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Original Research

Adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma: Health-related quality of life from the randomized phase 3 KEYNOTE-716 study



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KEYWORDS

Melanoma;
Adjuvant;
Immunotherapy;
Pembrolizumab;
Patient-reported
outcomes

Abstract Background: Adjuvant pembrolizumab significantly improved recurrence-free survival (RFS) versus placebo in resected stage IIB and IIC melanoma in the phase 3 KEYNOTE-716 study. Health-related quality of life (HRQoL) results are reported.

Methods: Patients were randomly assigned 1:1 to pembrolizumab 200 mg (2 mg/kg, patients ≥ 12 to < 18 years) Q3W or placebo for ≤ 17 cycles or until disease recurrence, unacceptable toxicity, or withdrawal. Change from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) was a prespecified exploratory end point. Change in EORTC QLQ-C30 functioning, symptom, and single-item scales, and EQ-5D-5L visual analog scale (VAS) were also summarized. Primary analyses were performed at week 48 to ensure adequate completion/compliance. The HRQoL population comprised patients who received ≥ 1 dose of treatment and completed ≥ 1 assessment.

Results: The HRQoL population included 969 patients (pembrolizumab, $n = 483$; placebo, $n = 486$). Compliance at week 48 was $\geq 80\%$ for both instruments. EORTC QLQ-C30 GHS/QoL, physical functioning, role functioning, and EQ-5D-5L VAS scores were stable from baseline to week 48 in both arms, with no clinically meaningful decline observed. Scores did not differ significantly between pembrolizumab and placebo. EORTC QLQ-C30 GHS/QoL, physical functioning, role functioning, and EQ-5D-5L VAS scores remained stable through week 96 in both arms.

Conclusions: HRQoL was stable with adjuvant pembrolizumab, with no clinically meaningful decline observed. Change from baseline in HRQoL was similar between arms. These results, in conjunction with the improved RFS and manageable safety previously reported, support the use of adjuvant pembrolizumab for high-risk stage II melanoma.

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1. Introduction

The phase 3 KEYNOTE-716 study investigated adjuvant pembrolizumab in patients aged ≥ 12 years with completely resected stage IIB or IIC melanoma [1]. The first interim analysis (IA) (median follow-up, 14.4 months) showed that adjuvant pembrolizumab significantly reduced the risk of recurrence or death compared with placebo (hazard ratio [HR], 0.65 [95% CI, 0.46–0.92]; $p = 0.0066$) [1]. Recurrence-free survival (RFS) results were consistent at second IA (median follow-up, 20.9 months; HR, 0.61 [95% CI, 0.45–0.82]), and there was a two-fold reduction in the rate of distant metastases as a first recurrence (6% pembrolizumab vs. 12% placebo) [1]. At the first IA, treatment-related adverse events (AEs) occurred in 80% of patients in the pembrolizumab arm versus 60.9% in the placebo arm, and immune-mediated AEs and infusion reactions occurred in 36.2% and 8.4% of patients, respectively [1]. Safety at second IA remained consistent, with few additional events observed [1]. Pembrolizumab was considered to have manageable safety, with most immune-mediated AEs managed using hormone replacement therapy [1]. These results led to the approval of pembrolizumab by the US Food and Drug Administration for the adjuvant treatment of adult and paediatric (age ≥ 12 years) patients with stage IIB or IIC melanoma following complete resection, and

the subsequent inclusion of adjuvant pembrolizumab as an option for patients with pathologically staged IIB or IIC melanoma in treatment guidelines [2,3]. Although results of the KEYNOTE-716 study showed that adjuvant pembrolizumab is effective in high-risk stage II melanoma, it is important to ensure adjuvant therapies do not negatively impact health-related quality of life (HRQoL), because some patients may be cured by surgery alone [4]. We report the results of the HRQoL analysis of KEYNOTE-716.

2. Materials and methods

2.1. Study design and patients

KEYNOTE-716 (NCT03553836) is a randomized, double-blind, and phase 3 trial investigating adjuvant pembrolizumab versus placebo in surgically resected, high-risk, stage II melanoma ([Supplementary methods](#)) [1].

2.2. HRQoL instruments and assessments

HRQoL was assessed using the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Euro-QoL five dimension and five level (EQ-5D-5L) instruments ([Supplementary methods](#)). These were completed electronically at baseline; cycles 5, 9, 13, and

17 during year 1; every 12 weeks during year 2; and every 6 months during year 3. HRQoL assessments were completed regardless of disease recurrence or progression status, AEs, or treatment completion, unless the patient had withdrawn from that portion of the study. EORTC QLQ-C30 was administered only to adults because it is not validated in paediatric populations. EQ-5D-5L was administered to all patients.

Compliance was defined as the proportion of patients who completed an assessment among those who were expected to complete the assessment at a given timepoint. Patients missing by design (i.e. those who had not completed the questionnaire because of death, translation not being available, visit not being reached, or visit not being scheduled) or patients who withdrew from the trial were not included in the denominator for compliance. Completion was defined as the proportion of patients who completed the HRQoL assessment at a given timepoint among all patients in the HRQoL analysis population.

2.3. End points

The primary end point was RFS, as reported previously [1]. HRQoL assessments were evaluated during and after the adjuvant treatment period (17 cycles; ~1 year). Change from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) score was included as a prespecified exploratory end point. Changes from baseline in EORTC QLQ-C30 functioning, symptom, and single-item scores, and EQ-5D-5L visual analog scale (VAS) were also summarized. Change from baseline in these measures was evaluated at a single, postbaseline timepoint based on a prespecified rule requiring minimum completion of ~60% and compliance of ~80% to ensure data quality. Changes from baseline in EORTC QLQ-C30 GHS/QoL, physical functioning, role functioning, and EQ-5D-5L VAS scores were also evaluated descriptively over time using all available data through month 30 (~130 weeks).

A responder analysis was conducted for EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning scales. Using all available data, individual scores at each visit were used to categorize patients according to the change in EORTC QLQ-C30 scores. A clinically meaningful improvement was defined as a ≥ 10 -point increase from baseline at any time during the study, confirmed by a ≥ 10 -point increase at a visit scheduled ≥ 6 weeks later. Stability was defined by a < 10 -point decrease in score from baseline at any time during the study confirmed by a < 10 -point decrease at a visit scheduled ≥ 6 weeks later, when criteria for improvement were not met. Deterioration was defined as a > 10 -point decrease in score from baseline at any time during the study where the criteria for improvement or stability were not met.

2.4. Statistical analysis

The HRQoL analysis population included all patients who received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL assessment. Change in least squares mean (LSM) from baseline to a postbaseline timepoint in EORTC QLQ-C30 GHS/QoL, physical and role functioning scores, and EQ-5D-5L VAS score was assessed using a constrained longitudinal data analysis model, with patient-reported outcome scores as the response variable and treatment by time interaction and the randomization T-stage stratification factor as covariates. For the responder analysis, the proportion of patients with improved, stable, or deteriorated EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning scores was assessed using the binomial exact method; between-group differences in the proportion of patients with improved or non-deteriorated scores (i.e. improved or stable) were evaluated using the stratified Miettinen and Nurminen method. All other HRQoL analyses were descriptive. No alpha was allocated for these analyses. In this analysis, p values are nominal; no adjustment was made for multiplicity. The data cutoff was June 21, 2021 (second IA).

3. Results

3.1. Patient disposition and baseline characteristics

Between September 23, 2018, and November 4, 2020, 976 patients were randomly assigned to pembrolizumab ($n = 487$) or placebo ($n = 489$). Of those patients, 969 were included in the HRQoL analysis population (pembrolizumab, $n = 483$; placebo, $n = 486$) (Fig. 1). The median time from randomization to data cutoff in the HRQoL population was 20.9 months (range, 8.0–33.0). Baseline characteristics were balanced between treatment arms (Table S1). The median age was 60.0 years in the pembrolizumab arm and 61.0 years in the placebo arm; 38.1% and 39.3% of patients were ≥ 65 years old, respectively. Most patients had an Eastern Cooperative Oncology Group performance status of 0 (93.2% pembrolizumab; 92.4% placebo) and stage IIB disease (63.4% pembrolizumab; 65.0% placebo).

Baseline mean scores for EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning were similar for pembrolizumab and placebo (Table 1), as were baseline mean scores for the EQ-5D-5L VAS (Table 2).

3.2. Completion and compliance

At baseline, EORTC QLQ-C30 compliance rates were 93.2% (449/482) for pembrolizumab and 95.0% (459/483) for placebo, and completion rates were 93.0% (449/483) and 94.4% (459/486), respectively (Table S2). EQ-

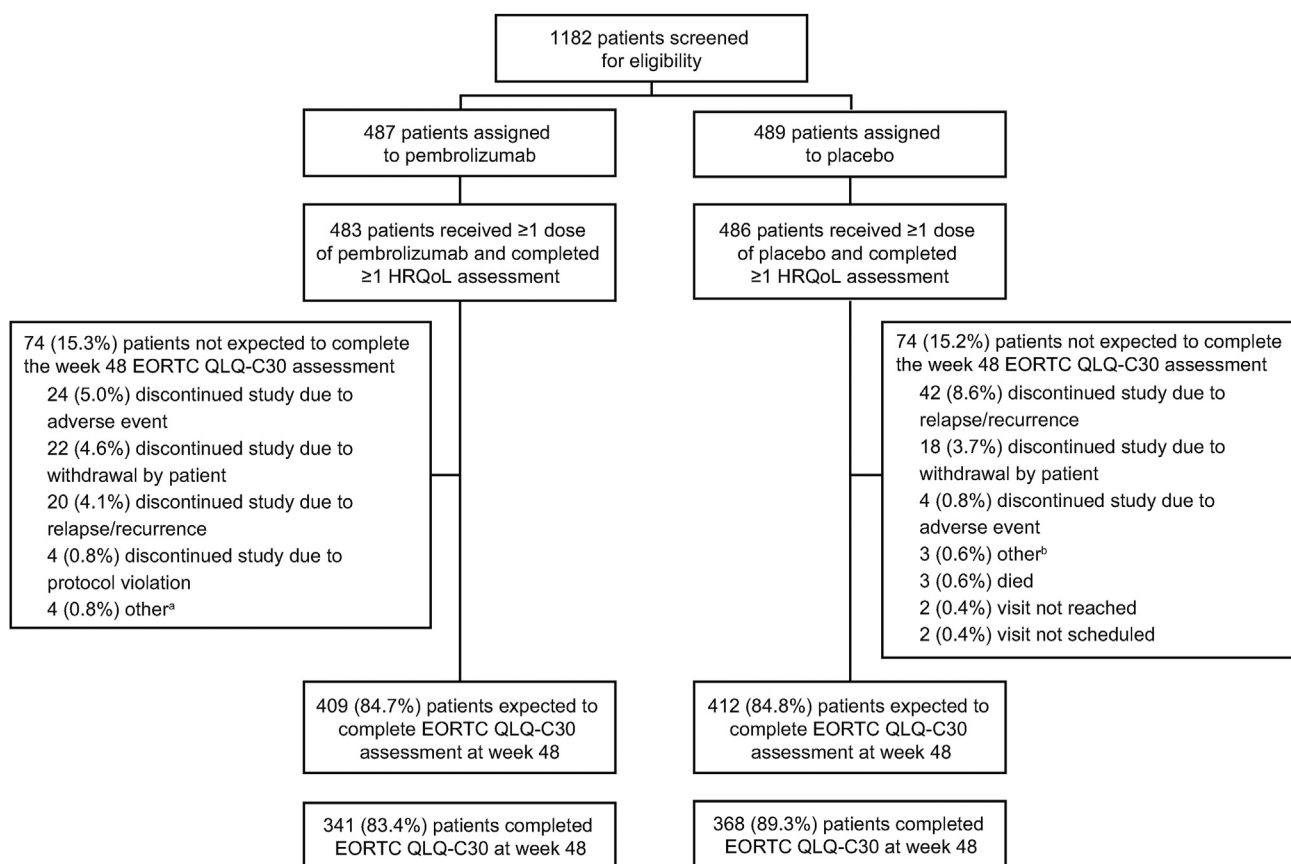


Fig. 1. **Patient disposition: EORTC QLQ-C30.** Abbreviations: EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; HRQoL, health-related quality of life. ^aOther included translation unavailable, discontinued study because of physician decision, visit not reached, and visit not scheduled (all $n = 1$). ^bOther included translation unavailable, lost to follow-up, and discontinued study because of protocol violation (all $n = 1$).

5D-5L compliance rates at baseline were 94.6% (456/482) for pembrolizumab and 96.5% (466/483) for placebo, and completion rates were 94.4% (456/483) and 95.9% (466/486), respectively (Table S3). Week 48 was the latest timepoint that met the prespecified compliance and completion requirements (compliance, ~80%; completion, ~60%). At week 48, EORTC QLQ-C30 compliance rates were 83.4% (341/409) for pembrolizumab and 89.3% (368/412) for placebo, and completion rates were 70.6% (341/483) and 75.7% (368/486), respectively (Table S2 and Fig. 1). At week 48, EQ-5D-5L compliance rates were 84.1% (344/409) for pembrolizumab and 90.0% (371/412) for placebo, and completion rates were 71.2% (344/483) and 76.3% (371/486), respectively (Table S3 and Fig. S1). At month 30, few patients (~5%) were expected to complete the HRQoL assessments due to data maturity.

3.3. Change from baseline in patient-reported HRQoL scores

EORTC QLQ-C30 GHS/QoL, physical and role functioning, and EQ-5D-5L VAS scores remained stable, with no clinically meaningful declines observed at week

48 relative to baseline in either arm (Tables 1 and 2). Although nominal p values of <0.05 for comparison between arms were reported for some scales, the differences in LSM scores between arms did not meet the threshold for a clinically meaningful difference. The LSM change from baseline to week 48 in EORTC QLQ-C30 GHS/QoL scores was -4.49 (95% CI, -6.19 to -2.79) for pembrolizumab and -0.82 (95% CI, -2.47 to 0.83) for placebo (LSM difference, -3.67 [95% CI, -5.91 to -1.44]; nominal two-sided $p = 0.0013$) (Table 1). The LSM change from baseline to week 48 in EORTC QLQ-C30 physical functioning scores was -3.27 (95% CI, -4.61 to -1.92) for pembrolizumab and -1.77 (95% CI, -3.07 to -0.46) for placebo (LSM difference, -1.50 [95% CI, -3.33 to 0.32]; nominal two-sided $p = 0.1069$) (Table 1). The LSM change from baseline to week 48 in EORTC QLQ-C30 role functioning scores was -2.94 (95% CI, -5.03 to -0.85) for pembrolizumab and -0.06 (95% CI, -2.08 to 1.96) for placebo (LSM difference, -2.88 [95% CI, -5.57 to -0.18]; nominal two-sided $p = 0.0365$) (Table 1). Patients in both treatment arms also had stable scores in all other EORTC QLQ-C30 functioning, symptom, and single-item scales at week 48 relative to baseline (Fig. 2).

Table 1

Change from baseline to week 48 in EORTC QLQ-C30 scores.

	Pembrolizumab <i>n</i> = 483	Placebo <i>n</i> = 486
GHS/QoL		
Baseline, mean (SD)	81.94 (16.15)	80.97 (15.99)
<i>n</i> ^a	449	459
Week 48, mean (SD)	77.93 (18.46)	80.98 (16.01)
<i>n</i> ^a	341	368
Change from baseline to week 48, LSM (95% CI) ^b	−4.49 (−6.19 to −2.79)	−0.82 (−2.47 to 0.83)
<i>n</i> ^a	480	484
Difference in LSM (95% CI) ^b		−3.67 (−5.91 to −1.44)
Nominal two-sided <i>p</i> value ^{b,c}		0.0013
Physical functioning		
Baseline, mean (SD)	92.00 (12.47)	91.72 (13.78)
<i>n</i> ^a	449	459
Week 48, mean (SD)	89.40 (15.40)	90.78 (15.26)
<i>n</i> ^a	341	368
Change from baseline to week 48, LSM (95% CI) ^b	−3.27 (−4.61 to −1.92)	−1.77 (−3.07 to −0.46)
<i>n</i> ^a	480	484
Difference in LSM (95% CI) ^b		−1.50 (−3.33 to 0.32)
Nominal two-sided <i>p</i> value ^{b,c}		0.1069
Role functioning		
Baseline, mean (SD)	90.53 (18.97)	88.96 (20.91)
<i>n</i> ^a	449	459
Week 48, mean (SD)	87.19 (20.66)	89.58 (19.46)
<i>n</i> ^a	341	368
Change from baseline to week 48, LSM (95% CI) ^b	−2.94 (−5.03 to −0.85)	−0.06 (−2.08 to 1.96)
<i>n</i> ^a	473	477
Difference in LSM (95% CI) ^b		−2.88 (−5.57 to −0.18)
Nominal two-sided <i>p</i> value ^{b,c}		0.0365

Abbreviations: CI, confidence interval; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; GHS, global health status; LSM, least squares mean; QoL, quality of life; SD, standard deviation.

^a For baseline and week 48, *n* is the number of patients in each treatment group with non-missing assessments at the specific timepoint; for change from baseline, *n* is the number of subjects in the analysis population in each treatment group.

^b Based on a constrained longitudinal data analysis model with the patient-reported outcome scores as the response variable, with treatment by time interaction and T stage (IIB T3b > 2.0–4.0 mm with ulceration versus IIB T4a > 4.0 mm without ulceration versus IIC T4b > 4.0 mm with ulceration) as covariates.

^c No alpha was allocated for this analysis. Two-sided *p* values are nominal, and no adjustment was made for multiplicity.

The LSM change from baseline to week 48 in EQ-5D-5L VAS scores was −2.19 (95% CI, −3.52 to −0.85) for pembrolizumab and −0.25 (95% CI, −1.54 to 1.04) for placebo (LSM difference, −1.94 [95% CI, −3.72 to −0.16]; nominal *p* = 0.0326) (Table 2).

In the responder analysis, the proportion of patients with nondeteriorated EORTC QLQ-C30 GHS/QoL scores over all available data was 68.5% (95% CI, 64.2%–72.7%) in the pembrolizumab arm and 76.3% (95% CI, 73.2%–80.0%) in the placebo arm (difference, −7.8% [95% CI, −13.4% to −2.2%]; nominal one-sided *p* = 0.9967) (Table S4). The proportion of patients with nondeteriorated EORTC QLQ-C30 physical functioning scores was 75.2% (95% CI, 71.1%–78.9%) in the pembrolizumab arm and 81.9% (95% CI, 78.2%–85.2%) in the placebo arm (difference, −6.7% [95% CI, −11.9% to −1.6%]; nominal one-sided *p* = 0.9946) (Table S5). The proportion of patients with nondeteriorated EORTC QLQ-C30 role functioning scores was 71.2% (95% CI, 67.0%–75.2%) in the pembrolizumab arm and 80.5% (95% CI, 76.6%–83.9%) in the placebo arm (difference, −9.2% [95% CI, −14.6% to −3.9%]; nominal one-sided *p* = 0.9996) (Table S6).

Table 2

Change from baseline to week 48 in EQ-5D-5L VAS scores.

	Pembrolizumab <i>n</i> = 483	Placebo <i>n</i> = 486
Baseline, mean (SD)	84.28 (12.88)	84.84 (12.75)
<i>n</i> ^a	456	466
Week 48, mean (SD)	82.76 (14.93)	84.98 (13.43)
<i>n</i> ^a	344	371
Change from baseline to week 48, LSM (95% CI) ^b	−2.19 (−3.52 to −0.85)	−0.25 (−1.54 to 1.04)
<i>n</i> ^a	483	486
Difference in LSM (95% CI) ^b		−1.94 (−3.72 to −0.16)
Nominal two-sided <i>p</i> value ^{b,c}		0.0326

Abbreviations: CI, confidence interval; LSM, least squares mean; SD, standard deviation; VAS, visual analog scale.

^a For baseline and week 48, *n* is the number of patients in each treatment group with non-missing assessments at the specific timepoint; for change from baseline, *n* is the number of subjects in the analysis population in each treatment group.

^b Based on a constrained longitudinal data analysis model with the patient-reported outcome scores as the response variable with treatment by time interaction and T stage (IIB T3b > 2.0–4.0 mm with ulceration versus IIB T4a > 4.0 mm without ulceration versus IIC T4b > 4.0 mm with ulceration) as covariates.

^c No alpha was allocated for this analysis. Two-sided *p* values are nominal, and no adjustment was made for multiplicity.

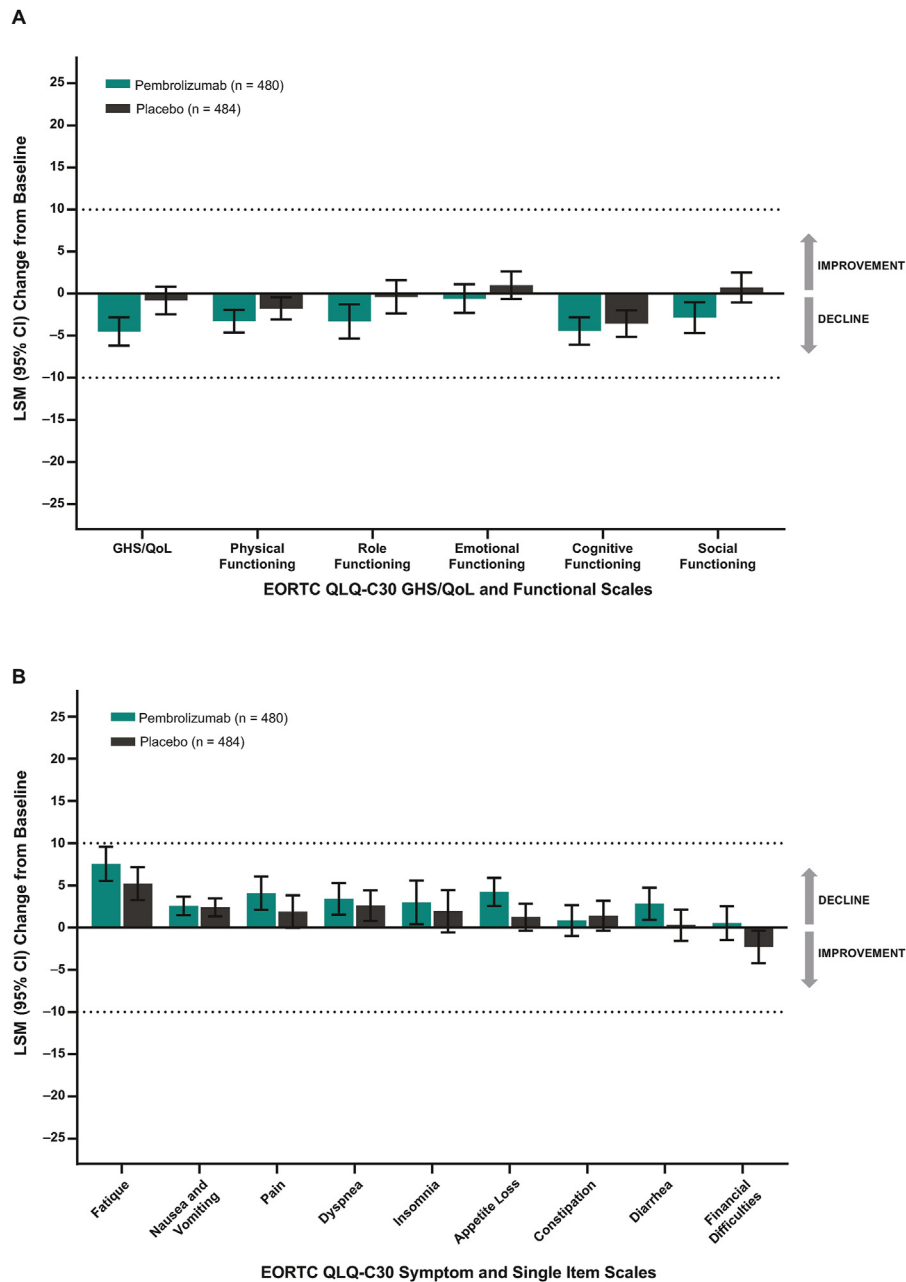


Fig. 2. LSM change from baseline to week 48 in EORTC QLQ-C30 (A) GHS/QoL and functional scales and (B) symptom and single-item scales. Abbreviations: CI, confidence interval; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; GHS, global health status; LSM, least squares mean; QoL, quality of life. Dotted lines indicate clinically meaningful difference (≥ 10 -point change from baseline for EORTC QLQ-C30 scales).

Descriptive analysis of EORTC QLQ-C30 GHS/QoL, physical and role functioning, and EQ-5D-5L VAS over time showed scores remained stable through week 96 in both treatment arms (Fig. 3A–D).

4. Discussion

Patients with stage IIB and IIC melanoma are at high risk of recurrence; however, until recently, adjuvant treatment was not recommended, and the standard of care was resection and observation [5]. The findings of KEYNOTE-

716 are the first reported from a large randomized clinical trial investigating a PD-1 inhibitor in high-risk stage II melanoma. Results of prespecified IAs showed that pembrolizumab significantly improved RFS and distant metastasis-free survival compared with placebo and had manageable safety in patients with stage IIB or IIC melanoma [1,6]. Consequently, adjuvant pembrolizumab is now recommended in treatment guidelines for pathologically staged IIB and IIC disease [3]. The findings of this exploratory analysis showed that pembrolizumab did not result in a clinically meaningful decline in HRQoL relative

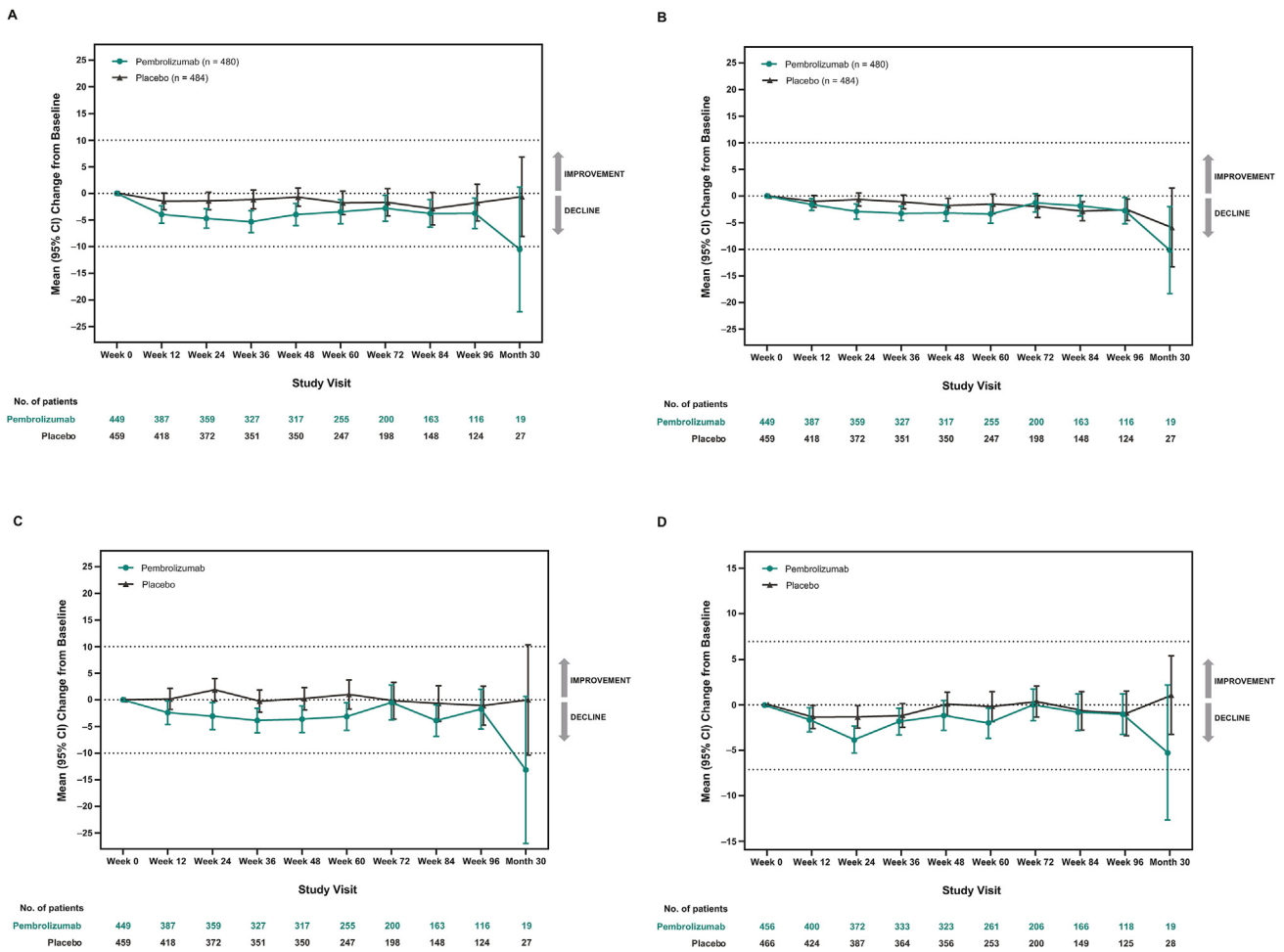


Fig. 3. Empirical mean change from baseline (95% CI) to month 30 in (A) EORTC QLQ-C30 GHS/QoL score, (B) physical functioning score, (C) role functioning score, and (D) EQ-5D-5L VAS score. Abbreviations: CI, confidence interval; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; GHS, global health status; QoL, quality of life; VAS, visual analog scale. Dotted lines indicate clinically meaningful difference (≥ 10 -point change from baseline for EORTC QLQ-C30 scales; ≥ 7 -point change from baseline in EQ-5D-5L VAS).

to baseline either during or after the completion of adjuvant treatment, as measured by two validated and commonly used HRQoL instruments. Importantly, change from baseline in HRQoL was not clinically different between the pembrolizumab and placebo arms.

In the current analysis, baseline EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning scores were high at baseline and comparable to reference values for the general population, suggesting that patients entered the study with good HRQoL [7]. The analysis of change from baseline to week 48 in EORTC QLQ-C30 GHS/QoL, physical functioning, role functioning, and EQ-5D-5L VAS scores showed that HRQoL was stable both within and between treatment arms. Although nominal p values for comparison between arms of <0.05 are reported for EORTC QLQ-C30 GHS/QoL and role functioning and EQ-5D-5L VAS scores at week 48, the difference in LSM between arms remained substantially below the 10- and 7-point

thresholds, respectively, for a clinically meaningful difference (difference in LSM: QLQ-C30 GHS/QoL, -3.67 [95% CI, -5.91 to -1.44]; QLQ-C30 role functioning, -2.88 [95% CI, -5.57 to -0.18]; EQ-5D-5L VAS, -1.94 [95% CI, -3.72 to -0.16]). Although only descriptively assessed, the analysis of additional EORTC QLQ-C30 functioning, symptom, and single-item scales supported this conclusion.

Descriptive analysis showing stable scores through week 96 (~ 22 months) indicated that pembrolizumab had no detrimental impact on HRQoL during or after adjuvant treatment. Longer-term analysis at month 30 followed this trend but was limited by the small number of patients with data available, because few were eligible to complete HRQoL assessments at this timepoint. In the responder analysis, most patients exhibited non-deteriorated (i.e. stable or improved) EORTC QLQ-C30 GHS/QoL, physical functioning, and role functioning scores during the study. The proportion of patients with

nondeteriorated HRQoL scores was similar between arms for all three EORTC QLQ-C30 scales ($p > 0.9$ for all comparisons).

Results of the phase 3 KEYNOTE-054 study showed that adjuvant pembrolizumab improved RFS and distant metastasis-free survival versus placebo in resected high-risk stage III melanoma and had manageable safety consistent with the known toxicity profile [8,9]. Analysis of HRQoL over 84 weeks in KEYNOTE-054 showed that pembrolizumab did not result in a clinically significant decrease in HRQoL relative to placebo in any analysis conducted, including change from baseline to two years, during treatment, or after treatment [10].

Important considerations for therapy choice in resectable melanoma include the risk of recurrence or death and toxicity of the treatment [3]. Both interferon alfa-2b and high-dose ipilimumab have been investigated as adjuvant therapies for melanoma; however, their use was limited by significant toxicity and deteriorated HRQoL [11–13].

Although missing data are a common limitation of HRQoL analyses, compliance remained high throughout the current analysis, and the number of patients who were expected to complete HRQoL assessments was adequate through 96 weeks (>140 patients). However, the number of patients with HRQoL data available at month 30 was small (<30) because few were expected to complete HRQoL assessments at this timepoint, limiting meaningful interpretation at 30 months. The EORTC QLQ-C30 and EQ-5D-5L are widely used instruments that allow for cross-trial comparison; however, they were initially validated in patients receiving chemotherapy and in mixed localized and metastatic disease populations [14,15]. Therefore, these instruments may lack sensitivity for immunotherapies and the purely adjuvant setting. Inclusion of a melanoma-specific instrument such as the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) instrument would have provided additional insight into melanoma-specific and surgery-related concerns, such as discomfort at the site of surgery [16,17]. However, the patient burden must be considered when choosing HRQoL assessments for a clinical trial, and the FACT-M includes 51 items. Patients were also required to have undergone complete resection in KEYNOTE-716, and treatment with pembrolizumab or placebo may be unlikely to differentially affect surgery-related considerations.

The efficacy and safety results of the KEYNOTE-716 study have led to a paradigm shift in the treatment of high-risk stage II melanoma, such that pembrolizumab is now recommended for adjuvant treatment of pathologically staged IIB and IIC melanoma [3]. The results of this analysis showed HRQoL remained stable with adjuvant pembrolizumab, with no clinically meaningful decrease in HRQoL scores in either treatment arm. This provides valuable information for physicians and their patients because the impact (risk/benefit) of adjuvant therapy on HRQoL may be an important component of

clinical decision-making. These results, in conjunction with the improved RFS and manageable safety previously reported for adjuvant pembrolizumab [1], further support the use of pembrolizumab for the adjuvant treatment of resected stage IIB and IIC melanoma.

Data sharing statement availability

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD 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 MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) 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 MSD 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 MSD 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 may prevent MSD 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 MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform 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 perform the proposed analyses.

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Author contribution statement

MK: formal analysis, validation, writing – original draft, writing – reviewing and editing, other – final approval.

JJL: conceptualization, data curation, formal analysis, validation, writing – original draft, writing – reviewing and editing, other – final approval.

GVL: data curation, formal analysis, validation, writing – original draft, writing – reviewing and editing, other – final approval.

PAA: formal analysis, validation, writing – reviewing and editing, other – final approval.

PR: data curation, validation, writing – reviewing and editing, other – final approval.

DS: data curation, validation, writing – reviewing and editing, other – final approval.

CR: conceptualization, data curation, validation, writing – reviewing and editing, other – final approval.

JJG: data curation, validation, writing – reviewing and editing, other – final approval.

LDLCM: data curation, writing – reviewing and editing, other – final approval.

MDV: data curation, formal analysis, validation, writing – reviewing and editing, other – final approval.

FS: data curation, writing – reviewing and editing, other – final approval.

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VCS: conceptualization, data curation, formal analysis, validation, writing – original draft, writing – reviewing and editing, other – final approval.

MSC: data curation, validation, writing – reviewing and editing, other – final approval.

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FDG: conceptualization, data curation, formal analysis, validation, writing – original draft, writing – reviewing and editing, other – final approval.

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RJ: validation, writing – original draft, writing – reviewing and editing, other – final approval.

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JMK: conceptualization, data curation, validation, other – final approval.

Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests:

MK has no conflicts of interest to declare.

JJL reports advisory/consultancy roles with AbbVie, Immutep, Evaxion, 7 Hills, Bright Peak, Exo, Fstar, Inzen, Reflexion, Xilio, Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, Pyxis, STipe, Tempest, Bayer, Bristol Myers Squibb, Castle, Checkmate, Codiak, Crown, Day One, Duke St, EMD Serono, Endeavor, Flame, Genentech, Gilead, Glenmark, HotSpot, Kadmon, Janssen, Ikena, Immunocore, Incyte, IO Biotech, MacroGenics, Merck, Nektar, Novartis, Partner, Pfizer, Regeneron, Roivant, Servier, STINGthera, Synlogic, and Synthekine; stock ownership in Actym, AlphamabOncology, Arch Oncology, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, Pyxis, STipe, and Tempest; research grants/funding to their institution from AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, Corvus, Day One, EMD Serono, Fstar, Genmab, Ikena, Immatics, Incyte, Kadmon, KHR, MacroGenics, Merck, Moderna, Nektar, Next Cure, Numab, Palleon, Pfizer, Replimmune, Rubius, Servier, Scholar Rock, Synlogic, Takeda, Trishula, Tizona, and Xencor; travel, accommodation, and/or expenses from Castle; and the following provisional patents: Serial #15/612,657 (Cancer Immunotherapy), PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: Diagnostic, Prognostic and Therapeutic Uses Thereof).

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CR worked in a consulting/advisory role for BMS, Roche, Amgen, Novartis, Pierre Fabre, MSD, Sanofi, Biothera, CureVac, and Merck. MAP worked in a consulting/advisory role for BMS, Merck, Eisai, Novartis, Incyte, NewLink Genetics, Aduro, and Pfizer; received research/grant support from BMS, Merck, Novartis, Array BioPharma, RGenix, Infinity, and AstraZeneca.

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KC is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ USA.

RJ, MFK, and CK are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ USA, and are stockholders of Merck & Co., Inc., Rahway, NJ USA.

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Appendix A. Supplementary data

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