Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background In the KEYNOTE-826 study, the addition of the anti-PD-1 monoclonal antibody pembrolizumab to chemotherapy with or without bevacizumab improved overall survival and progression-free survival (primary endpoints) versus placebo plus chemotherapy with or without bevacizumab, with manageable toxicity, in patients with persistent, recurrent, or metastatic cervical cancer. In this Article, we report patient-reported outcomes (PROs) from KEYNOTE-826.

Methods KEYNOTE-826 is a multicentre, randomised, phase 3 trial in 151 cancer treatment centres in 19 countries. Eligible patients were aged 18 years or older with persistent, recurrent, or metastatic cervical cancer not previously treated with systemic chemotherapy (previous radiosensitising chemotherapy was allowed) and not amenable to curative treatment and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) centrally by means of an interactive voice response system in a double-blind manner to receive either pembrolizumab 200 mg or placebo every 3 weeks intravenously for up to 35 cycles plus chemotherapy (paclitaxel 175 mg/m² plus cisplatin 50 mg/m² or carboplatin area under the curve 5 mg/mL per min, intravenously) with or without bevacizumab 15 mg/kg every 3 weeks intravenously. Randomisation (block size of 4) was stratified by metastatic disease at diagnosis, planned bevacizumab use, and PD-L1 combined positive score. Patients, investigators, and other study personnel involved in study treatment administration or clinical evaluation of patients were unaware of treatment group assignments. PRO instruments were the EORTC Quality-of-Life-Core 30 (QLQ-C30), the EORTC cervical cancer module (QLQ-CX24), and the EuroQol-5 dimension-5 level (EQ-5D-5L) visual analogue scale, each collected before treatment at cycles 1–14 and every other cycle thereafter. Primary endpoints were overall survival and progression-free survival per RECIST version 1.1 by investigator review. Change from baseline in QLQ-C30 global health status (GHS)–quality of life (QoL) was a prespecified secondary endpoint and was assessed in the PRO full analysis population (all patients who received at least one dose of study treatment and completed at least one post-baseline PRO assessment). Other PRO analyses were protocol-specified exploratory endpoints. The study is registered with ClinicalTrials.gov, NCT03635567, and is ongoing.

Findings Between Nov 20, 2018, and Jan 31, 2020, of 883 patients screened, 617 were randomly assigned (pembrolizumab group, n=308; placebo group, n=309). 587 (95%) of 617 patients received at least one dose of study treatment and completed at least one post-baseline PRO assessment and were therefore included in the PRO analyses (pembrolizumab group, n=290; placebo group, n=297). Median follow-up was 22·0 months (IQR 19·1–24·4). At week 30, QLQ-C30 completion was 199 (69%) of 290 patients in the pembrolizumab group and 168 (57%) of 297 patients in the placebo group; compliance was 199 (94%) of 211 and 168 (90%) of 186, respectively. The least squares mean change in QLQ-C30 GHS–QoL score from baseline to week 30 was –0·3 points (95% CI –3·1 to 2·6) in the pembrolizumab group and –1·3 points (–4·2 to 1·7) in the placebo group, with a between-group difference in least squares mean change of 1·0 point (95% CI –2·7 to 4·7). Median time to true deterioration in GHS–QoL was not reached (NR; 95% CI 13·4 months–NR) in the pembrolizumab group and 12·9 months (6·6–NR) in the placebo group (hazard ratio 0·84 [95% CI 0·65–1·09]). 122 (42%) of 290 patients in the pembrolizumab group versus 85 (29%) of 297 in the placebo group had improved GHS–QoL at any time during the study (p=0·0003).

Interpretation Addition of pembrolizumab to chemotherapy with or without bevacizumab did not negatively affect health-related quality of life. Along with the efficacy and safety results already reported from KEYNOTE-826, these data support the benefit of pembrolizumab and the value of immunotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

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Introduction

Cervical cancer is commonly associated with a constellation of symptoms that can include bleeding, fatigue, pain, bladder and bowel dysfunction, leg swelling, and sexual dysfunction.[1–6] Symptom severity is worse in patients with advanced or recurrent disease.[2] Disease-related symptoms in patients with advanced cervical cancer have been associated with decreased health-related quality of life (HRQoL), including reduced social wellbeing and social functioning, anxiety, and depression.[2,4,7] Additionally, toxicity associated with treatment might also negatively affect HRQoL in patients with cervical cancer.[1,2]

The goal of treatment in patients with advanced or recurrent cervical cancer is to prolong life while preserving or improving HRQoL. Platinum chemotherapy (cisplatin or carboplatin) plus paclitaxel with or without bevacizumab is a standard first-line treatment for persistent, recurrent, or metastatic cervical cancer.[8–10] Findings from the GOG-240 trial showed that addition of bevacizumab to platinum-based chemotherapy improved overall survival and progression-free survival.[11,12] Although the addition of bevacizumab to chemotherapy was associated with additional toxicity, treatment did not negatively affect HRQoL.[11–13]

At the protocol-specified first interim analysis of the KEYNOTE-826 trial, the addition of the anti-PD-1 monoclonal antibody pembrolizumab to platinum-based chemotherapy with or without bevacizumab as a first-line treatment significantly improved overall survival and progression-free survival (primary endpoints) in patients with persistent, recurrent, or metastatic cervical cancer with a PD-L1 combined positive score (CPS) of at least 1 (overall survival hazard ratio [HR] 0·64 [95% CI 0·50–0·81]; p<0·001; progression-free survival 0·62 [0·50–0·77]; p<0·001), the all-comer (ie, intention-to-treat population) population (overall survival 0·67 [0·54–0·84]; p<0·001; progression-free survival 0·65 [0·53–0·79]; p<0·001), and patients with PD-L1 CPS of at least 10 (overall survival 0·61 [0·44–0·84]; p=0·001; progression-free survival 0·58 [0·44–0·77]; p<0·001); toxicity was manageable.[14] To evaluate whether or not these overall survival and progression-free survival improvements were accompanied by changes in HRQoL, PROs were evaluated as prespecified secondary and exploratory endpoints in KEYNOTE-826. In this manuscript, we report outcomes from these patient-reported outcomes (PRO) analyses using validated instruments.

Methods

Study design and participants

KEYNOTE-826 is a multicentre, randomised, phase 3 trial done in 151 cancer treatment centres in Argentina, Australia, Canada, Chile, Columbia, France, Germany, Israel, Italy, Japan, South Korea, Mexico, Peru, Russia, Spain, Taiwan, Türkiye, Ukraine, and the USA (appendix pp 12–17). Detailed methods for KEYNOTE-826 have been previously reported.[14] Eligible patients were aged 18 years or older with histologically confirmed persistent, recurrent, or metastatic adenosquamous carcinoma, adenocarcinoma, or squamous cell carcinoma of the cervix not eligible for treatment with curative intent, with measurable disease per RECIST version 1.1; had tumour

Research in context

Evidence before this study

We did a literature review of the MEDLINE and EMBASE databases on Jan 17, 2023, using the following search terms (all fields) with no publication date or language restrictions: "pembrolizumab" AND ("patient-reported outcomes" OR "PROs" OR "health-related quality of life" OR "HRQoL") AND "cervical cancer" AND "random*". Our search did not identify any publications describing patient-reported outcomes with pembrolizumab treatment in patients with cervical cancer in a randomised study. Several previous publications (including the GOG-240 trial) were identified, which supported platinum-based chemotherapy and platinum-based chemotherapy plus bevacizumab as standard first-line therapy in this setting. Additionally, in the previously published primary efficacy analysis from the KEYNOTE-826 study, progression-free survival and overall survival were shown to be significantly improved with pembrolizumab plus chemotherapy with or without bevacizumab compared with placebo plus chemotherapy with or without bevacizumab in patients with persistent, recurrent, or metastatic cervical cancer.

Added value of this study

These results show that the previously reported significant improvements in overall survival and progression-free survival achieved with addition of pembrolizumab to chemotherapy with or without bevacizumab in the KEYNOTE-826 trial were not accompanied by a decrease in health-related quality of life (as assessed by a range of validated patient-reported outcome instruments) with this treatment regimen.

Implications of all the available evidence

These health-related quality of life data support the efficacy and safety findings from KEYNOTE-826 and provide further support for the use of pembrolizumab plus chemotherapy with or without bevacizumab as a new standard of care for patients with advanced cervical cancer.

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See Online for appendix

tissue available for determination of PD-L1 expression status; had not received previous treatment with systemic chemotherapy (previous radiotherapy, including chemo-radiotherapy, was permitted if it was completed at least 2 weeks before randomisation and all associated toxicities had resolved; a 1-week washout period was permitted for palliative radiotherapy to non-CNS lesions); and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. PD-L1 expression was assessed at a central laboratory with the use of PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA) according to the CPS, defined as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100. All patients were required to have adequate organ function as determined by haematological (absolute neutrophil count ≥1500 cells per µL, platelets ≥100 000 per µL, and haemoglobin ≥9 g/dL [≥5·6 mmol/L]), renal (creatinine ≤1·5 times the upper limit of normal [ULN] or creatinine clearance ≥60 mL/min if creatinine >1·5 times ULN), hepatic (serum total bilirubin ≤1·5 times ULN or direct bilirubin ≤ULN if total bilirubin >1·5 times ULN, aminotransferases ≤2·5 times ULN or ≤5 times ULN for patients with liver metastases), and coagulation (prothrombin time or activated partial thromboplastin time ≤1·5 times ULN or within the therapeutic range if receiving anticoagulant therapy) findings. Exclusion criteria included known active CNS metastases, carcinomatous meningitis, or both; additional malignancy that was progressing or required active treatment within the past 3 years; diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy (>10 mg/day prednisone equivalent) or any form of immunosuppressive therapy within the past 7 days; active autoimmune disease that required systemic treatment in the past 2 years (disease-modifying agents, corticosteroids, or immunosuppressive drugs); a history of (non-infectious) pneumonitis that required steroids or current pneumonitis; an active infection requiring systemic therapy; active tuberculosis; and a known history of HIV infection or hepatitis B virus infection or known active hepatitis C virus infection. The study protocol (appendix; and all its amendments) was approved by the appropriate ethics body at each study site. All patients provided written, informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) by means of an interactive response system to the pembrolizumab group or to the placebo group. The randomisation sequence (block size of 4) was generated by the sponsor using a schedule generation system and was stratified by metastatic disease at diagnosis (yes *vs* no), planned bevacizumab use (yes *vs* no), and PD-L1 CPS (<1 *vs* 1 to <10 *vs* ≥10).[14] This was a double-blind study. Participants, investigators, and other study personnel involved in the study treatment administration or clinical evaluation of patients were unaware of treatment group assignments and were not unmasked before analyses were complete Pembrolizumab and placebo were prepared in a masked fashion by an unmasked pharmacist.

Procedures

Patients received pembrolizumab 200 mg intravenously once every 3 weeks for up to 35 cycles; patients in the placebo group received placebo at the same schedule. All patients also received paclitaxel 175 mg/m² and cisplatin 50 mg/m² or carboplatin area under the concentration versus time curve (AUC) 5 mg/mL per min once every 3 weeks for six cycles. In consultation with the sponsor, chemotherapy could be continued for patients with ongoing clinical benefit without unacceptable adverse effects. Patients in both treatment groups could receive bevacizumab 15 mg/kg once every 3 weeks at the investigator's discretion with chemotherapy and during maintenance. Treatment was continued until the specified number of cycles had been administered or until disease progression, unacceptable toxicity, withdrawal of consent, or requirement for other treatment.[14] Individual trial agents could be interrupted or discontinued to manage toxicity at the investigator's discretion.

Site staff collected PROs from patients using an electronic tablet device at the beginning of each clinic visit and reported reasons for non-completion. Sites were contacted by the study sponsor in cases of missing PRO data. All questionnaires were made available in the local language and completed by patients before treatment was administered on a clinic visit on day 1 of cycles 1–14 and every other cycle thereafter, at the cessation of study treatment (ie, the timepoint at which patients discontinued all study treatment), and at the safety follow-up visit (ie, 30 days after the last dose of study treatment). The EuroQol-5 dimension-5 level (EQ-5D-5L) questionnaire was administered first, followed by the EORTC Quality-of-Life-Core 30 (QLQ-C30) and cervical cancer module (QLQ-CX24). An instrument was considered complete if at least one valid score was available according to the missing item rule (ie, requiring at least one item to be completed). Electronic tablet devices used in the study were set up such that patients were unable to skip individual items within a questionnaire.

Completion rates were defined as the number of patients completing at least one item of the specified questionnaire (QLQ-C30, EQ-5D-5L, or QLQ-CX24) divided by the total number of patients in the PRO population. Compliance rates were defined as the number of patients completing at least one item of the specified questionnaire divided by the total number of eligible patients expected to complete the instrument at the specific visit. Patients who were not expected to complete a questionnaire at a given timepoint were missing by design. Reasons for missing by design included patient discontinuation, death, translation being unavailable in patient's language, and no study visit scheduled.

The EORTC QLQ-C30 is a self-reported, 30-item, cancer-specific PRO instrument. It evaluates a total of 15 domains: five functional scales (physical, role, emotional, cognitive, and social functioning), nine symptom scales or single items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and global health status (GHS)–quality of life (QoL).[15] The EQ-5D-5L is a standardised measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. It comprises two separate elements: utility score and visual analogue scale (VAS).[16]

For QLQ-C30 GHS–QoL and functional scales, higher scores indicate higher (better) level of function. EQ-5D-5L VAS scores range from 0 (worst imaginable health state) to 100 (best imaginable health state). The QLQ-CX24 is a disease-specific questionnaire to address measurements specific to cervical cancer; higher QLQ-C30 and QLQ-CX24 symptom scores indicate increased (worse) severity of symptoms.[17]

Outcomes

The primary study endpoints were investigator-assessed progression-free survival per RECIST version 1.1 and overall survival.[14] Secondary efficacy endpoints were the objective response rate, duration of response, 12-month progression-free survival per RECIST version 1.1 by investigator, and progression-free survival per RECIST version 1.1 by masked independent central review. The incidence of adverse events in each treatment group was a secondary endpoint. Efficacy and safety outcomes have been previously reported.[14] The protocol-specified secondary PRO endpoint was the change in QLQ-C30 GHS–QoL score from baseline. Protocol-specified exploratory PRO endpoints were changes in patient-reported QoL assessed by the QLQ-C30 (other than the GHS–QoL; including the physical functioning scale [identified as of interest given the importance of physical functioning to the wellbeing of patients]), the EQ-5D-5L (including the VAS), and the EORTC QLQ-CX24 symptom scales.

Statistical analysis

Statistical methods for the primary analyses have been previously described.[14] The all-comer full analysis set for the PRO endpoints included all patients who received at least one dose of study treatment and completed at least one post-baseline PRO assessment (PRO full analysis population). In the present analysis, PRO results are reported for the all-comer population and the subset of patients in the PRO population with a PD-L1 CPS of at least 1; both these analyses were prespecified. CPS scores can be used to identify a population most likely to respond to pembrolizumab. Results from KEYNOTE-826 led to regulatory approval of pembrolizumab plus chemotherapy with or without bevacizumab in patients with advanced cervical cancer whose tumours express PD-L1 CPS of at least 1. PROs are not reported for the subset of patients in the PRO population with PD-L1 CPS of at least 10 because this analysis would not provide clinically relevant information and because all such patients are captured in the all-comer patient population and in the population of patients with a PD-L1 CPS of at least 1. No formal hypotheses were tested for PRO assessments. No alpha was assigned to the PRO analyses and all p values are nominal and are without adjustment for multiple comparisons. The primary timepoint for the PRO analysis was prespecified as the latest timepoint at which completion was approximately 60% and compliance was approximately 80% for both treatment groups. This approach was selected to allow flexibility in selecting a timepoint that maximised the follow-up period for assessment while simultaneously including a majority of patients in the analysis. A masked data review was done to determine the primary assessment timepoint. HRQoL assessments were consistent with that recommended by the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQOL) consortium.[18]

A constrained longitudinal data analysis (cLDA) model, as described by Liang and Zeger,[19] was used to assess the change in score from baseline (ie, cycle 1, day 1) to the primary PRO assessment timepoint for the QLQ-C30 GHS–QoL and physical functioning scale and the EQ-5D-5L VAS, with the PRO score as the response variable and treatment-by-study-visit and randomisation stratification factors as covariates (two-sided). For each questionnaire, the treatment difference in terms of least squares mean change from baseline was estimated from this model together with 95% CIs (calculated using Student's t distribution). Missing data were treated as missing at random. Line plots for empirical mean change (in contrast to the model-based mean estimated from the cLDA model) from baseline in PROs up to the final assessment timepoint were provided as a supportive analysis.

Time to true deterioration (TTD) in score for the QLQ-C30 GHS–QoL and physical functioning scales was defined as time from baseline to the first deterioration of at least 10 points in PRO score with confirmation by a second adjacent deterioration of at least 10 points or death.[20] TTD in score for the EQ-5D-5L VAS was defined as time from baseline to the first deterioration of at least 7 points in PRO score with confirmation by a second adjacent deterioration of at least 7 points or death. Kaplan-Meier analyses were used to estimate TTD curves for each treatment group and provide median (95% CI) TTD. Treatment differences in TTD were assessed by means of the stratified log-rank test. The magnitude of treatment difference was assessed by means of a stratified Cox proportional hazard model with the Efron method of tie handling (two-sided). Proportionality of hazards was evaluated by visual inspection of the Kaplan-Meier curves. The stratified Miettinen and Nurminen method

(one-sided) was used for comparison of the proportion of patients with improvement or improvement–stability between the two groups.

Overall improvement or stability in scores for QLQ-C30 GHS–QoL and physical functioning scales, EQ-5D-5L VAS, and QLQ-CX24 were assessed. For QLQ-C30 GHS–QoL and physical functioning scales and QLQ-CX24, an improved score was defined as at least a 10-point improvement in score at any time during the study, confirmed at the next visit; stable as a less than 10-point change in score at any time during the study, confirmed at the next visit; and deterioration as at least a 10-point worsening in score at any time during the study in patients not otherwise meeting criteria for improved or stable score. A 7-point change in score was used to define an improved or stable score on the EQ-5D-5L VAS.

SAS version 9.4 was used for all statistical analyses. This study is registered with ClinicalTrials.gov, NCT03635567.

Role of the funding source

The funder participated in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Nov 20, 2018, and Jan 31, 2020, 617 patients were randomly assigned (308 to the pembrolizumab group and 309 to the placebo group; figure 1). 548 (89%) of 617 patients had a PD-L1 CPS of at least 1 (pembrolizumab group, n=273; placebo group, n=275). As previously reported,[14] baseline characteristics were generally similar between the treatment groups (appendix pp 2–3). 138 (45%) of 308 patients in the pembrolizumab group and 119 (39%) of 309 in the placebo group recorded as non-White (65 [21%] and 45 [15%] were Asian). 110 (36%) patients in the pembrolizumab group and 121 (39%) in the placebo group were Hispanic. Median time from randomisation to data cutoff (May 3, 2021) was 22·0 months (IQR 19·1–24·4). 587 (95%) of 617 patients (290 in the pembrolizumab group and 297 in the placebo group) were included in the PRO analyses (ie, received at least one dose of study treatment and completed at least one post-baseline PRO assessment; figure 1). The all-comer PRO analysis population comprised 562 patients who completed at least one QLQ-C30 item, 566 patients who completed at least one EQ-5D-5L item, and 558 patients who completed at least one QLQ-CX24 item (appendix pp 4–6).

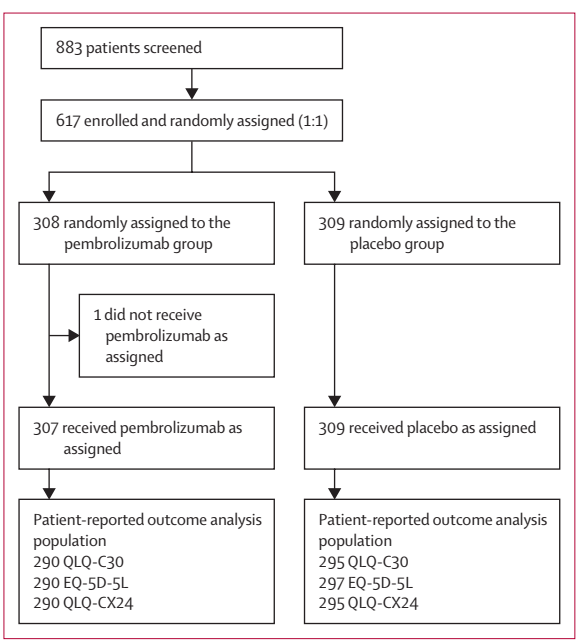

Figure 1: **Trial profile**
The patient-reported outcome analysis population included patients who have at least one patient-reported outcome assessment available and have received at least one dose of study medication. EQ-5D-5L=EuroQol 5-dimension 5-level questionnaire. QLQ-CX24=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Cervical Cancer. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

Compliance and completion rates with the QLQ-C30, EQ-5D-5L, and QLQ-CX24 instruments were at least 95% in both treatment groups at baseline (table; appendix pp 4–5). Completion rates decreased over time to 129 (44%) of 290 in the pembrolizumab group versus 100 (34%) of 297 in the placebo group at week 51 (ie, approximately 1 year) for the QLQ-C30, EQ-5D-5L, and QLQ-CX24 instruments (appendix pp 4–5). Compliance rates remained at least 85% in both treatment groups up to week 51 (appendix pp 4–5). Week 30 was selected as the primary PRO assessment timepoint for the analysis on the basis of completion (approximately 60%) and compliance (>80%) across both treatment groups (appendix p 4). At week 30, QLQ-C30 completion was 199 (69%) of 290 patients in the pembrolizumab group and 168 (57%) of 297 patients in the placebo group; compliance was 199 (94%) of 211 and 168 (90%) of 186, respectively.

Mean QLQ-C30 GHS–QoL change from baseline scores for the pembrolizumab group and for the placebo group are shown in figure 2A. Baseline mean QLQ-C30 GHS–QoL scores were 63·0 (SD 23·3) and 66·3 (21·9), respectively. In the assessment of the secondary endpoint, the least squares mean change in QLQ-C30 GHS–QoL score from baseline to week 30 (the primary PRO assessment timepoint) in the all-comers group was –0·3 points (95% CI –3·1 to 2·6) in the pembrolizumab group and –1·3 points (–4·2 to 1·7) in the placebo group; the between-group difference in least squares mean GHS–QoL score was 1·0 point (95% CI –2·7 to 4·7; p=0·60; table). In patients with PD-L1 CPS of at least 1, the least squares mean change in QLQ-C30 GHS–QoL score from baseline to week 30 was 0·6 points (95% CI –2·4 to 3·5) in the pembrolizumab group and –0·8 points (–3·9 to 2·4) in the placebo group

	QLQ-C30 GHS–QoL		QLQ-C30 physical functioning		EQ-5D-5L VAS	
	Pembrolizumab group	Placebo group	Pembrolizumab group	Placebo group	Pembrolizumab group	Placebo group
Baseline						
Completed questionnaire, n	279	283	279	283	281	285
Mean score (SD)	63·0 (23·3)	66·3 (21·9)	76·4 (23·0)	77·1 (20·9)	70·5 (21·3)	71·9 (20·2)
Week 30						
Completed questionnaire, n	199	168	199	168	200	168
Mean score (SD)	67·1 (21·4)	68·5 (18·5)	73·0 (23·5)	75·6 (20·4)	74·6 (19·4)	74·7 (18·9)
Change from baseline*						
Included in analysis, n	290	295	290	295	290	297
Least squares mean score (95% CI)	−0·3 (−3·1 to 2·6)	−1·3 (−4·2 to 1·7)	−8·3 (−11·1 to −5·5)	−6·1 (−9·0 to −3·2)	0·3 (−2·2 to 2·8)	−1·5 (−4·1 to 1·1)
Difference in least squares mean (95% CI) p value	1·0 (−2·7 to 4·7) p=0·60†	..	−2·1 (−6·0 to 1·8) p=0·28†	..	1·8 (−1·6 to 5·1) p=0·29†	..

EQ-5D-5L=EuroQol 5-dimension 5-level questionnaire. GHS–QoL=global health status–quality of life. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. VAS=visual analogue scale. *Based on a constrained longitudinal data analysis model with the patient-reported outcome score as the response variable and treatment-by-study-visit interaction and randomisation stratification factors as covariates. †p values are two-sided and nominal.

Table: **Mean changes from baseline in QLQ-C30 GHS–QoL score, QLQ-C30 physical functioning score, and EQ-5D-5L VAS**

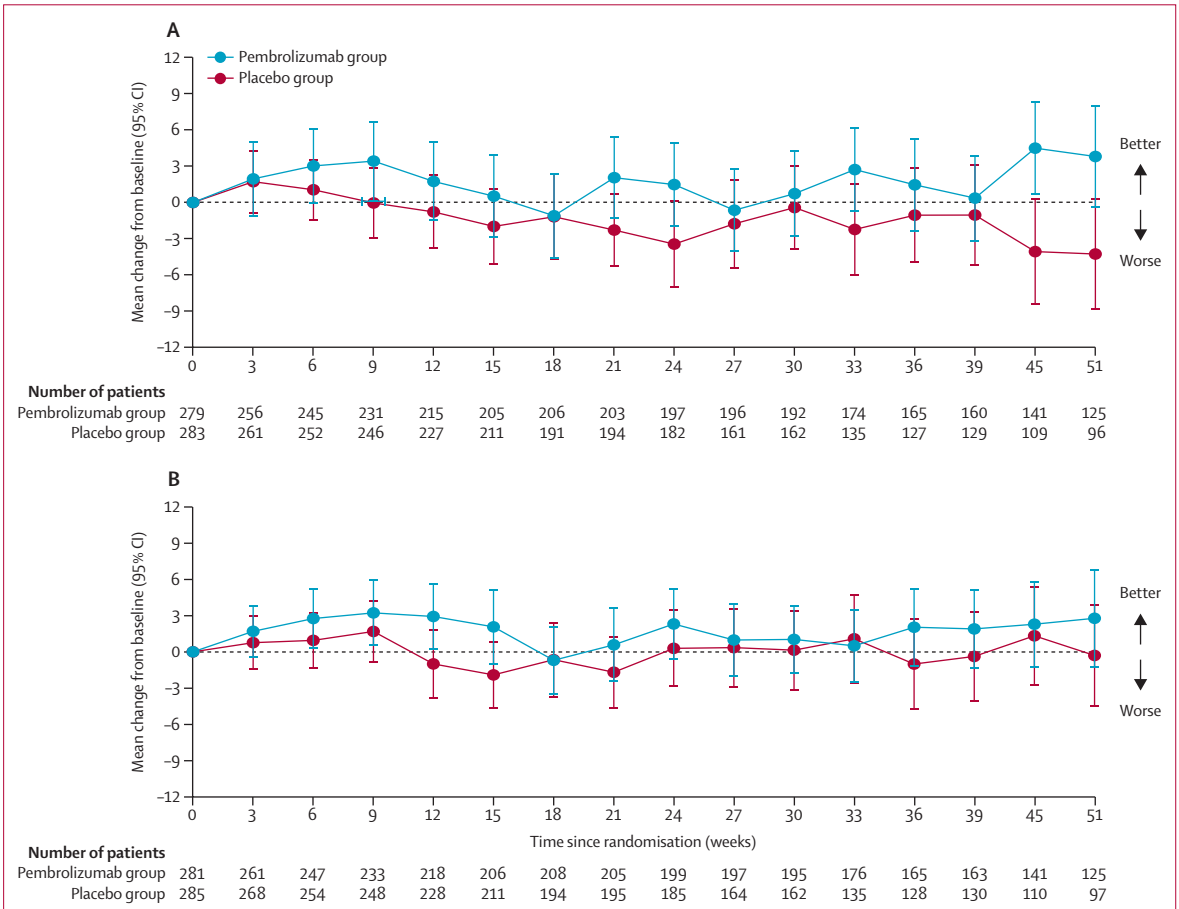

Figure 2: **Empirical mean (95% CI) change from baseline in PRO scores**
(A) QLQ-C30 GHS–QoL. (B) EuroQol 5-dimension 5-level visual analogue scale. GHS–QoL=global health status–quality of life. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

(between-group difference of 1·3 points [95% CI −2·6 to 5·2]; p=0·50; appendix p 10).

The least squares mean scores for QLQ-C30 physical, role, social, and cognitive functioning scales decreased (indicative of worse functioning) from baseline to week 30 in both treatment groups; emotional functioning scores improved in both treatment groups (figure 3A). There was no between-group difference in QLQ-C30 physical functioning scores at week 30 (table).

122 (42%) of 290 patients in the pembrolizumab group and 85 (29%) of 297 in the placebo group had improved QLQ-C30 GHS–QoL scores (defined as ≥10-point improvement in score at any time during the study, confirmed by next visit; p=0·0003); 104 (36%) and 140 (47%), respectively, had stable scores (defined as <10-point change in score at any time during the study, confirmed by next visit); and 44 (15%) and 48 (16%), respectively, had deteriorated scores (defined as ≥10-point worsening in score at any time during the study in patients not otherwise meeting criteria for improved or stable score); figure 3D). The overall improvement or stability rate for QLQ-C30 GHS–QoL was 226 (78%) of 290 in the pembrolizumab group and 225 (76%) of 297 in the placebo group (p=0·27).

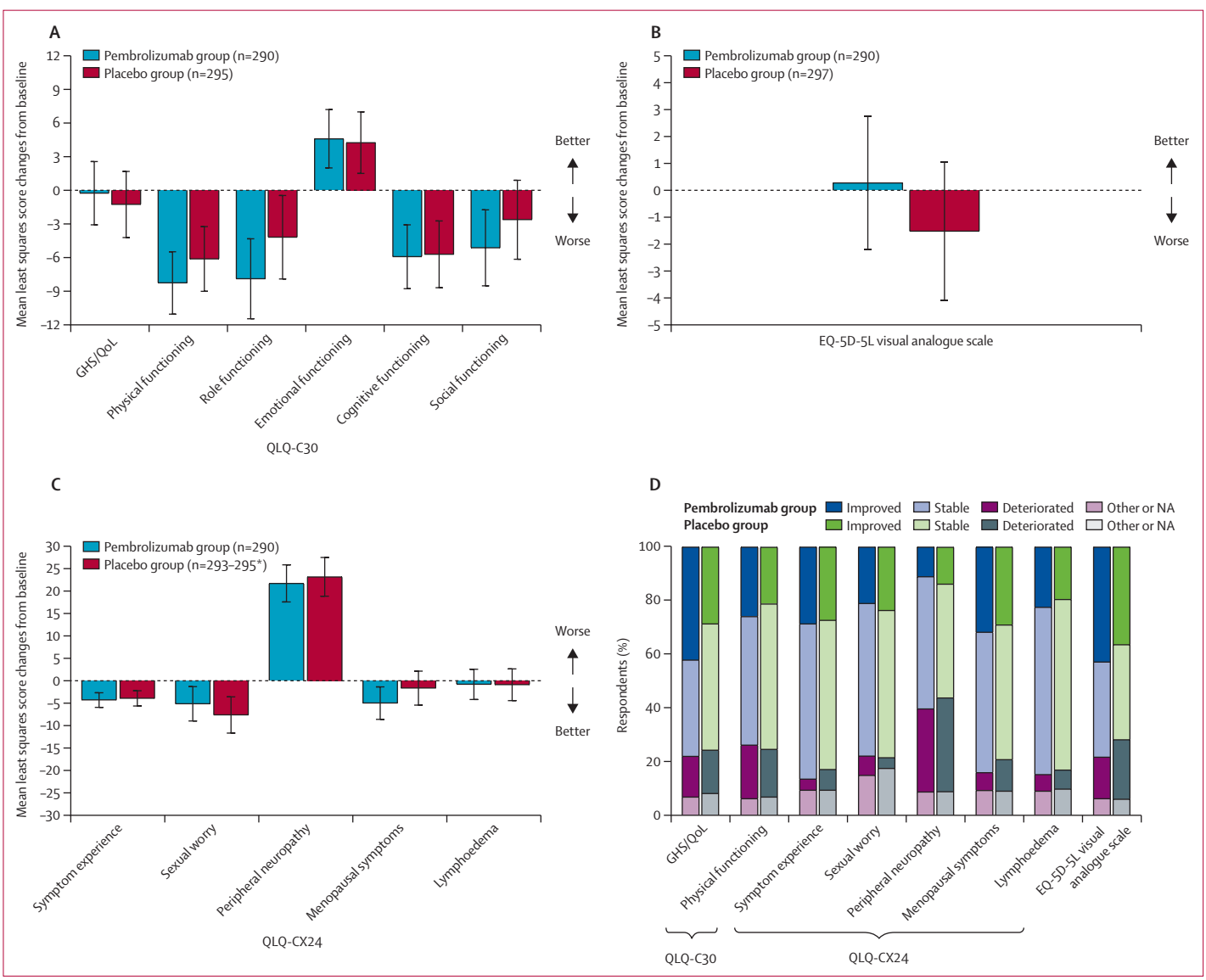

Figure 3: **Mean (95% CI) change from baseline to week 30 in PRO scores**
(A) QLQ-C30 GHS–QoL and functional scores (higher scores denote better HRQoL or function). (B) EQ-5D-5L visual analogue scale scores (higher scores denote better HRQoL). (C) QLQ-CX24 scores (higher scores denote worse symptom severity). (D) Proportions of patients with improved, stable, and deteriorated PROs based on best outcome at any time during the study. EQ-5D-5L=EuroQol 5-dimension 5-level questionnaire. GHS–QoL=global health status–quality of life. HRQoL=health-related quality of life. NA=no assessment. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. QLQ-CX24=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Cervical Cancer. *QLQ-CX24 cervical symptoms: n=295, with the exception of sexual worry (n=293).

For QLQ-C30 physical functioning, overall improvement or stability rate was 214 (74%) of 290 in the pembrolizumab group and 224 (75%) of 297 in the placebo group (p=0·67); 75 (26%) and 63 (21%) had improved QLQ-C30 physical functioning score (p=0·090), 139 (48%) and 161 (54%) had stable scores, and 58 (20%) and 53 (18%) patients had deteriorated scores, respectively (figure 3D).

Median TTD in QLQ-C30 GHS–QoL was not reached (NR; 95% CI 13·4 months–NR) in the pembrolizumab group and was 12·9 months (6·6–NR) in the placebo group (HR 0·84 [95% CI 0·65–1·09], p=0·19; figure 4A). Median TTD for QLQ-C30 physical functioning score was 8·9 months (95% CI 6·0–19·7) in the pembrolizumab group and 10·6 months (7·0–NR) in the placebo group (HR 1·11 [95% CI 0·87–1·42]; p=0·39; figure 4B).

During the study, EQ-5D-5L VAS scores were generally similar to baseline for both treatment groups up to week 51 (figure 2B). Baseline least squares mean EQ-5D-5L VAS scores were 70·5 (SD 21·3) in the pembrolizumab group and 71·9 (20·2) in the placebo group. The least squares mean change in EQ-5D-5L VAS score from baseline to week 30 was 0·3 points (95% CI –2·2 to 2·8) in the pembrolizumab group and –1·5 points (–4·1 to 1·1) in the placebo group. The least squares mean difference in scores between treatment groups was 1·8 points (95% CI –1·6 to 5·1; p=0·29; table; figure 3B).

Median TTD in EQ-5D-5L VAS was NR (95% CI 17·2 months–NR) in the pembrolizumab group and 7·7 months (6·0–NR) in the placebo group (HR 0·75 [95% CI 0·58–0·97], p=0·027; figure 4C).

The overall improvement or stability rate for EQ-5D-5L VAS scores was 227 (78%) of 290 in the pembrolizumab group and 213 (72%) of 297 in the placebo group (p=0·033); 124 (43%) of 290 patients in the pembrolizumab group and 108 (36%) of 297 in the placebo group had improved scores (defined as ≥7-point improvement in score at any time during the study, confirmed by next visit; p=0·058), 103 (36%) and 105 (35%), respectively, had stable scores (defined as <7-point change in score at any time during the study, confirmed by next visit) and 45 (16%) and 66 (22%), respectively, had deteriorated scores (defined as ≥7-point worsening in score at any time during the study in patients not otherwise meeting criteria for improved or stable score; figure 3D).

The changes from baseline to week 30 for QLQ-CX24 subscale scores are shown in figure 3C. Scores for QLQ-CX24 subscales either decreased (indicative of improved symptoms) or were unchanged from baseline to week 30 in both treatment groups, with the exception of the QLQ-CX24 score for peripheral neuropathy, which increased from baseline to week 30 in both treatment groups.

The improvement or stability rates for QLQ-CX24 subscales were generally similar between the treatment groups. A slightly higher proportion of patients in the pembrolizumab group had improved scores versus the placebo group for the QLQ-CX24 cervical symptoms of lymphoedema, menopausal symptoms, and symptom experience, whereas more patients in the placebo group

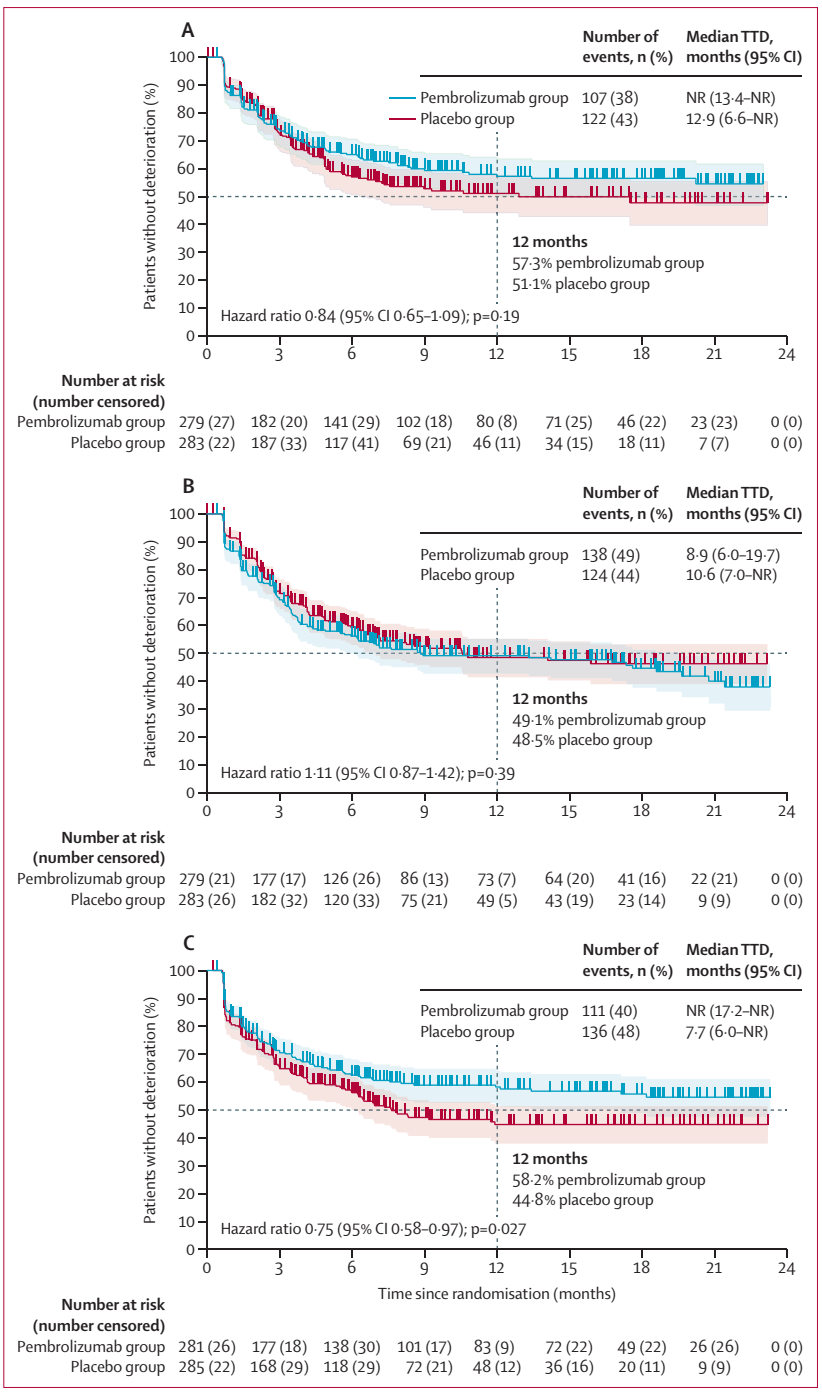

Figure 4: **Kaplan-Meier estimates of time to true deterioration in PRO scores**
(A) QLQ-C30 GHS–QoL. (B) QLQ-C30 physical functioning. (C) EuroQol-5 dimension-5 level visual analogue scale. p values are 2-sided and nominal. The shaded area indicates 95% CI for each group. GHS–QoL=global health status–quality of life. NR=not reached. QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. TTD=time to true deterioration.

had deteriorated scores across most QLQ-CX24 subscales (figure 3D).

Complete PRO results for the population of patients with a PD-L1 CPS of at least 1 are presented in the appendix (pp 7–11, 18–24) and were generally similar to those for patients in the all-comers population.

Discussion

In this Article, we show that the significant improvements in overall survival and progression-free survival with addition of pembrolizumab to the standard-of-care reported in the efficacy analysis of KEYNOTE-826 were not accompanied by deterioration in HRQoL compared with placebo in the all-comer (ie, intention-to-treat) population and in patients with PD-L1 CPS of at least 1. Overall, findings from this PRO analysis provide further support for the use of pembrolizumab plus chemotherapy with or without bevacizumab as a new standard-of-care for persistent, recurrent, or metastatic cervical cancer. Notably, the diversity of patients enrolled in KEYNOTE-826 is unprecedented in such a pivotal, practice-changing study, with more than a third of enrolled patients being non-White. Pembrolizumab plus chemotherapy with or without bevacizumab was approved by the US Food and Drug Administration on Oct 13, 2021, for the treatment of patients with advanced cervical cancer whose tumours express PD-L1 CPS of at least 1 on the basis of results from the KEYNOTE-826 study.[21]

Although there were minimal changes in QLQ-C30 GHS–QoL scores from baseline to week 30 in both treatment groups, and no between-group difference, mean QLQ-C30 GHS–QoL scores typically favoured the pembrolizumab group versus the placebo group over the course of the study. There was little evidence of between-group differences in QLQ-C30 physical functioning scores, EQ-5D-5L VAS scores, and QLQ-CX24 subscale scores. As previously reported,[14] TTD in EQ-5D-5L VAS scores was longer in the pembrolizumab group than in the placebo group. TTD in QLQ-C30 GHS–QoL scores was not significantly longer in the pembrolizumab group than in the placebo group; however, there was a separation in the Kaplan-Meier curves beginning at approximately 4 months, and the curves remained separated during the study. All patients in the study received platinum–paclitaxel chemotherapy with optional bevacizumab; toxicity associated with these agents might have attenuated any improvements in PROs among patients in the pembrolizumab group.

Findings from the analysis of the overall improvement, stability, or deterioration in PRO scores showed that more patients had improved QLQ-C30 GHS–QoL in the pembrolizumab group than in the placebo group. Consistent with this finding, a slightly higher proportion of patients in the pembrolizumab group had improved EQ-5D-5L VAS scores compared with the placebo group, and fewer patients had deteriorated scores.

Patients with cervical cancer have reported deterioration in symptoms, including sexual dysfunction or sexual worry, leg swelling, menopausal symptoms, and peripheral neuropathy, after anticancer treatments.[1–4,6] Results from the current analysis showed that mean scores for the QLQ-CX24 subscales of most cervical symptoms (including the symptoms of lymphoedema, which typically manifests as leg swelling; menopausal symptoms; and symptom experience) were improved or unchanged from baseline in both treatment groups, with the exception of peripheral neuropathy, which worsened in both treatment groups. The worsened scores for peripheral neuropathy were not unanticipated given the platinum–paclitaxel chemotherapy regimen used.[22]

These PRO findings provide important context for the assessment of safety data from the KEYNOTE-826 study and inform the patient experience.[14] Although the incidence of adverse events (particularly immune-mediated adverse events) was higher in the pembrolizumab group than in the placebo group in the primary analysis,[14] findings from the current analysis indicate this did not appear to have a meaningful effect on HRQoL. The longer time to disease progression in the pembrolizumab group versus the placebo group might have contributed to the reported HRQoL outcomes despite increased toxicity.

The findings from the current analysis are consistent with those in the GOG-240 study, in which HRQoL was not impaired by the addition of bevacizumab to chemotherapy in patients with advanced cervical cancer, as assessed by the Functional Assessment of Cancer Therapy (FACT)–Cervix Trial Outcome Index, the FACT–GOG Neurotoxicity four-item subscale, and the Brief Pain Inventory single item assessing worst pain in the past 24 h.[13] Although cross-study comparisons are challenging (particularly given the different PRO instruments used), results from the GOG-240 study and from KEYNOTE-826 suggest that the addition of the biological agents pembrolizumab and bevacizumab to platinum-based chemotherapy does not worsen HRQoL in patients with cervical cancer. The phase 3 EMPOWER-Cervical 1–GOG-3016–ENGOT-cx9 study found that the QLQ-C30 GHS–QoL score did not worsen following treatment with cemiplimab but did with chemotherapy in patients with recurrent or metastatic cervical cancer who had disease progression after first-line chemotherapy.[23] Furthermore, consistent with our results, HRQoL was not decreased in patients with treated versus untreated cervical cancer in a real-world setting involving five European countries.[24]

This study has some limitations. Because PRO assessments were collected up to the 30-day safety follow-up visit after discontinuation of treatment, it was not possible for us to evaluate HRQoL after cessation of treatment. The selection of timepoints at which PROs were collected enabled us to evaluate the influence of the study treatments on patients' self-reported assessment of their own HRQoL, and were selected to coincide

with efficacy and safety assessment in order to be less burdensome for patients. Furthermore, the timing of longitudinal PRO analyses was selected on the basis of a predefined rule to limit the level of intermittent and monotone missingness. Notably, compliance remained high over the course of the study at 85% or higher. Furthermore, changes in HRQoL might have been of a magnitude too small to detect with the PRO instruments used. However, we were able to detect deterioration in PRO scores from baseline, suggesting that the PRO instruments used were sufficiently sensitive to evaluate changes. Moreover, the findings from our analysis showed that PRO outcomes were generally consistent when assessed by a range of validated PRO instruments (QLQ-C30, EQ-5D-5L, and QLQ-CX24). QLQ-C30 and EQ-5D-5L are extensively used HRQoL instruments in cancer.[15,16] QLQ-CX24 is validated to address measurements specific to cervical cancer[17] and is the most commonly used instrument in cervical cancer trials; QLQ-CX24 is frequently administered in addition to QLQ-C30 in cervical cancer trials.[25] The HRQoL instruments used in the current analysis were not developed for assessment of outcomes in patients receiving immune checkpoint inhibitors. As such, it is possible that the effect of certain toxicities on PROs might not be fully captured.

In conclusion, the addition of pembrolizumab to chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer did not negatively affect HRQoL. Along with the efficacy and safety observed in KEYNOTE-826, these HRQoL data support the benefit of pembrolizumab and the value of immunotherapy in a diverse population of women diagnosed with persistent, recurrent, or metastatic cervical cancer.

Contributors

AA, BJM, KL, KST, MJM, and CT conceived, designed, and planned the study. AA, AMN, BJM, DL, CD, EY, KL, KH, KST, MG, MJM, MOHdM, NC, PS, RS-F, MVC, VS, VC, and CT acquired, analysed, and interpreted the data. BJM, DL, CD, EY, MOHdM, and RS-F provided the study materials and patients. BJM drafted the manuscript. All authors participated in critically reviewing and revising the manuscript and approved the manuscript for submission; are accountable for all aspects of the work; and accessed and verified the data reported in the article.

Declaration of interests

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Data sharing

Merck Sharp & Dohme, a subsidiary of Merck, Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of doing legitimate scientific research. Merck Sharp & Dohme 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 Merck Sharp & Dohme data sharing website outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of Merck Sharp & Dohme subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with Merck Sharp & Dohme before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that might prevent Merck Sharp & Dohme from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and Merck Sharp & Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp & Dohme will either do the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can do the proposed analyses.

For the **data sharing website** see http://engagezone.msd.com/ds_documentation.php

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