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Original Research

# Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma☆

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**KEYWORDS**
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**Abstract** ***Objective:*** Report results of patient-reported health-related quality of life (HRQoL) and symptoms from phase III KEYNOTE-006 study of pembrolizumab versus ipilimumab in patients with ipilimumab-naive advanced melanoma.
***Patients and methods:*** Patients received pembrolizumab 10 mg/kg every 2 (Q2W) or every 3 weeks (Q3W) for up to 2 years, or four cycles of ipilimumab 3 mg/kg Q3W. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) was administered at baseline and throughout the study. Patient-reported outcome (PRO) analyses were pre-specified exploratory endpoints; the primary PRO assessment was the score change from baseline to week 12 in EORTC QLQ-C30 global health status (GHS)/HRQoL score between the arms using constrained longitudinal data analysis.
***Results:*** The PRO analysis population included 776 patients: pembrolizumab Q2W (n = 270); pembrolizumab Q3W (n = 266); ipilimumab (n = 240). Baseline GHS was similar across arms. QLQ-C30 compliance rates at week 12 were 87% (n = 214), 97% (n = 226), and 96% (n = 178), for the pembrolizumab Q2W, pembrolizumab Q3W, and ipilimumab arms, respectively. From baseline to week 12, GHS/HRQoL scores were better maintained with pembrolizumab than with ipilimumab (decrease of −1.9 and −2.5 for pembrolizumab versus −10.0 for ipilimumab; $p < 0.001$ for each pembrolizumab arm versus ipilimumab). Fewer patients treated with pembrolizumab experienced deterioration in GHS at week 12 (31% for pembrolizumab Q2W; 29% for Q3W and 44% for ipilimumab), with similar trends observed for individual functioning and symptoms scales.
***Conclusions:*** HRQoL was better maintained with pembrolizumab than with ipilimumab in patients with ipilimumab-naive advanced melanoma.
***ClinicalTrials.gov identifier:*** NCT01866319.


## 1. Introduction

Interaction between the programmed death 1 (PD-1) receptor and its ligands, PD-L1 and PD-L2, inhibits T-cell receptor signalling and results in downregulation of the T-cell–mediated antitumour immune response [1–3]. Some tumour types, including melanoma, hijack this pathway through altered expression of the PD-1 receptor and/or ligands, dampening the antitumour immune response [4,5]. Pembrolizumab and nivolumab are approved anti–PD-1 therapies for the treatment of advanced melanoma. Pembrolizumab is an immunoglobulin G4κ-humanised monoclonal antibody that blocks the interaction between PD-1 and its ligands, allowing an antitumour immune response to be reinstated [6–10]. Ipilimumab, also approved for use in advanced melanoma, is a monoclonal antibody that blocks cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), a co-inhibitory immune checkpoint receptor [11–13].

Patient-reported outcomes (PROs) are increasingly used as a complement to biological data to inform patient-centred care and clinical decision-making [14]. Indeed, research has indicated that health-related quality of life (HRQoL) impairment may affect the survival rate of patients with melanoma [15,16]. Recently, phase III randomised clinical trials have included PROs as a predefined study endpoint. In the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase III trial, overall HRQoL as measured by the EORTC Quality of Life Questionnaire C30 (QLQ-C30) showed that, compared with placebo, adjuvant ipilimumab had no significant impact on global health status (GHS) after induction in patients with high-risk stage III melanoma [17]. In an analysis of the phase III CheckMate 067 study of patients with previously untreated advanced melanoma, treatment with either nivolumab monotherapy or in combination with ipilimumab did not result in a deterioration of HRQoL, compared with ipilimumab monotherapy [18]. Furthermore, in the phase III KEYNOTE-002 study of patients with ipilimumab-refractory melanoma, progression-free survival (PFS) was prolonged, toxicity was reduced, and HRQoL was better maintained in pembrolizumab-treated patients than in patients treated with chemotherapy.

KEYNOTE-006 is a randomised, controlled, phase III study of pembrolizumab versus ipilimumab in patients with ipilimumab-naive advanced melanoma who received one or no prior therapies. Results from KEYNOTE-006 demonstrated that pembrolizumab prolongs overall survival (OS) and PFS and is associated with fewer high-grade toxicity events than ipilimumab [19]. PROs, including HRQoL, were exploratory endpoints with pre-specified analysis in KEYNOTE-006 designed to help elucidate the treatment effect from the

patient perspective. Changes in patient-reported HRQoL and symptoms in patients with ipilimumab-naive advanced melanoma treated with pembrolizumab versus ipilimumab in KEYNOTE-006 are reported herein. We hypothesised that pembrolizumab will extend OS and PFS without the deterioration in HRQoL or symptoms that we predict will be observed in patients treated with ipilimumab.

## 2. Methods

### 2.1. Study design

Full details of the international, randomised, open-label, controlled, phase III KEYNOTE-006 study (ClinicalTrials.gov identifier: NCT01866319) are published elsewhere [19]. In brief, patients eligible for enrolment were aged 18 years or older; had histologically confirmed, unresectable stage III or IV melanoma; and had received no more than one previous systemic therapy for advanced disease. Patients were randomly assigned (1:1:1) to receive pembrolizumab 10 mg/kg either every 2 weeks (Q2W) or every 3 weeks (Q3W) for up to 2 years or to receive four doses of ipilimumab 3 mg/kg Q3W. Randomisation was stratified according to line of therapy (first versus second), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and PD-L1 expression status (positive versus negative). Treatment continued until disease progression, unacceptable toxicity, or investigator/patient decision to discontinue or for a total of 24 months (pembrolizumab arms). Response was assessed at week 12 and Q6W thereafter per Response Evaluation Criteria in Solid Tumours, version 1.1, by central imaging vendor review. Primary endpoints were PFS and OS; patient-reported HRQoL was an exploratory endpoints with pre-specified analyses.

### 2.2. PRO assessments

PROs were assessed using the EORTC QLQ-C30 [20] and EuroQoL EQ-5D [21] questionnaires. The QLQ-C30 includes 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact), and a GHS/quality of life (QoL) scale. A score change decrease of 10 points for the QLQ-C30 GHS/QoL scale is considered clinically meaningful [22]. The EuroQoL EQ-5D includes five health state dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is rated on a three-point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D also includes a graded (0–100) vertical visual analogue scale (VAS), on which patients rate their general state of health at the time of the assessment; differences in utility scores of approximately 0.10 are considered clinically meaningful for patients with cancer [23].

To avoid influence of response, patients completed the self-administered questionnaires in the clinic using an electronic device before any other clinical procedures were performed. The EQ-5D was completed before the QLQ-C30. Questionnaires were collected at baseline, weeks 3 (or 2 for the pembrolizumab Q2W arm), 6, 12, 24, and 36; at treatment discontinuation; and at the 30-day safety follow-up visit. If a patient did not complete the PRO instruments at a scheduled visit, the reason was recorded from predefined choices on a PRO Miss-Mode form.

### 2.3. Statistical analyses

All PRO analyses were pre-specified. The analysis population included all randomly assigned patients who received at least one dose of study drug and completed at least one PRO assessment (full analysis set [FAS]). An instrument was considered complete if at least one valid score was available according to the missing item rules outlined in the EORTC QLQ-C30 and EQ-5D manuals. The PRO compliance rate was defined as the proportion of patients who completed the PRO instrument among those who were expected to complete at each visit, excluding those missing by design (e.g. death, discontinuation of treatment, instrument translations not available, or no visit scheduled). The PRO completion rate was defined as the proportion of patients who completed the PRO instrument among the PRO FAS population.

Based on previous data, >50% of the patients in the ipilimumab arm were expected to have disease progression at week 12 and might not have PRO data available after this time point [18,24]; therefore, the primary PRO analysis was performed on data collected at week 12 to ensure a large enough sample size in the ipilimumab arm. Data collected at week 24 would be included in the analysis if the completion rate in the ipilimumab arm was >50%. The key PRO endpoints was the score change from baseline and the proportions of improvement/deterioration at week 12, as measured by the EORTC QLQ-C30 GHS/QoL score. Supportive PRO endpoints were score changes from baseline and proportions of improvement/deterioration at week 12 as measured by each of the EORTC QLQ-C30 functional subscales and symptom subscale scores. Other analyses included time to deterioration in the GHS/QOL score of the QLQ-C30. Raw scores were standardised to a range of 0–100 by linear transformation, as described in the EORTC QLQ-C30 scoring manual, with a 10-point change from baseline considered clinically meaningful [22]. Changes from baseline to week

12 of the EQ-5D utility score and VAS were also summarised.

Constrained longitudinal data analysis models were the primary method of assessing the effect of the different treatments and disease progression on PRO score changes, using a mixed-effect model with multiple imputation based on missing at random (MAR) assumption. A Cox regression model was used to compare the time to deterioration in the GHS/QOL score, defined as the time to first onset of a decrease from baseline ≥10 points confirmed by the second adjacent ≥10-point decrease using the right-censoring rule.

## 3. Results

### 3.1. Patients

Eight hundred thirty-four patients were enrolled and randomly assigned to receive pembrolizumab 10 mg/kg Q2W (n = 279; 278 treated), pembrolizumab 10 mg/kg Q3W (n = 277; all treated), or ipilimumab 3 mg/kg Q3W (n = 278; 256 treated). Patient baseline characteristics (published in detail elsewhere) [19] were well balanced between treatment groups. Median age was 62 years, 66% of patients were treatment naive, and 69% of patients had an ECOG performance status of 0.

### 3.2. Completion and compliance rates of PRO questionnaires

The PRO analysis population for EORTC QLQ-C30 included 776 patients: pembrolizumab Q2W (n = 270), pembrolizumab Q3W (n = 266), and ipilimumab (n = 240). The QLQ-C30 completion rate decreased over time in all treatment groups (Table 1), likely because of the reduction in the number of patients scheduled to finish the questionnaires at each time point as a result of disease progression, adverse event, or death. EORTC QLQ-C30 compliance rates (Table 1) were very high at baseline (>98% in all arms) and at week 12 (87% for pembrolizumab Q2W, 97% for pembrolizumab Q3W, and 96% for ipilimumab). At week 24, compliance rates were 95% for both pembrolizumab arms and 56% with ipilimumab; compliance rates at week 36 were 78%, 92%, and 42%, respectively. The

Table 1
Completion and compliance rates of the EORTC QLQ-C30 by visit.

| Treatment visit | Category | Pembrolizumab Q2W | Pembrolizumab Q3W | Ipilimumab |
|---|---|---|---|---|
| | | N = 270 | N = 266 | N = 240 |
| Baseline | Expected to complete, n | 270 | 266 | 240 |
| | Completed, n | 267 | 263 | 237 |
| | Compliance, %[a] | 99 | 99 | 99 |
| | Completion, %[b] | 99 | 99 | 99 |
| Week 2/3 | Expected to complete, n | 269 | 261 | 235 |
| | Completed, n | 264 | 252 | 223 |
| | Compliance, %[a] | 98 | 97 | 95 |
| | Completion, %[b] | 98 | 95 | 93 |
| Week 6 | Expected to complete, n | 259 | 252 | 224 |
| | Completed, n | 251 | 242 | 206 |
| | Compliance, %[a] | 97 | 96 | 92 |
| | Completion, %[b] | 93 | 91 | 86 |
| Week 12 | Expected to complete, n | 246 | 233 | 185 |
| | Completed, n | 214 | 226 | 178 |
| | Compliance, %[a] | 87 | 97 | 96 |
| | Completion, %[b] | 79 | 85 | 74 |
| Week 24 | Expected to complete, n | 189 | 178 | 142 |
| | Completed, n | 180 | 169 | 80 |
| | Compliance, %[a] | 95 | 95 | 56 |
| | Completion, %[b] | 67 | 64 | 33 |
| Week 36 | Expected to complete, n | 143 | 131 | 128 |
| | Completed, n | 112 | 120 | 54 |
| | Compliance, %[a] | 78 | 92 | 42 |
| | Completion, %[b] | 42 | 45 | 23 |

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; Q2W, every 2 weeks; Q3W, every 3 weeks.

[a] The compliance rate is the proportion of patients who completed the patient-reported outcomes (PROs) questionnaire among those expected to complete at each time point, excluding those missing by design.

[b] The completion rate is the proportion of patients who completed the PROs questionnaire among the PRO analysis population (all randomly assigned patients who received at least one dose of study treatment and completed at least one PRO assessment).

lower compliance rates in the ipilimumab arm at weeks 24 and 36 were mainly a result of patients missing the study visit or of an 'unknown reason'. Similar trends in compliance and completion rates were observed for the EQ-5D questionnaire.

### 3.3. Change from baseline in HRQoL and symptoms at week 12

Week 12 was the primary time point for the constrained longitudinal data analysis. Data collected at week 24 were not included in the analysis because the completion rate in the ipilimumab arm (33%) was lower than the pre-specified threshold of 50%. Baseline mean ± standard deviation QLQ-C30 GHS/QoL scores were similar across treatment arms: pembrolizumab Q2W: 71.4 ± 20.4; pembrolizumab Q3W: 70.5 ± 21.9; and ipilimumab: 67.4 ± 24.0 (Table 2). Pembrolizumab-treated patients had significantly smaller decreases from baseline in the EORTC QLQ-C30 GHS/QOL score at week 12 than ipilimumab-treated patients ($p < 0.001$), with a least-squares mean of −1.9 (95% confidence interval [CI], −4.9 to 1.0) for pembrolizumab Q2W, −2.5 (95% CI, −5.3 to 0.4) for pembrolizumab Q3W, and −10.0 (95% CI, −13.2 to −6.9) for ipilimumab (Table 2).

Similar findings were observed for the EORTC QLQ-C30 individual function scales (Fig. 1A). The longitudinal score changes from baseline to week 12 for different functional scales in the two pembrolizumab arms were consistently <5 points but were generally >5 points in the ipilimumab arm (except for emotional function) and >10 points in the role and social function scales. There were no significant differences between the pembrolizumab arms. Ipilimumab was associated with decreases in all function scale scores, whereas pembrolizumab was associated with improvement in emotional functioning. Patients receiving pembrolizumab had smaller increases from baseline in the symptom scale scores of fatigue, pain, dyspnoea, appetite loss, and diarrhoea than those receiving ipilimumab (Fig. 1B), and patients receiving pembrolizumab experienced improvement over baseline in nausea, vomiting, and insomnia, whereas these symptoms worsened with ipilimumab. Consistent results were observed when using other cut-offs (i.e. 15 and 20 points) in the sensitivity analyses (data not shown).

Similar results were observed for the EQ-5D analyses. For the EQ-5D utility score using the European weighting algorithm of the five health state dimension scores, the difference in the utility score between the pembrolizumab Q2W and ipilimumab arms was 0.08 (95% CI, 0.04 to 0.12; $p < 0.0001$); that between the pembrolizumab Q3W and ipilimumab arms was 0.08 (95% CI, 0.04 to 0.12; $p = 0.001$). The difference in VAS scores between the pembrolizumab Q2W and ipilimumab arms was 5.33 (95% CI, 1.70 to 8.97; $p = 0.004$); that between the pembrolizumab Q3W and ipilimumab arms was 3.39 (95% CI, 0.20 to 6.98; $p = 0.06$).

### 3.4. PRO 'responders' analyses: deterioration of the EORTC QLQ-C30 GHS/QoL score, functional and symptom scales

The proportion of 'improved', 'stable', or 'deteriorated' EORTC QLQ-C30 GHS/QoL and different functional and symptom scale scores at week 12 was assessed according to a ≥10-point change from baseline [22]. Fewer patients treated with pembrolizumab experienced deterioration in EORTC QLQ-C30 GHS/QoL at week 12 (pembrolizumab Q2W, 31%; pembrolizumab Q3W, 29%; and ipilimumab, 44%); similar trends were observed for individual functioning and symptoms scales (Table 3) and when other cut-offs (i.e. 15 and 20 points) were used in the sensitivity analyses (data not shown). Comparable results were observed

Table 2
Change from baseline to week 12 in the global health status score of the EORTC QLQ-C30.

| Treatment | N[a] | Baseline | | Week 12 | | Global health status/quality-of-life change from baseline at week 12 | |
|---|---|---|---|---|---|---|---|
| | | Mean (SD) | N[a] | Mean (SD) | N[b] | Mean (SD) | LS mean (95% CI)[c] |
| Pembrolizumab 10 mg/kg Q2W | 239 | 71.4 (20.4) | 172 | 71.1 (19.3) | 159 | −2.2 (19.2) | −1.9 (−4.86 to 1.01) |
| Pembrolizumab 10 mg/kg Q3W | 230 | 70.5 (21.9) | 188 | 69.5 (22.3) | 168 | −2.2 (18.0) | −2.5 (−5.32 to 0.37) |
| Ipilimumab | 213 | 67.4 (24.0) | 149 | 64.3 (25.8) | 132 | −9.0 (23.9) | −10.0 (−13.16 to −6.85) |

| **Pairwise comparison** | **Difference in LS mean (95% CI)** | ***p* value** |
|---|---|---|
| Pembrolizumab 10 mg/kg Q2W versus ipilimumab | 8.1 (3.89 to 12.27) | 0.0002 |
| Pembrolizumab 10 mg/kg Q3W versus ipilimumab | 7.5 (3.40 to 11.66) | 0.0004 |
| Pembrolizumab 10 mg/kg Q3W versus pembrolizumab 10 mg/kg Q2W | −0.5 (−4.51 to 3.41) | 0.7856 |

CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; LS, least squares; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; SD, standard deviation.

[a] N = Number of patients in the PRO analysis population with each time point observation.

[b] N = Number of patients in the PRO analysis population with baseline and week 12 observations.

[c] Based on a constrained longitudinal data analysis model with the PRO scores as the response variable and treatment by study visit interaction, stratification factors (stratified by line of therapy [first versus second], programmed death ligand 1 status [positive versus negative], and Eastern Cooperative Oncology Group performance status [0 versus 1]) as covariates.

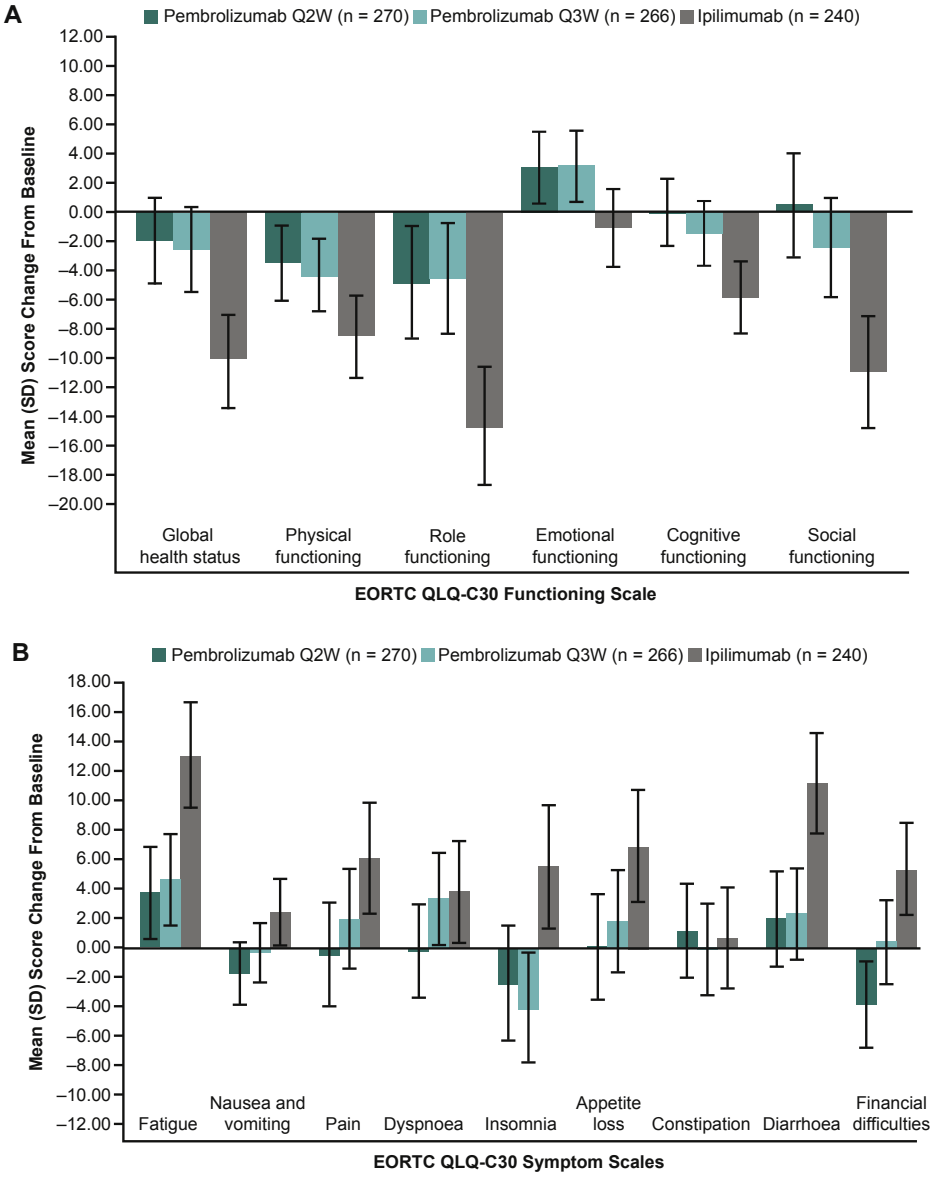


Fig. 1. Change from baseline to week 12 in scores for the (A) global health status and function scales and (B) symptom scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30). Q2W, every 2 weeks; Q3W, every 3 weeks; SD, standard deviation.

at other time points (data not shown). The time to deterioration in the EORTC QLQ-C30 GHS/QoL score was significantly longer with pembrolizumab than with ipilimumab, with a hazard ratio of 0.68 (95% CI, 0.50 to 0.92; $p = 0.01$) for pembrolizumab Q2W and 0.67 (95% CI, 0.49 to 0.91; $p = 0.01$) for pembrolizumab Q3W.

In addition to the constrained longitudinal data analyses using the MAR assumption, the observed mean EORTC QLQ-C30 GHS/QoL scores were summarised at different time points (baseline and weeks 3, 6, 12, 24, and 36) for each of the treatment groups, without any imputation of missing data. Among patients who remained on treatment and had available PRO data, the EORTC QLQ-C30 GHS/QoL score remained fairly stable, similar to—or even better than—the baseline score (Table 4). As expected, more patients remained on therapy and had PRO data in the two pembrolizumab arms than in the ipilimumab arm.

### 3.5. Effect of disease progression on EORTC QLQ-C30 score changes

Analysis of the association between disease progression status and subsequent EORTC QLQ-C30 score changes for GHS/QoL revealed a negative impact of disease progression on GHS score; the longitudinal score change from baseline to week 12 was −7.16 (95% CI,

Table 3
Patients with deterioration in EORTC QLQ-C30 scores at week 12.

| EORTC QLQ-C30 at week 12, deteriorated | Pembrolizumab 10 mg/kg Q2W | Pembrolizumab 10 mg/kg Q3W | Ipilimumab |
|---|---|---|---|
| | N = 270[a] | N = 266[a] | N = 240[a] |
| | n (%) | n (%) | n (%) |
| Global health status/quality of life | 84 (31.1) | 78 (29.3) | 106 (44.2) |
| Physical functioning | 79 (29.3) | 75 (28.2) | 88 (36.7) |
| Role functioning | 106 (39.3) | 93 (35.0) | 110 (45.8) |
| Emotional functioning | 46 (17.0) | 50 (18.8) | 57 (23.8) |
| Cognitive functioning | 53 (19.6) | 69 (25.9) | 78 (32.5) |
| Social functioning | 69 (25.6) | 89 (33.5) | 95 (39.6) |
| Fatigue | 100 (37.0) | 104 (39.1) | 131 (54.6) |
| Nausea and vomiting | 32 (11.9) | 51 (19.2) | 53 (22.1) |
| Pain | 78 (28.9) | 88 (33.1) | 94 (39.2) |
| Dyspnoea | 55 (20.4) | 62 (23.3) | 77 (32.1) |
| Insomnia | 69 (25.6) | 60 (22.6) | 85 (35.4) |
| Appetite loss | 63 (23.3) | 66 (24.8) | 80 (33.3) |
| Constipation | 66 (24.4) | 53 (19.9) | 53 (22.1) |
| Diarrhoea | 72 (26.7) | 56 (21.1) | 88 (36.7) |
| Financial difficulties | 40 (14.8) | 55 (20.7) | 68 (28.3) |

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a] Number of patients in the patient-reported outcome (PRO) analysis population (all randomly assigned patients who received at least one dose of study treatment and completed at least one PRO assessment).

Table 4
Observed EORTC QLQ-C30 global health status score at each study visit.

| Study visit | Pembrolizumab 10 mg/kg Q2W | | Pembrolizumab 10 mg/kg Q3W | | Ipilimumab | |
|---|---|---|---|---|---|---|
| | N = 270[a] | | N = 266[a] | | N = 240[a] | |
| | n | Mean (SE) | n | Mean (SE) | n | Mean (SE) |
| Baseline | 239 | 71.4 (1.3) | 230 | 70.5 (1.4) | 213 | 67.4 (1.6) |
| Week 3 | 230 | 69.2 (1.3) | 215 | 68.5 (1.4) | 194 | 66.4 (1.7) |
| Week 6 | 216 | 72.0 (1.3) | 196 | 71.9 (1.4) | 176 | 66.9 (1.7) |
| Week 12 | 172 | 71.1 (1.5) | 188 | 69.5 (1.6) | 149 | 64.3 (2.1) |
| Week 24 | 148 | 71.3 (1.5) | 139 | 74.6 (1.6) | 58 | 70.4 (2.5) |
| Week 36 | 72 | 77.1 (2.1) | 102 | 75.0 (2.1) | 37 | 75.5 (2.7) |

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; Q2W, every 2 weeks; Q3W, every 3 weeks; SE, standard error.
[a] Number of patients in the patient-reported outcome (PRO) analysis population (all randomly assigned patients who received at least one dose of study treatment and completed at least one PRO assessment).

Table 5
Analysis of change from baseline of global health status/quality of life at week 12 by progressive disease status.

| Treatment | Without PD | With PD | Difference by PD status |
|---|---|---|---|
| | LS mean (95% CI)[a] | LS mean (95% CI)[a] | LS mean (95% CI)[a] |
| Pembrolizumab 10 mg/kg Q2W | −0.12 (−3.12 to 2.89) | −7.27 (−10.96 to −3.59) | −7.16 (−10.18 to −4.14) |
| Pembrolizumab 10 mg/kg Q3W | −0.60 (−3.53 to 2.33) | −7.76 (−11.36 to −4.16) | |
| Ipilimumab | −7.52 (−10.82 to −4.22) | −14.68 (−18.38 to −10.98) | |

CI, confidence interval; Q2W, every 2 weeks; Q3W, every 3 weeks; PD, progressive disease; LS, least squares.
[a] Based on constrained longitudinal data analysis model with the patient-reported outcome scores as the response variable and treatment by study visit interaction, stratification factors (Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, and *BRAF* mutation) as covariates. Assumes the PD effect is the same across different treatment arms.

−10.18 to −4.14) across the treatment arms (Table 5). There were almost no longitudinal score changes from baseline to week 12 among patients without disease progression in the two pembrolizumab treatment arms (−0.12 [95% CI, −3.12 to 2.89] for pembrolizumab Q2W and −0.60 [95% CI, −3.53 to 2.33] for pembrolizumab Q3W), whereas a −7.52 decrease (95% CI, −10.82 to −4.22) was observed for the control arm. Similar trends

were observed for the different functional and symptom scales (data not shown).

## 4. Discussion

Although treatment outcomes for patients with cancer are generally measured in terms of survival and treatment response, patient-reported HRQoL is an important consideration to help understand the treatment effect from the patient perspective [25–27]. For example, in a study of 178 patients with advanced melanoma, Chiarion-Sileni *et al.* [28] (2003) demonstrated that overall QoL was a significant predictor of survival in multivariate analysis. Thus, for metastatic melanoma in particular, it is important to understand how recently approved therapies that prolong survival [29–31] affect patient QoL. The KEYNOTE-002 study showed that pembrolizumab better maintained HRQoL than did chemotherapy in ipilimumab-refractory melanoma [10]. We report in KEYNOTE-006 that pembrolizumab was associated with consistently smaller PRO score changes than ipilimumab from baseline to week 12 for the different functional and symptom scales. A smaller percentage of EORTC QLQ-C30 change scores for patients receiving pembrolizumab were categorised as 'deteriorated' than for those who received ipilimumab. These differences were observed for all functional and symptom scales, with the exception of constipation.

PROs are increasingly recognised as important measures of functional and symptomatic benefit in metastatic melanoma. In the randomised BREAK-3 study of patients with $BRAF^{V600E}$ metastatic melanoma, compared with chemotherapy, the BRAF inhibitor dabrafenib was shown to prolong PFS. Importantly, all functional dimensions of the EORTC QLQ-C30 remained stable relative to baseline or improved at week 6 in patients treated with dabrafenib, whereas all functional dimensions worsened in patients administered with chemotherapy [32]. In a similar phase III study (COMBI-d), compared with dabrafenib monotherapy, the combination of dabrafenib and the MEK inhibitor trametinib in patients with advanced $BRAF^{V600}$ melanoma resulted in prolonged PFS and comparable HRQoL and pain improvement [31]. Thus, HRQoL seems to be associated with prolonged PFS in patients with advanced $BRAF^{V600}$ melanoma who are treated with BRAF and MEK inhibitors.

To date, few studies have reported the effect of checkpoint inhibitors on HRQoL in advanced melanoma. In the phase III, double-blind CheckMate 067 study, a slight deterioration from baseline EORTC QLQ-C30 scores was observed at week 5 through week 25 in patients treated with either ipilimumab in combination with nivolumab or nivolumab monotherapy [18]. Nonetheless, no clinically relevant differences (>10 points) were found between study arms. Similarly, in the phase III, double-blind, EORTC 18071 study of adjuvant ipilimumab after resection of advanced melanoma, ipilimumab treatment resulted in a significant 4.35-point decrease in means compared with placebo; however, this decrease did not exceed the clinically relevant threshold (>10 points) for any time point assessed [17]. In the context of these studies, the results of pembrolizumab treatment in the KEYNOTE-006 study are favourable, demonstrating consistently smaller and clinically relevant PRO score changes compared with ipilimumab treatment.

A 10-point change from baseline in EORTC QLQ-C30 GHS/QoL score is considered clinically meaningful [22,33]. In the two pembrolizumab arms, the least-squares mean for EORTC QLQ-C30 GHS/QoL score changes from baseline to week 12 were minimal; in the pembrolizumab Q2W and Q3W arms, a −1.9-point (95% CI, −4.8 to 1.1) change and a −2.5-point (95% CI, −5.3 to 0.4) change were observed, respectively. For the ipilimumab arm, there was a clinically meaningful −10.0 (95% CI, −13.2 to −6.9) point change. In addition to the longitudinal analyses of score changes from baseline, the PRO 'responder' analyses also demonstrated consistently that across all functional and symptom scales of the EORTC QLQ-C30 GHS/QoL score, fewer patients treated with pembrolizumab experienced deterioration than did patients treated with ipilimumab (Table 3). Similarly, the time to deterioration in the EORTC QLQ-C30 GHS/QoL score was significantly longer with pembrolizumab than with ipilimumab, with a hazard ratio of 0.68 (95% CI, 0.50 to 0.92; $p = 0.01$) for pembrolizumab Q2W and 0.67 (95% CI, 0.49 to 0.91; $p = 0.01$) for pembrolizumab Q3W. The results were further supported when different cut-offs (i.e. 15 and 20 points) were used in the sensitivity analyses or when data collected was at additional time points (Table 4). Finally, a statistically significant difference in the EQ-5D utility scores was observed between both pembrolizumab arms and the ipilimumab arm. No differences in the results of EORTC QLQ-C30 and EQ-5D were observed between the two pembrolizumab schedules.

These differences in PRO score changes observed in KEYNOTE-006 can be attributed to the treatment difference between pembrolizumab and ipilimumab and to the higher rate of disease progression among patients treated with ipilimumab. In addition to demonstrating higher OS and PFS compared with ipilimumab, pembrolizumab also demonstrated a better toxicity profile consistent with less deterioration of QoL, including reduced rates of diarrhoea and colitis [19]. As shown in Table 5, among patients without disease progression, there was almost no change from baseline to week 12 for the EORTC QLQ-C30 GHS/QoL score in the two pembrolizumab treatment arms, whereas a −7.52-point

decrease was observed for the ipilimumab arm. Similarly, a much larger decrease in EORTC QLQ-C30 GHS/QoL score from baseline was seen among patients with disease progression who were receiving ipilimumab (−14.68) than in those receiving pembrolizumab (−7.27 and −7.76, respectively; Table 5). Therefore, ipilimumab treatment and disease progression both seem to have a negative impact on HRQoL.

### 4.1. Strengths and limitations

The strengths of this study include its randomised trial design, pre-specified comprehensive PRO analysis plan, large sample sizes, and high PRO compliance rates, particularly within the two pembrolizumab arms. A potential limitation of these findings is that clinical trial populations might differ from patients with melanoma in the general population. The HRQoL outcomes reported herein are probably associated with tumour progression and ipilimumab-related side effects. Furthermore, the open-label design of KEYNOTE-006 introduced potential bias, allowing patients to envision or expect improved tolerability with the anti−PD-1 agent compared with the anti−CTLA-4 therapy.

## 5. Conclusions

These exploratory PRO analyses from KEYNOTE-006 indicate that HRQoL was better maintained with pembrolizumab than with ipilimumab when administered as first- or second-line therapy in patients with metastatic melanoma. Approximately, 13−15% more patients treated with ipilimumab than with pembrolizumab experienced deterioration in EORTC QLQ-C30 GHS/QoL score by week 12. Irrespective of the treatment arm, EORTC QLQ-C30 GHS/QoL score decreased in patients who experienced disease progression. Combined with prolonged PFS and OS and a decreased incidence of high-grade toxicity provided by pembrolizumab compared with ipilimumab, the better HRQoL profile reported for pembrolizumab over ipilimumab supports pembrolizumab as a standard of care for patients with advanced melanoma.

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## Authors' contributions

Dr. Cebon was involved with the acquisition of the data; Dr. Hille was involved with the analysis of the data, and the interpretation of results; Drs. Ibrahim and Robert were involved in the study design, the analysis of the data and the interpretation of the results; Drs. Lebbe, Middleton, Richtig, and Walpole were involved in the acquisition of the data and interpretation of results; Dr. Masucci was involved in the interpretation of results; Dr. Miller was involved in the acquisition and analysis of the data and the interpretation of results; Dr. Petrella was involved in the interpretation of results; and Dr. Zhou was involved in the study design, the analysis and acquisition of the data, and the interpretation of the results. All authors were involved in reviewing and revising the manuscript, and all provided the final approval of the manuscript.

## Conflict of interest statement

TMP reports personal fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ; Roche; Bristol-Myers Squibb; and Novartis, outside the submitted work. CR reports personal fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ; Roche; Bristol-Myers Squibb; Amgen; and Novartis, outside the submitted work. ER reports fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, during the duration of the study. WHM reports personal fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ; GlaxoSmithKline; and Amgen, outside the submitted work. GVM reports nothing to disclose. EW reports grants from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. CL reports grants and personal fees from Roche and Bristol-Myers Squibb; personal fees from Novartis; Merck & Co., Inc., Kenilworth, NJ; Amgen; and GlaxoSmithKline, outside the submitted work. NS reports personal fees as a contributor to advisory boards for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, outside the submitted work. MRM reports personal fees from Amgen; grants and personal fees from Roche and GlaxoSmithKline; other from Novartis, Astellas (was OSI), Millennium Pharmaceuticals, Vertex, Abbott (now Abbvie), Clovis, Pfizer, and Rigontec; nonfinancial support and other from Immunocore; personal fees and other from Bristol-Myers Squibb and Eisai; grants from AstraZeneca and personal fees, nonfinancial support, and other from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. DH, WZ, and NI are all employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, and own stock in the company. NI owns stock in GlaxoSmithKline.

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