor pembrolizumab (Figure S1).

Change From Baseline in HRQoL Scores

EORTC QLQ-C30 GHS/QoL scores remained stable relative to baseline for patients treated with pembrolizumab who remained on study at week 15, with an LSM change of 0.4 points (95% CI: –3.0, 3.8) (Table 2). By contrast, the GHS/QoL score worsened in patients treated with SOC, with an LSM change of –5.9 points (95% CI: –9.7, –2.0). Difference in LSM between groups was 6.3 points (95% CI: 1.3, 11.2; nominal 2-sided *P* = .013), indicating a modest improvement with pembrolizumab versus SOC. Sensitivity analyses using the control-based mean imputation method further identified a modest improvement in mean GHS/QoL scores between pembrolizumab and SOC (mean difference, 5.2 points; 95% CI: 1.5, 8.9; nominal 2-sided *P* = .008), and the two rank-based methods produced similar findings (Table S2). When stratified by time of patient dropout, trends in mean GHS/QoL scores with pembrolizumab remained stable for patients who sequentially completed questionnaires through weeks 6-15, whereas a trend in decline was observed with SOC over time (Figure S2). As expected, patients able to complete HRQoL assessments until week 15 exhibited higher GHS/QoL scores at baseline and over time in both treatment groups. Descriptive analysis of mean change from baseline further revealed that the GHS/QoL score was stable relative to baseline at each time

point through week 51 in both treatment groups for those who were on study and able to complete questionnaires at later time points (Figure 3A).

Descriptive trends in change from baseline in GHS/QoL at each time point through week 51 appeared to differ according to investigator's choice of SOC therapy (Figure 3B-D). EORTC QLQ-C30 GHS/QoL scores worsened relative to baseline for patients treated with docetaxel but were generally stable for those treated with cetuximab or methotrexate (descriptive analysis only), although numbers of patients receiving SOC therapies were very low beyond the 15-week time point for further assessment. From baseline to week 15, the LSM change in EORTC QLQ-C30 GHS/QoL scores was stable for patients treated with cetuximab (–1.8 points) and methotrexate (–3.5 points), whereas a notable decline of –9.7 points was observed among patients treated with docetaxel (95% CI: –15.1, –4.3) (Table 2). Consequently, a greater clinically meaningful difference between groups in LSM change in GHS/QoL scores was observed with pembrolizumab versus docetaxel (difference in LSM, 10.2 points) than with pembrolizumab versus methotrexate (6.2 points) or cetuximab (–1.4 points) (Table 2). Notably, imbalances across treatment groups in the distribution of investigator's choice of methotrexate and cetuximab were seen at week 15 (Table 1), which could have impacted the validity of these comparisons; in contrast, the proportion of patients assigned to SOC of docetaxel remained balanced at week 15. Additional sensitivity analyses of the GHS/QoL scores by investigator's choice of SOC therapy are provided in Table S2.

Descriptive analyses conducted at week 15 indicated greater improvement in GHS/QoL scores with pembrolizumab versus SOC in patients without disease progression (difference in LSM between groups, 9.40 points; 95% CI: 3.83, 14.97), whereas no clinically meaningful difference in GHS/QoL scores between treatment

groups was observed for patients with disease progression (difference in LSM between groups, 6.27 points; 95% CI: –4.87, 17.41) (Table S3). GHS/QoL remained stable at week 15 for patients treated with pembrolizumab whose disease did not progress (LSM change, 4.30 points; 95% CI: 0.48, 8.12) and for patients whose disease progressed (LSM change, –3.56 points; 95% CI: –7.39, 0.26). In contrast, in patients treated with SOC, those whose disease did not progress experienced moderate decline in GHS/QoL scores from baseline to week 15 (LSM change, –5.09 points; 95% CI: –9.35, –0.83), and those whose disease progressed experienced greater decline from baseline to week 15 (LSM change, –9.83 points; 95% CI: –14.03, –5.63) (Table S3).

For those on study at week 15, pembrolizumab-treated patients exhibited stable functioning and stable symptom scores for EORTC QLQ-C30 and QLQ-H&N35, with few exceptions (decline in physical and cognitive functioning, decline in social contact scores; Figure 4A-C). SOC-treated patients exhibited declines from baseline in the physical, role, cognitive functioning, fatigue, pain, and social contact symptoms of EORTC QLQ-C30 and QLQ-H&N35 but otherwise stable functioning and stable symptom scores at week 15. No notable between-group differences were observed (Figure 4A-C). EQ-5D utility index and visual analog scale scores were also stable at week 15 for patients treated with pembrolizumab, with no notable differences versus SOC (Figure S3A-B). Subgroup analyses according to SOC choice of therapy for the functioning, symptom, and health status scales of the EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D instruments were generally consistent with the main results; no notable between-group differences were observed (Figure S4).

When assessed by PD-L1 biomarker status at week 15, LSM differences between treatment groups were similar to overall treatment effects for each of the EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D scales, suggesting no evidence of a differential HRQoL benefit according to PD-L1 status (Figures S5-6).

Proportion With Deteriorated/Stable/Improved HRQoL Scores

Smaller proportions of patients treated with pembrolizumab than SOC experienced deterioration based on a ≥10-point change from baseline in the GHS/QoL score for those on study at week 15 (24.9% vs 42.5%) (Figure S7A). For the functioning and symptom scales of EORTC QLQ-C30 and QLQ-H&N35, the proportion of patients who experienced deterioration in the pembrolizumab group was generally smaller than or similar to that in the SOC group at week 15, with few exceptions (dry mouth at week 15) (Figure S7B-D).

Discussion

Therapies that prolong survival without reducing HRQoL are needed for patients with R/M HNSCC. In KEYNOTE-040, pembrolizumab demonstrated clinically meaningful improvements in OS and a better safety profile over SOC in patients with R/M HNSCC (22). In this HRQoL analysis from KEYNOTE-040, patients treated with pembrolizumab who remained on study at week 15 demonstrated stable GHS/QoL, whereas those treated with SOC experienced a small but clinically meaningful decline. Pembrolizumab-treated patients also had stable functioning and stable symptoms over 15 weeks, further underscoring the clinical benefits of pembrolizumab in R/M HNSCC.

Previous exploratory HRQoL analyses in pembrolizumab trials across several tumor types have consistently demonstrated HRQoL benefit. In the KEYNOTE-024

study of non–small cell lung cancer (NSCLC), pembrolizumab-treated patients who remained on study at week 15 demonstrated greater improvement or maintenance in HRQoL than those treated with chemotherapy (38). In the KEYNOTE-045 study of urothelial cancer, prolonged TTD in GHS/QoL and greater stability or improvement in HRQoL and symptom scores were observed with pembrolizumab than with chemotherapy among those on study at week 15 (39). In KEYNOTE-002, fewer patients with advanced or treatment-refractory melanoma exhibited deterioration in HRQoL scores with pembrolizumab than with chemotherapy among those on study at week 12 (40).

Recently, HRQoL has been investigated in patients with R/M HNSCC who were treated with immunotherapy. In an exploratory analysis of CheckMate 141 in patients with platinum-refractory R/M HNSCC, nivolumab stabilized GHS/QoL, symptoms, and functioning for patients on study at weeks 9 and 15, whereas investigator's choice of chemotherapy led to clinically meaningful deterioration (19). In this analysis, pembrolizumab-treated patients also exhibited stable GHS/QoL at week 15, whereas a modest decline in GHS/QoL was observed with SOC. To our knowledge, this analysis of KEYNOTE-040 is novel and shows that the descriptive trend in stable GHS/QoL extends for as long as 51 weeks in patients with R/M HNSCC treated with immunotherapy.

HRQoL has been assessed in phase 3 trials of other targeted therapies, such as tyrosine kinase inhibitors afatinib and gefitinib, in platinum-refractory R/M HNSCC (9,13). Both agents demonstrated stable HRQoL relative to baseline; modest improvements in HRQoL were seen for afatinib and gefitinib versus methotrexate but not in OS (9,13), as observed in recent immunotherapy trials of pembrolizumab and nivolumab (16,22).

Interestingly, in the present study, a greater between-group difference in GHS/QoL was observed in the comparison of pembrolizumab with docetaxel (10.23) than with either methotrexate (6.21) or cetuximab (–1.44) for patients who remained on study at week 15. This finding is important because docetaxel was also determined to be the most efficacious of the SOC therapies in both KEYNOTE-040 and CheckMate 141 (16,22). In addition, in situations in which anti–PD-1 therapy is not available to patients, docetaxel is the most likely therapy to be administered by clinicians in real-world practice (43-47). These data evaluating PD-1 inhibitors versus docetaxel are consistent with results from NSCLC in KEYNOTE-010; patients treated with pembrolizumab versus docetaxel showed improved survival and HRQoL (48,49). Similarly, in the CheckMate 017 study in NSCLC, nivolumab improved both survival and HRQoL versus docetaxel in the second-line setting (50,51). Indeed, toxicity of systemic agents in patients with R/M HNSCC varies, as does their burden on HRQoL (52).

In the present study, differences between groups in HRQoL appeared to be correlated with response to therapy. For patients on study at week 15, greater improvement in GHS/QoL was observed with pembrolizumab than SOC in patients without disease progression; however, no such clinically meaningful difference in GHS/QoL was found in patients with disease progression. GHS/QoL remained stable in pembrolizumab-treated patients with and without disease progression, whereas GHS/QoL declined with SOC regardless of disease progression status at week 15. The overall treatment effect on HRQoL was similar among PD-L1 subgroups. These findings are consistent with those of CheckMate 141, which noted no meaningful influence of PD-L1 status on HRQoL (19).

Limitations of these HRQoL analyses include the open-label KEYNOTE-040 trial design, which might have influenced patient responses, and may explain why HRQoL was not worse in the experimental arm in this and other open-label trials in this indication (9,13,19). Further, as is common with HRQoL assessments (19), analyses were limited to week 15 to ensure sufficient completion rates for treatment comparisons. Although formal statistical analyses on change from baseline in GHS/QoL scores were limited to week 15, sensitivity analyses testing different assumptions about missing data consistently confirmed a modest improvement in GHS/QoL with pembrolizumab versus SOC. In addition, trends observed at week 15 remained consistent through week 51, indicating stable GHS/QoL with pembrolizumab for those on study at later time points. Last, the exploratory nature of the HRQoL analyses should be interpreted in light of the multiple comparisons performed, which might have contributed to possibility of false findings.

Conclusions

Pembrolizumab-treated patients had stable GHS/QoL, whereas SOC-treated patients who remained on study at week 15 experienced modest declines in GHS/QoL. Additionally, pembrolizumab-treated patients exhibited stable functioning and symptoms at week 15. Along with previously presented efficacy and safety results, these data support the clinically meaningful benefit of pembrolizumab in patients with R/M HNSCC.

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Conflict of Interest

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RF Swaby: Employee and stockholder of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and stockholder of Merck & Co., Inc., Kenilworth, NJ, USA.

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Author Contributions

Dr Harrington had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Harrington, Burtness, Cheng, Chirovsky, Cohen

Provision of study materials or patients: Harrington, Le Tourneau, Dinis, Burtness

Collection and assembly of data: Harrington, Souliéres, Licitra, Soria, Mach, Mehra, Burtness, Swaby, Cohen

Data analysis and interpretation: Harrington, Souliéres, Le Tourneau, Dinis, Licitra, Ahn, Soria, Machiels, Mehra, Ellison, Cheng, Chirovsky, Swaby, Cohen

Statistical analysis: Ellison, Chirovsky

Drafting of the manuscript: Chirovsky

Critical revision of the manuscript for important intellectual content: All authors

Final approval of manuscript: All authors

Data Sharing Statement

Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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Table 1. Baseline characteristics of the overall HRQoL population* and the HRQoL population at week 15†

Characteristic	Overall HRQoL population*				HRQoL population at week 15†			
	Pembrolizumab n = 241		Standard of care n = 228		Pembrolizumab n = 116		Standard of care n = 85	
Age, median (range), y	60.0 (19-85)		60.0 (34-78)		60.5 (31-85)		60.0 (36-78)	
Sex, n (%)								
Male	204	(84.6)	188	(82.5)	96	(82.8)	65	(76.5)
Female	37	(15.4)	40	(17.5)	20	(17.2)	20	(23.5)
Race, n (%)								
American Indian or Alaska Native	2	(0.8)	0	(0)	2	(1.7)	0	(0)
Black or African American	3	(1.2)	7	(3.1)	1	(0.9)	5	(5.9)
White	201	(83.4)	189	(82.9)	98	(84.5)	68	(80.0)
Asian	15	(6.2)	15	(6.6)	6	(5.2)	6	(7.1)
Multiracial	4	(1.7)	3	(1.3)	1	(0.9)	0	(0)
Unknown	16	(6.6)	14	(6.1)	8	(6.9)	6	(7.1)

Ethnicity, n (%)							
Hispanic or Latino	20	(8.3)	12	(5.3)	11	(9.5)	3	(3.5)
Not Hispanic or Latino	179	(74.3)	178	(78.1)	81	(69.8)	68	(80.0)
Not reported or unknown	42	(17.4)	38	(16.7)	11	(9.5)	5	(5.9)
Region, n (%)								
Europe	142	(58.9)	144	(63.2)	71	(61.2)	54	(63.5)
North America	72	(29.9)	54	(23.7)	31	(26.7)	17	(20.0)
Rest of world	27	(11.2)	30	(13.2)	14	(12.1)	14	(16.5)
ECOG PS, n (%)								
0	71	(29.5)	63	(27.6)	48	(41.4)	32	(37.6)
1	170	(70.5)	165	(72.4)	68	(58.6)	53	(62.4)
Smoking status, n (%)								
Never smoked	67	(27.8)	58	(25.4)	26	(22.4)	21	(24.7)
Former smoker	143	(59.3)	136	(59.6)	72	(62.1)	50	(58.8)
Current smoker	31	(12.9)	34	(14.9)	18	(15.5)	14	(16.5)
HPV status, n (%)								

Positive	58	(24.1)	51	(22.4)	24	(20.7)	16	(18.8)
Negative	183	(75.9)	177	(77.6)	92	(79.3)	69	(81.2)
PD-L1 TPS status, n (%)								
TPS = 0%	100	(41.5)	85	(37.3)	45	(38.8)	36	(42.4)
1% ≤ TPS < 50%	76	(31.5)	83	(36.4)	35	(30.2)	29	(34.1)
TPS ≥50%	64	(26.6)	57	(25.0)	35	(30.2)	19	(22.4)
Missing	1	(0.4)	3	(1.3)	1	(0.9)	1	(1.2)
PD-L1 CPS status, n (%)								
CPS <1	48	(19.9)	48	(21.1)	16	(13.8)	19	(22.4)
CPS ≥1	192	(79.7)	177	(77.6)	99	(85.3)	65	(76.5)
Missing	1	(0.4)	3	(1.3)	1	(0.9)	1	(1.2)
Current disease overall stage, n (%)								
Stage II	5	(2.1)	7	(3.1)	3	(2.6)	4	(4.7)
Stage III	9	(3.7)	16	(7.0)	8	(6.9)	9	(10.6)
Stage IV	82	(34.0)	69	(30.3)	32	(27.6)	28	(32.9)
Stage IV A	22	(9.1)	28	(12.3)	11	(9.5)	8	(9.4)

Stage IV B	11	(4.6)	12	(5.3)	8	(6.9)	3	(3.5)
Stage IV C	112	(46.5)	96	(42.1)	54	(46.6)	33	(38.8)
Investigator's choice of SOC before randomization,‡ n (%)								
Methotrexate	70	(29.0)	63	(27.6)	35	(30.2)	15	(17.6)
Docetaxel	118	(49.0)	95	(41.7)	51	(44.0)	39	(45.9)
Cetuximab	53	(22.0)	70	(30.7)	30	(25.9)	31	(36.5)
Setting of previous systemic therapy, n (%)								
Adjuvant, neoadjuvant, or definitive	33	(13.7)	38	(16.7)	22	(19.0)	20	(23.5)
First-line	138	(57.3)	130	(57.0)	64	(55.2)	43	(50.6)
Second-line	67	(27.8)	58	(25.4)	28	(24.1)	21	(24.7)
Third-line	3	(1.2)	2	(0.9)	2	(1.7)	1	(1.2)
Most recent oncologic radiation, n (%)								
Neoadjuvant	22	(9.1)	29	(12.7)	12	(10.3)	12	(14.1)
Adjuvant	120	(49.8)	118	(51.8)	53	(45.7)	42	(49.4)
In combination with first-line	29	(12.0)	15	(6.6)	14	(12.1)	10	(11.8)

treatment							
In combination with second-line treatment	3	(1.2)	3	(1.3)	3	(2.6)	1	(1.2)
Control of metastatic or recurrent disease or refractory	13	(5.4)	10	(4.4)	7	(6.0)	1	(1.2)
Palliative treatment or symptom control	25	(10.4)	19	(8.3)	12	(10.3)	5	(5.9)
No radiation	29	(12.0)	34	(14.9)	15	(12.9)	14	(16.5)
HRQoL score								
EORTC QLQ-C30 GHS/QoL, mean (SD)	56.02[§]	(21.24)	55.81[§]	(21.63)	62.03	(20.66)	59.18	(19.59)

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

[†]The HRQoL population at week 15 included all patients who received ≥1 dose of study treatment and completed the HRQoL assessment at week 15.

‡Investigators chose between methotrexate, docetaxel, and cetuximab based on product characteristics and according to local guidelines before patients were randomly assigned to receive pembrolizumab or SOC. For patients randomly assigned to SOC, the investigator's choice of SOC also reflected the regimen assigned and delivered.

§Mean scores are reported in the HRQoL population, who completed the EORTC QLQ-C30 questionnaire at baseline; n = 231 for pembrolizumab and n = 215 for SOC.

CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; GHS/QoL = global health status/quality of life; HPV = human papillomavirus; PD-L1 = programmed death ligand 1; SOC = standard of care; TPS = tumor proportion score.

Table 2. Difference in LSM change from baseline in the EORTC QLQ-C30 GHS/QoL score by investigator's choice of SOC in patients who remained on study at week 15

Treatment	Baseline score, mean (SD)*	Week 15 score, mean (SD)*	Change from baseline to week 15, LSM (95% CI)**†	Difference in LSMs (95% CI)*†
Pembrolizumab vs SOC				
Pembrolizumab	n = 231§ 56.02 (21.24)	n = 116§ 61.71 (19.72)	n = 241‖ 0.39 (–3.00 to 3.78)	6.25 (1.32 to 11.18)¶
SOC	n = 215§ 55.81 (21.63)	n = 85§ 55.69 (22.02)	n = 228‖ –5.86 (–9.68 to –2.04)	
Pembrolizumab vs docetaxel‡				
Pembrolizumab	n = 115§ 53.33 (21.08)	n = 51§ 60.62 (18.34)	n = 118‖ 0.51 (–4.24 to 5.36)	10.23 (3.15 to 17.30)
‡Docetaxel	n = 93§ 59.50 (21.14)	n = 39§ 53.63 (21.10)	n = 95‖ –9.71 (–15.12 to –4.31)	
Pembrolizumab vs cetuximab‡				
Pembrolizumab	n = 50§ 58.50 (21.20)	n = 30§ 58.06 (19.01)	n = 53‖ –3.23 (–10.55 to 4.10)	–1.44 (–11.43 to 8.56)
‡Cetuximab	n = 66§ 55.43 (20.49)	n = 31§ 58.06 (24.95)	n = 70‖ –1.79 (–8.90 to 5.33)	
Pembrolizumab vs methotrexate‡				
Pembrolizumab	n = 66§	n = 35§	n = 70‖	

	58.84 (21.28)	66.43 (21.81)	2.76 (–3.75 to 9.27)	
‡Methotrexate	n = 56§ 50.15 (21.17)	n = 15§ 56.11 (18.49)	n = 63‖ –3.45 (–12.45 to 5.64)	6.21 (–4.57 to 16.99)

*Mean scores were calculated among patients with available scores at each time point.

**Based on cLDA model with the HRQoL scores as the response variable and treatment-by-study-visit interaction and stratification factors (ECOG PS [0 or 1], HPV status [positive vs negative], and PD-L1 status [TPS ≥50% vs TPS <50%]) as covariates.

†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 (29,30).

‡Analyses were conducted in the subgroup of patients for whom investigators chose SOC of methotrexate, docetaxel, or cetuximab before patients were randomly assigned to receive pembrolizumab or SOC. The division of pembrolizumab-treated patients was based on the corresponding SOC treatment chosen by the investigator before randomization.

§Number of patients in each group who completed the EORTC QLQ-C30 questionnaire at that time point.

‖Number of patients in the total HRQoL analysis population.

¶$P = 0.013$.

CI = confidence interval; cLDA = constrained longitudinal data analysis; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core 30 quality-of-life questionnaire; GHS = global health status; HPV = human papillomavirus; HRQoL = health-related quality of life; LSM = least squares mean; PD-L1 = programmed death ligand 1; QoL = quality of life; SD = standard deviation; SOC = standard of care; TPS = tumor proportion score.

Figure Legends

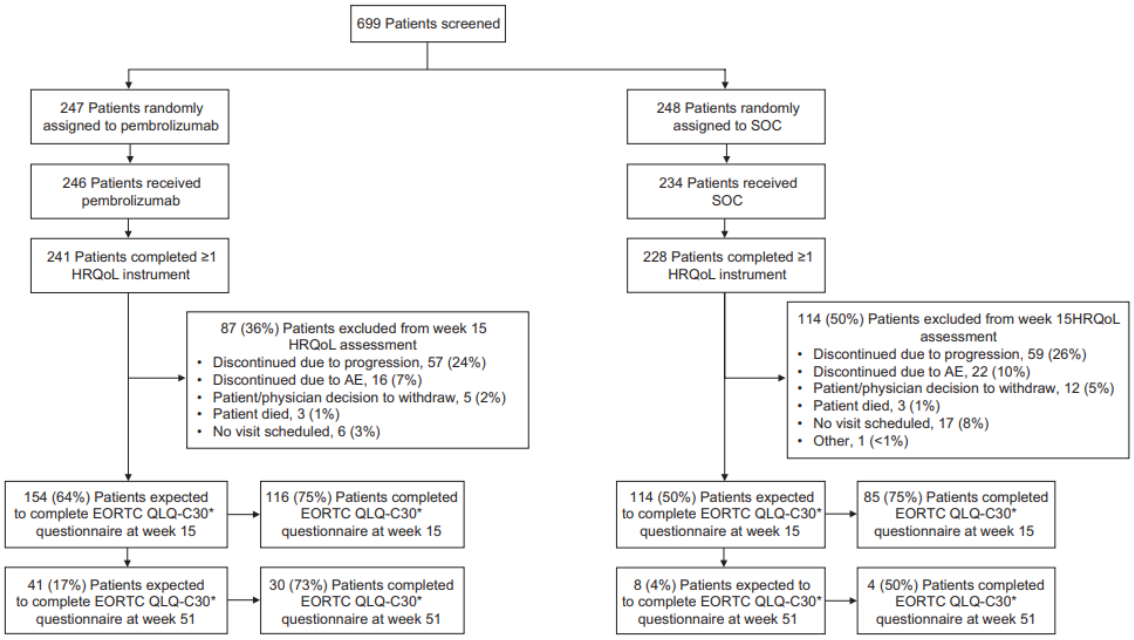


Figure 1. CONSORT diagram. *EORTC QLQ-H&N35 and EQ-5D compliance rates were nearly identical to those observed for EORTC QLQ-C30.

AE = adverse event; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer core 30 quality-of-life questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer 35-question quality of life head and neck cancer-specific module; EQ-5D = EuroQoL 5-dimensions; HRQoL = health-related quality of life; SOC = standard of care.

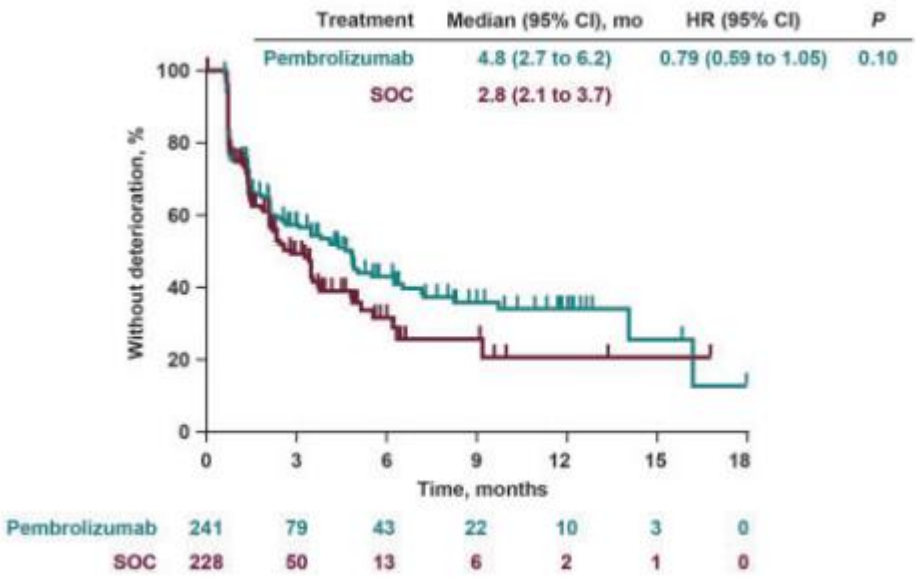


Figure 2. Time to deterioration in the EORTC QLQ-C30 GHS/QoL score.

*Nominal 2-sided *P* value based on log-rank test.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer scale 30 quality-of-life questionnaire; GHS = global health status; HR = hazard ratio; QoL = quality of life; SOC = standard of care.

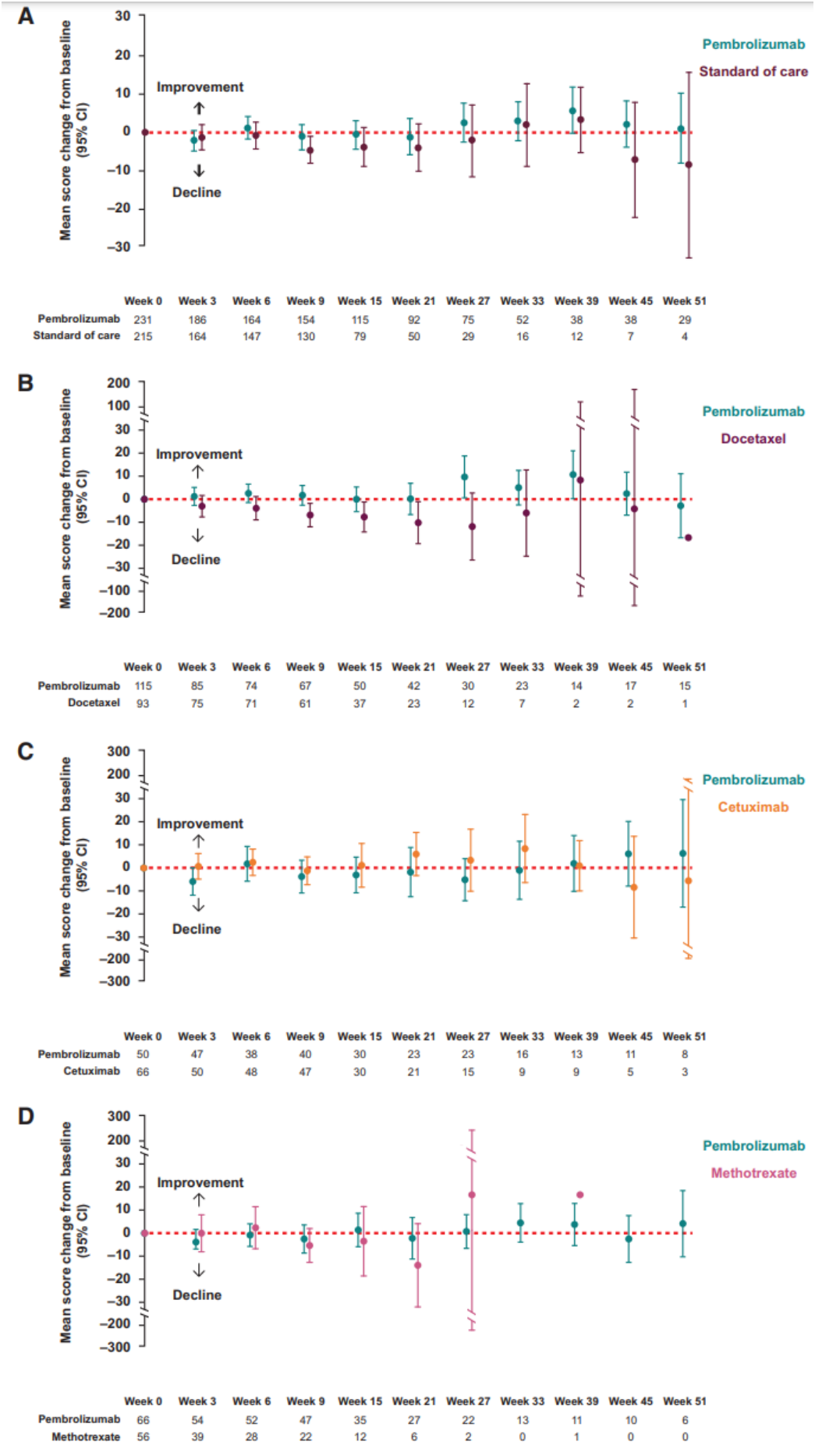
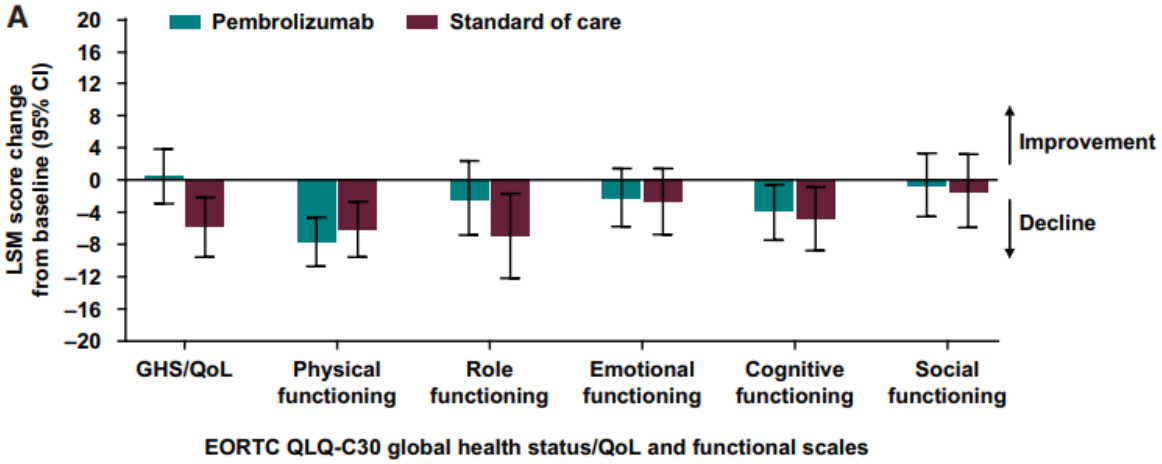
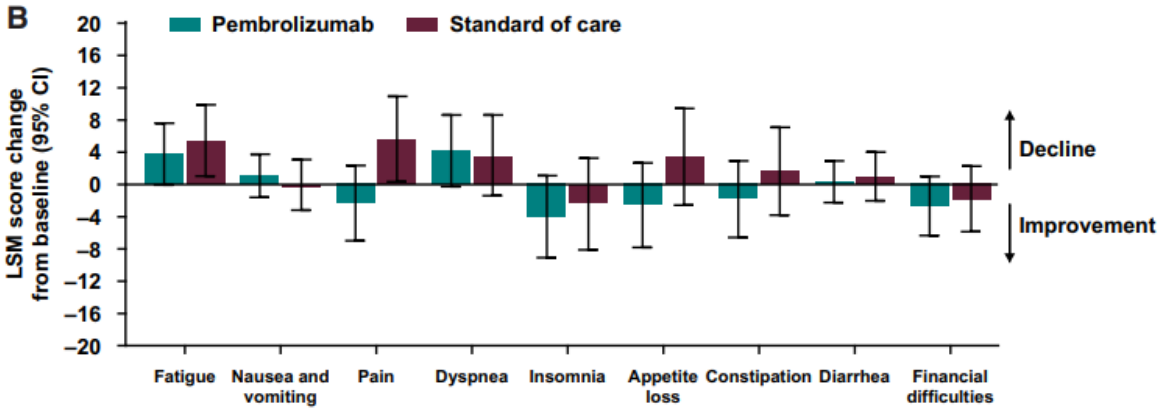

A
Mean score change from baseline (95% CI)
30
20
10
0
−10
−20
−30
Improvement
Decline
Pembrolizumab
Standard of care
Week 0 Week 3 Week 6 Week 9 Week 15 Week 21 Week 27 Week 33 Week 39 Week 45 Week 51
Pembrolizumab 231 186 164 154 115 92 75 52 38 38 29
Standard of care 215 164 147 130 79 50 29 16 12 7 4
B
Mean score change from baseline (95% CI)
200
100
30
20
10
0
−10
−20
−30
−100
−200
Improvement
Decline
Pembrolizumab
Docetaxel
Week 0 Week 3 Week 6 Week 9 Week 15 Week 21 Week 27 Week 33 Week 39 Week 45 Week 51
Pembrolizumab 115 85 74 67 50 42 30 23 14 17 15
Docetaxel 93 75 71 61 37 23 12 7 2 2 1
C
Mean score change from baseline (95% CI)
300
200
30
20
10
0
−10
−20
−30
−200
−300
Improvement
Decline
Pembrolizumab
Cetuximab
Week 0 Week 3 Week 6 Week 9 Week 15 Week 21 Week 27 Week 33 Week 39 Week 45 Week 51
Pembrolizumab 50 47 38 40 30 23 23 16 13 11 8
Cetuximab 66 50 48 47 30 21 15 9 9 5 3
D
Mean score change from baseline (95% CI)
300
200
30
20
10
0
−10
−20
−30
−200
−300
Improvement
Decline
Pembrolizumab
Methotrexate
Week 0 Week 3 Week 6 Week 9 Week 15 Week 21 Week 27 Week 33 Week 39 Week 45 Week 51
Pembrolizumab 66 54 52 47 35 27 22 13 11 10 6
Methotrexate 56 39 28 22 12 6 2 0 1 0 0

Figure 3. Change from baseline in the EORTC QLQ-C30 GHS/QoL score over time by investigator's choice of SOC in patients who were on study at each time point. (**A**) Pembrolizumab vs SOC. *95% CIs (week 51): –7.85, 10.14 (pembrolizumab) and –32.54, 15.88 (SOC). (**B**) ‡‡‡Pembrolizumab vs docetaxel. †95% CIs (week 39): –6.86, 11.76 (pembrolizumab) and –97.55, 114.22 (docetaxel). ‡95% CIs (week 45): –0.30, 21.12 (pembrolizumab) and –162.99, 154.66 (docetaxel). (**C**) ‡‡‡Pembrolizumab vs cetuximab. §95% CIs (week 45): –7.90, 20.02 (pembrolizumab) and –30.28, 13.62 (cetuximab). ‖95% CIs (week 51): –16.93, 29.43 (pembrolizumab) and –48.65, 37.54 (cetuximab). (**D**) ‡‡‡Pembrolizumab vs methotrexate. ¶95% CIs (week 21): –11.19, 6.87 (pembrolizumab) and –31.95, 4.18 (methotrexate). **95% CIs (week 27): –6.54, 8.05 (pembrolizumab) and –195.10, 228.44 (methotrexate). ††One patient did not complete a questionnaire at week 33 but did so at week 39. ‡‡‡Analyses were conducted in the subgroup of patients for whom investigators chose SOC of methotrexate, docetaxel, or cetuximab before patients were randomly assigned to receive pembrolizumab or SOC. The division of pembrolizumab-treated patients in panels B, C, and D was based on the corresponding SOC treatment chosen by the investigator before randomization.

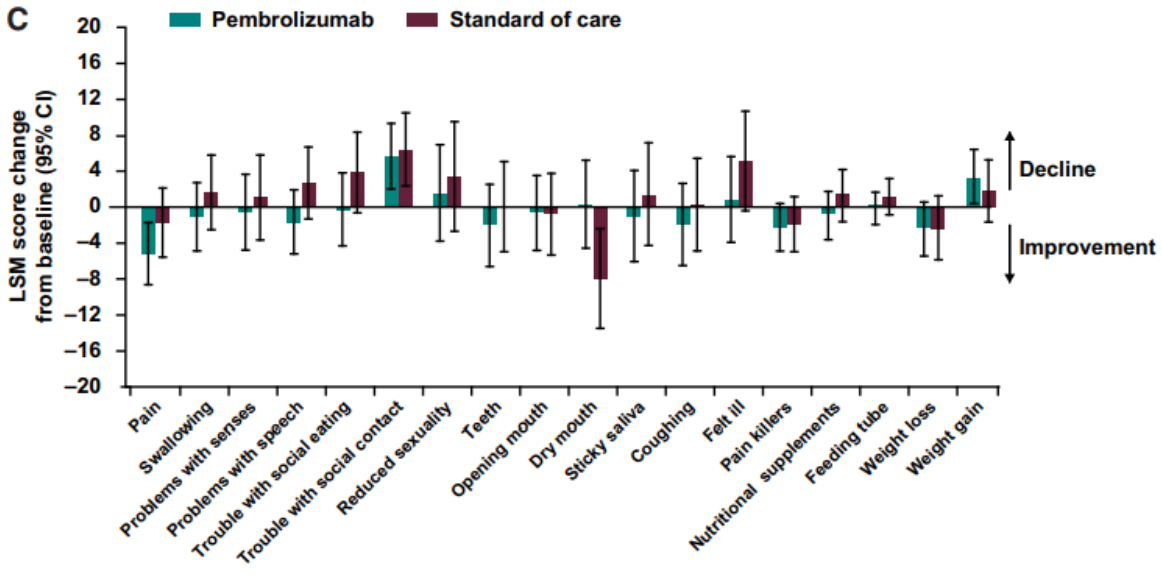
CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core 30 quality-of-life questionnaire; GHS = global health scale; QoL = quality of life; SOC = standard of care.



EORTC QLQ-C30 global health status/QoL and functional scales



EORTC QLQ-C30 symptom scales



EORTC QLQ-H&N35 symptom scales

Figure 4. Difference in LSM from baseline in EORTC QLQ-C30 and EORTC QLQ-H&N35 GHS/QoL functional and symptom scales for patients who remained on study at week 15. (**A**) EORTC QLQ-C30 GHS/QoL and functional scales. A positive GHS/QoL or functioning score indicates improvement in HRQoL or function, whereas a negative score indicates decline. (**B**) EORTC QLQ-C30 symptom scales. A positive symptom score indicates decline or more severe symptoms, whereas a negative score indicates symptom improvement. (**C**) EORTC QLQ-H&N35 multi-item and single-item symptom scales. A positive symptom score indicates decline or more severe symptoms, whereas a negative score indicates symptom improvement.
CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core 30 quality-of-life questionnaire; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer 35-question quality of life head and neck cancer-specific module; GHS = global health status; HRQoL = health-related quality of life; LSM = least squares mean; QoL = quality of life.