Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054)

EORTC Melanoma Group; Bottomley, Andrew; Coens, Corneel; Mierzynska, Justyna; Blank, Christian U.; Mandalà, Mario; Long, Georgina V.; Atkinson, Victoria G.; Dalle, Stéphane; Haydon, Andrew M.

Published in:
The Lancet Oncology

DOI:
10.1016/S1470-2045(21)00081-4

Publication date:
2021

Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): health-related quality-of-life results from a double-blind, randomised, controlled, phase 3 trial

Andrew Bottomley, Corneel Coens, Justyna Mierzynska, Christian U Blank, Mario Mandalà, Georgina V Long, Victoria G Atkinson, Stéphane Dalle, Andrew M Haydon, Andrey Meshcheryakov, Adnan Khattak, Matteo S Carlino, Shahneen Sandhu, Susana Puig, Paolo A Ascierto, James Larkin, Paul C Lorigan, Piotr Rutkowski, Dirk Schadendorf, Rutger Koornstra, Leonel Hernandez-Aya, Anna Maria Di Giacomo, Alfonsus J M van den Eertwegh, Jean-Jacques Grob, Ralf Gutzmer, Rahima Jamal, Alexander C J van Akkooi, Clemens Krepler, Nageatte Ibrahim, Sandrine Marreaud, Michal Kicinski, Stefan Suciu, Caroline Robert, Alexander M M Eggermont, for the EORTC Melanoma Group

Summary

Background The European Organisation for Research and Treatment of Cancer (EORTC) 1325-MG/KEYNOTE-054 trial in patients with resected, high-risk stage III melanoma demonstrated improved recurrence-free survival with adjuvant pembrolizumab compared with placebo (hazard ratio 0·57 [98·4% CI 0·43–0·74]; p<0·0001). This study reports the results from the health-related quality-of-life (HRQOL) exploratory endpoint.

Methods This double-blind, randomised, controlled, phase 3 trial was done at 123 academic centres and community hospitals across 23 countries. Patients aged 18 years or older with previously untreated histologically confirmed stage IIIA, IIIB, or IIIC resected cutaneous melanoma, and an Eastern Cooperative Oncology Group performance status score of 1 or 0 were eligible. Patients were randomly assigned (1:1) using a central interactive voice-response system on the basis of a minimisation technique stratified for stage and geographic region to receive intravenously 200 mg pembrolizumab or placebo. Treatment was administered every 3 weeks for 1 year, or until disease recurrence, unacceptable toxicity, or death. The primary endpoint of the trial was recurrence-free survival (reported elsewhere). HRQOL was a prespecified exploratory endpoint, with global health/quality of life (GHQ) over 2 years measured by the EORTC QLQ-C30 as the primary analysis. Analyses were done in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT02362594, and EudraCT, 2014-004944-37, and long-term follow-up is ongoing.

Findings Between Aug 26, 2015, and Nov 14, 2016, 1019 patients were assigned to pembrolizumab (n=514) or placebo (n=505). Median follow-up was 15·1 months (IQR 12·8–16·9) at the time of this analysis. HRQOL compliance was greater than 90% at baseline, greater than 70% during the first year, and greater than 60% thereafter for both groups. Because of low absolute compliance numbers at later follow-up, the analysis was truncated to week 84. Baseline GHQ scores were similar between groups (77·55 [SD 18·20] in the pembrolizumab group and 76·54 [17·81] in the placebo group) and remained stable over time. The difference in average GHQ score between the two groups over the 2 years was –2·2 points (95% CI –4·3 to –0·2). The difference in average score during treatment was –1·1 points (95% CI –3·2 to 0·9) and the difference in average score after treatment was –2·2 points (–4·8 to 0·4). These differences are within the 5-point clinical relevance threshold for the QLQ-C30 and are therefore clinically non-significant.

Interpretation Pembrolizumab does not result in a clinically significant decrease in HRQOL compared with placebo when given as adjuvant therapy for patients with resected, high-risk stage III melanoma. These results support the use of adjuvant pembrolizumab in this setting.

Funding Merck Sharp & Dohme.

Lancet Oncol 2021; 22: 655–64

Published Online
April 12, 2021
https://doi.org/10.1016/S1470-2045(21)00081-4

See Comment page 573

EORTC Headquarters, Brussels, Belgium (A Bottomley PhD, C Coens MSc, J Mierzynska MSc, S Marreaud MD, M Kicinski PhD, S Suciu PhD); **Netherlands Cancer Institute—Antoni van Leeuwenhoek, Amsterdam, Netherlands** (C U Blank MD, A C J van Akkooi PhD); **University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy** (M Mandalà MD); **Melanoma Institute Australia, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia** (Prof G V Long PhD); **Princess Alexandra Hospital, Gallipoli Medical Research Foundation, University of Queensland, Brisbane, QLD, Australia** (V G Atkinson MBBS); **Hospices Civils de Lyon Cancer Institute, Lyon, France** (Prof S Dalle MD); **Alfred Hospital, Melbourne, VIC, Australia** (A M Haydon PhD); **N N Blokhin Cancer Research Center, Moscow, Russia** (Prof A Meshcheryakov MD); **Fiona Stanley Hospital & Edith Cowan University, Perth, WA, Australia** (A Khattak MD); **Westmead and Blacktown Hospitals, Melanoma Institute Australia and the University of Sydney, NSW, Australia** (M S Carlino PhD); **Peter Maccallum Cancer Centre, Melbourne, VIC, Australia** (Prof S Sandhu MD); **Hospital Clinic de Barcelona &**

Introduction

Effective drug therapies have revolutionised the management of both advanced-stage and high-risk resected, early-stage melanoma, with improved survival times because of both BRAF-targeted and anti-PD-1 immune therapies.[1,2] These improvements have also positively impacted health-related quality of life (HRQOL). However, the assessment of HRQOL is not an easy task, because it often presents challenges in trial design, data analyses,[3,4] and data interpretation.[5] HRQOL measures are nevertheless crucial because they help inform the patients' decisions regarding treatments.[6] Patients with high-risk, stage III melanoma are at risk of relapse, thus treatment with surgery alone is not sufficient. Given the need for

Universitat de Barcelona & CIBERER, ISCIII, Barcelona, Spain (S Puig MD); **Istituto Nazionale Tumori IRCCS, Fondazione G Pascale, Naples, Italy** (Prof P A Ascierto MD); **Royal Marsden Hospital, London, UK** (Prof J Larkin PhD); **Christie NHS Foundation Trust, Manchester, UK** (Prof P C Lorigan MD); **Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland** (Prof P Rutkowski MD); **University Hospital Essen, Essen and German Cancer Consortium, Heidelberg, Germany** (Prof D Schadendorf MD); **Radboud University Medical Center Nijmegen, Nijmegen, Netherlands** (R Koornstra MD); **Washington University School of Medicine, St Louis, MO, USA** (L Hernandez-Aya MD); **Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy** (Prof A M Di Giacomo MD); **Amsterdam University Medical Center, VUMC, Amsterdam, Netherlands** (Prof A J M van den Eertwegh MD); **Aix-Marseille University, Hôpital de la Timone, Marseille, France** (Prof J-J Grob MD); **Skin Cancer Center, Hannover Medical School, Hannover, Germany** (Prof R Gutzmer MD); **Centre Hospitalier de l'Université de Montréal (CHUM), Centre de Recherche du CHUM, Montreal, QC, Canada** (R Jamal MD); **Merck & Co, Kenilworth, NJ, USA** (C Krepler MD, N Ibrahim MD); **Gustave Roussy Cancer Institute & University Paris-Saclay, Villejuif, France** (Prof C Robert MD); **Princess Máxima Center, Utrecht, Netherlands** (Prof A M M Eggermont MD); **University Medical Center Utrecht, Utrecht, Netherlands** (Prof A M M Eggermont);

Correspondence to:
Dr Andrew Bottomley,
EORTC Headquarters,
Brussels 1200, Belgium
andrew.bottomley@eortc.org

See Online for appendix

Research in context

Evidence before this study

Patients with stage III melanoma are at high risk of relapse. Surgery alone is insufficient to avoid a recurrence in most of these patients. Thus, systemic adjuvant therapy has been investigated over the past decades in these patients. We did not do a systematic search of the literature, but several randomised, controlled trials assessing adjuvant drug therapies in patients with resected, high-risk melanoma have shown improved survival outcomes. The EORTC 1325-MG/KEYNOTE-054 trial supports previous results by demonstrating improved recurrence-free survival with pembrolizumab (200 mg) administered every 3 weeks for up to 1 year compared with placebo in patients with resected stage III melanoma. However, previous studies show that adjuvant immunotherapy might interfere with health-related quality of life (HRQOL) because of side-effects.

Added value of this study

This study shows that pembrolizumab does not result in a clinically significant decrease in global HRQOL compared with placebo when given as adjuvant therapy in patients with resected, high-risk, stage III melanoma. Differences in HRQOL between groups and over time remained below the clinical relevance threshold, thus demonstrating no clinically relevant impairment on patients' HRQOL in the treatment group and supporting the use of pembrolizumab in patients with resected stage III melanoma.

Implications of all the available evidence

To the best of our knowledge, this is the first large randomised, controlled trial to publish results on HRQOL having reported earlier on improved recurrence-free survival with adjuvant pembrolizumab compared with placebo, therefore supporting the clinical use of the immune PD-1 inhibitor in this setting.

safe and effective adjuvant therapies, assessment of HRQOL is increasingly important, in part because of serious adverse events associated with melanoma drug therapies. The importance of the patients' perspective is increasingly acknowledged in clinical practice and research, with HRQOL becoming a standard endpoint in cancer research and specifically in melanoma randomised, controlled trials.[7]

Adjuvant therapies in patients after complete resection of high-risk stage III melanoma improve recurrence-free survival. For example, the European Organisation for Research and Treatment of Cancer (EORTC) 18991 study showed in an adjuvant therapy trial comparing pegylated interferon alfa-2b with observation in patients with resected stage III melanoma, that pegylated interferon alfa-2b leads to a significant and sustained improvement in recurrence-free survival.[8] However, the trial found an expected negative treatment effect on global HRQOL and on selected symptom scales that included appetite loss, fatigue, and dyspnoea.[9,10] Subsequently, the EORTC 18071 phase III trial, comparing adjuvant ipilimumab with placebo in patients with resected stage III melanoma,[11] showed longer recurrence-free survival in the ipilimumab group. The recurrence-free survival benefit translated into long-term overall survival benefits.[12,13] However, 52% of the patients in the ipilimumab group discontinued treatment because of adverse events and 1% died due to drug-related adverse events. The trial results showed no relevant impairments in HRQOL with ipilimumab, despite 54% of patients having grade 3–4 investigator-reported adverse events.[14] These clinical results led to the approval of this drug by the US Food and Drug Administration (FDA).

Our study, which involves the same population with resected, high-risk stage III melanoma as EORTC 18071, compares pembrolizumab with placebo. The clinical results were published in 2018 showing a significantly longer recurrence-free survival in the pembrolizumab group than the placebo group at a median follow-up of 1·25 years,[15] which led to European Medicines Agency (2018) and FDA (2019) approvals of pembrolizumab in the adjuvant setting for stage III melanoma. Adverse events of grade 3 or worse related to trial treatment occurred in 15% of the patients in the pembrolizumab group, including one death due to myositis. Of the 509 patients who started pembrolizumab, 70 (14%) discontinued treatment because of adverse events.[15] The updated results of this trial at a median follow up of 3·5 years showed a recurrence-free survival rate in the overall population of 59·8% (95% CI 55·3–64·1) in the pembrolizumab group and 41·4% (37·0–45·8) in the placebo group (HR 0·59 [95% CI 0·49–0·70]).[16,17] Here, we report the HRQOL results from the EORTC 1325-MG/KEYNOTE-054 trial.

Methods

Study design and participants

The EORTC 1325-MG/KEYNOTE-054 double-blind, randomised, controlled, phase 3 trial was done at 123 academic centres and community hospitals across 23 countries (appendix pp 19–23). Eligible patients were aged 18 years or older presenting with histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes (stage IIIA [at least one lymph node metastasis >1 mm], IIIB, or IIIC disease [without in-transit metastases], according to the American Joint Committee on Cancer staging system, seventh edition). Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of more than 1, autoimmune disease, uncontrolled infections, use of

systemic glucocorticoids, or previous systemic therapy for melanoma were excluded from this trial. Full eligibility criteria are in the protocol.[15] A tumour sample from melanoma-positive lymph nodes was required to be sent for central pathological assessment of PD-L1 expression. Membranous expression of PD-L1 in tumour cells and tumour-associated immune cells was assessed by means of a clinical trial immunohistochemistry assay. Full details are reported in the main study.[15]

The study protocol was approved by the EORTC protocol review committee and independent ethics committees. The trial was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference of Harmonization. All patients provided written informed consent.

Randomisation and masking

Registration was done at EORTC headquarters (Brussels, Belgium). Patients were randomly assigned (1:1) to receive pembrolizumab or placebo. Randomisation was done using a central interactive voice-response system based on a minimisation technique. Disease stage (AJCC-7 stage IIIA *vs* stage IIIB *vs* stage IIIC with 1–3 positive nodes *vs* stage IIIC with more than three positive nodes) and geographic region (17 regions, each formed by one to three countries) were used as stratification factors for randomisation. According to the main clinical study, the clinical investigators, patients, and those collecting or analysing data were not aware of trial group assignments except for the local pharmacists. Placebo was normal saline solution that was dosed and administered in the same manner as the investigational product. Both preparations looked the same.

Procedures

Patients received either an intravenous infusion of 200 mg of pembrolizumab or placebo every 3 weeks for a total of 18 doses (about 1 year) or until disease recurrence, unacceptable toxic effects, a major protocol violation, or withdrawal of consent. The rules regarding the withholding of a dose of pembrolizumab or placebo and the management of immune-related adverse events are detailed in the main study.[15]

The EORTC QLQ-C30 questionnaire was used to collect HRQOL data in this study. The EORTC-QLQ-C30 was selected for its robust psychometric properties and it is also one of the most frequently used measures for QOL assessments. Administration of HRQOL questionnaires took place at the hospital when patients came for a scheduled visit according to the EORTC guidelines for assessing QOL in EORTC clinical trials[18] and followed the clinical assessment schedule of the trial.

The EORTC QLQ-C30 (version 3.0) includes 30 items, which are transformed into 15 scales according to a standardised scoring procedure.[19] The QLQ-C30 includes five function scales (physical, role, emotional, cognitive, and social), eight symptom scales (fatigue, pain, nausea or vomiting, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), a scale to assess financial difficulties, and one global health status/quality-of-life scale (GHQ).[20] All EORTC QLQ-C30 scale scores range 0–100. A high score for a function scale represents a high level of functioning, whereas a high score for a symptom scale represents a high level of symptoms.[19] Extensively validated[19] and translated into more than 110 languages,[18] it has been used in numerous randomised, controlled trials involving patients with melanoma.[6,9,21]

GHQ was preselected for the study as the main HRQOL endpoint because it was used in previous melanoma studies and it can detect general or overall improvements or deteriorations in patients' QOL. Of the 30 items on the QLQ-C30, GHQ score is obtained from two items that assess the overall HRQOL of a patient: how would you rate your overall health during the past week?; and how would you rate your overall QOL during the past week? These items are assessed on a 7-point Likert-scale with the lowest value indicating very poor overall health and QOL and a high value indicating excellent overall health and QOL. These two items are grouped and transformed into a single 0–100 score according to the standard scoring procedure described in the EORTC QLQ-C30 scoring manual.[19]

The EORTC QLQ-C30 was completed at baseline (in the 6 weeks before randomisation) and subsequently every 12 weeks after commencing treatment for the first 2 years regardless of disease recurrence or treatment discontinuation.

Outcomes

The primary endpoint of the trial was recurrence-free survival in the intention-to-treat (ITT) population and in the subgroup of patients with PD-L1-positive tumours,[15] defined as the time from randomisation to the date of the first recurrence (local, regional, or distant metastasis) or death from any cause. The secondary endpoints included distant metastasis-free survival[17] and overall survival, which are being reported elsewhere.[15] In this Article, we report the prespecified exploratory QOL and health outcomes endpoints.

Statistical analysis

This study primarily aimed to test the hypothesis of no clinically relevant differences in global HRQOL between the two treatment groups, during the first 2 years after treatment commencement, despite the additional side-effects. Secondary objectives included evaluation of the effect of adjuvant pembrolizumab on HRQOL specifically during and after the treatment period. In addition, all other QLQ-C30 scales were analysed on a descriptive basis for exploratory purposes. A difference of 10 points on the 100-point QLQ-C30 scale between the two groups was considered clinically relevant. The standard deviation of this scale is about 20 points. With the two-sided α set at 5% and a power of 80% to detect a

difference of 10 points (effect size of 0·5), a minimum of 128 patients (64 per treatment group) is required. The planned sample size was 900 patients based on recurrence-free survival, the primary endpoint.[15]

All HRQOL scores from the two groups were compared using three summary statistics per patients: (1) the average change from baseline reported during the first 2 years; (2) the average change from baseline reported during treatment up to 21 days after last administration (average during pembrolizumab or placebo); and (3) the average change from baseline reported after treatment from 21 days to 2 years after last administration (average after pembrolizumab or placebo).

Non-parametric Wilcoxon rank-order tests were performed using a two-sided significance level of 5% to compare the treatment groups. Change from baseline per timepoint was reported in a descriptive manner to provide support for the main results. Data was scored according to the algorithm described in the EORTC scoring manual.[19] All questions were scored on categorical scales and linearly converted to 0–100 scales.

Because the study was overpowered for HRQOL endpoints, both statistical significance and clinical relevance were taken into consideration. Statistical significance can sometimes be achieved for small changes in patient-reported outcome measures that might not be clinically meaningful, thus differences were only considered as clinically relevant if they exceeded the protocol prespecified 10-point difference.[7] The scores for all HRQOL domains and cross-sectional descriptions of the average scores were presented descriptively and with a graphical display over time, by treatment group at each timepoint of assessment. 95% CIs for the means and mean differences were constructed using the Wilcoxon rank-sum test. All HRQOL analyses were performed according to the ITT principle. Compliance is presented as percentages without full numerator and denominators because these would otherwise divulge long-term follow-up that is ongoing.

As missing data are potential major sources of bias in HRQOL assessment, compliance rates were defined as the proportion of valid forms received versus the number expected and described by visit and treatment group using absolute numbers and relative percentage. At each timepoint, the Fisher's exact test was used to compare the compliance rates between the two treatment groups.

Sensitivity analyses to assess the robustness of the results were done by comparing the change from baseline scores per timepoint by treatment group, the change from baseline for the average after pembrolizumab or placebo and average during pembrolizumab or placebo summaries and repeating the main analysis after imputation of missing data. Missing (ie, expected but not received) GHQ values were imputed via a general linear regression model for the QOL scales with the absence or presence of an expected HRQOL form as a binary dependent variable. A general linear regression model with identity link, normal distribution of errors, and least squares estimation was fitted to the data. The following covariates were used to impute the missing QOL scores: treatment group, timepoint, and the stratification factors (disease stage and region) together with age (at time of randomisation), ECOG performance status (at baseline), sex, site of primary tumour, and Breslow thickness. In addition, a linear mixed-effects model was constructed adjusting for the stratification factors together with age (at time of randomisation; continuous), ECOG performance status (at baseline), sex, site of primary tumour, and Breslow thickness and baseline HRQOL score with treatment, a timepoint, and time–treatment interactions as fixed effects and a patient-specific random effect. Mean score estimates, standard errors, associated confidence intervals, and resulting test statistics were obtained from this model. On the basis of the observed results, a post-hoc analysis of the association between the

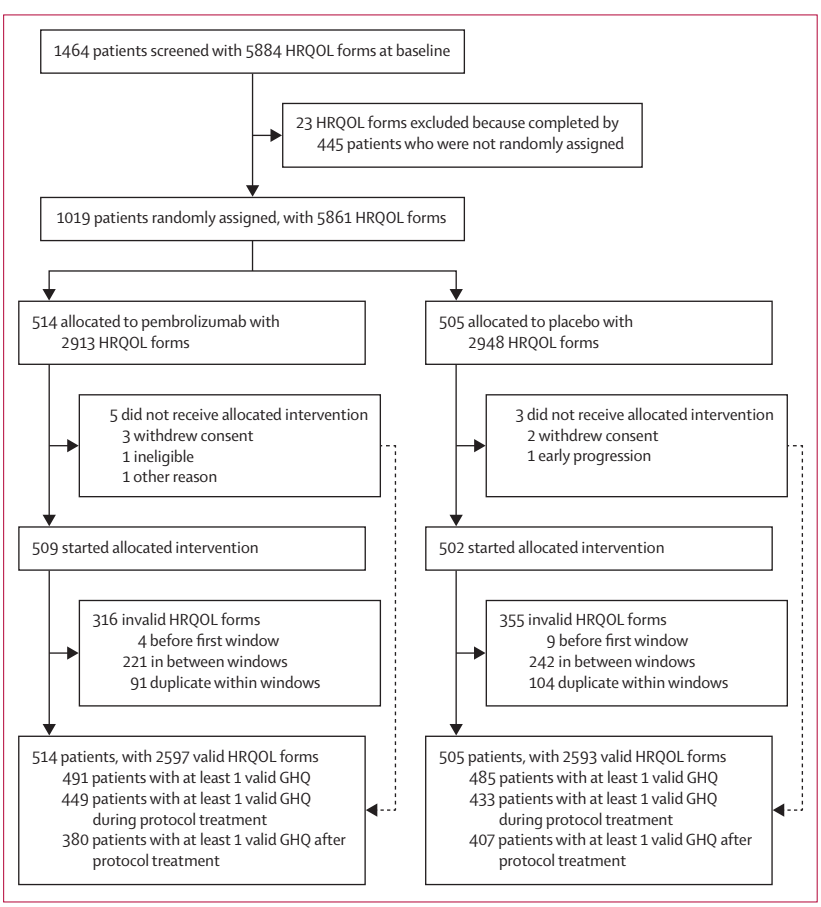


Figure 1: **Trial profile showing HRQOL compliance**
HRQOL forms were considered valid if they were collected within the prespecified time windows in relation to the target assessment time. Forms were considered invalid if any of the following were true: (1) all questions on the form were blank; (2) the completion date was unknown or it could not be assigned to a single assessment timepoint; (3) the completion date fell outside the time windows; or (4) multiple forms were received during the same time window. In the case of multiple forms for the same timepoint, the form closest to the intended assessment time was kept. In case of equidistance, the earlier form was kept. HRQOL=health-related quality of life. GHQ=global health/quality of life.

reported adverse events and QLQ-C30 outcomes was performed to investigate the sensitivity of the QLQ-C30 scales (appendix pp 16–18).

On Sept 25, 2017, the EORTC 1325 protocol was amended to include an interim analysis of recurrence-free survival. This amendment did not affect the HRQOL endpoints and has been described in more detail in the main publication.[15]

All analyses were done in accordance with the recent International Standards for the Analysis of Quality of Life and Patient Reported Data from Clinical trials[4,22] using SAS (version 9.4). The results were reported according to EORTC[18] and CONSORT-PRO extension guidelines.[23] The study is registered at ClinicalTrials.gov, NCT02362594, and EudraCT, 2014-004944-37.

Role of the funding source

The funders of the study had a role in study design, data interpretation, and writing of the report, but not data collection or data analysis.

Results

Between Aug 26, 2015 and Nov 14, 2016, 1019 patients were randomly assigned to pembrolizumab (n=514) or placebo (n=505) and constitute the ITT population. In December, 2017, the independent data and safety monitoring committee reviewed the unmasked results and recommended the reporting of the trial results as the final analysis. Median follow-up duration was 15·1 months (IQR 12·8–16·9) overall and was similar between the two treatment groups (14·7 months [IQR 12·7–16·9] in the pembrolizumab group and 15·4 months [12·9–16·7] in the placebo group). Baseline demographics and clinical characteristics were well balanced between the two groups (appendix p 2).[15]

HRQOL questionnaire completion rate in the ITT population was high at baseline (93·6%), but decreased over time, remaining greater than 70% during the first year, with the lowest rate at week 96 (62·1%; figure 1). Because of low absolute compliance numbers at later follow-up, the analysis was truncated to week 84 for all the subsequent analyses. The distributions of HRQOL scores at baseline for the scales of the EORTC QLQ-C30 were similar between the two treatment groups. Fisher's exact test showed no significant differences in compliance between the two groups (appendix pp 4, 14–15).

Only data from valid HRQOL forms were included in the analysis (figure 1). The baseline mean GHQ score was 77·55 (SD 18·20) in the pembrolizumab group and 76·54 (17·81) in the placebo group (table 1).

The primary test for overall treatment differences between the two treatment groups in the GHQ scale from baseline to 2 years was significant, but not clinically relevant at –2·2 points (95% CI –4·3 to –0·2; p=0·042; table 2). The treatment differences for average score during treatment and after treatment in the GHQ scale were neither statistically nor clinically significant (table 2). The GHQ scores assessed at each of the post-baseline assessments were similar at all timepoints for the two treatment groups (table 1; figure 2).

	Pembrolizumab group	Placebo group
Baseline	77·55 (18·20)	76·54 (17·81)
Week 12	75·89 (18·77)	77·99 (17·79)
Week 24	76·27 (18·54)	77·42 (17·44)
Week 36	75·21 (20·08)	76·98 (18·35)
Week 48	76·62 (18·42)	76·91 (19·08)
Week 60	76·81 (18·60)	78·08 (18·54)
Week 72	78·94 (17·23)	78·67 (16·63)
Week 84	81·43 (16·80)	80·05 (18·92)

Data are mean (SD).

Table 1: **Descriptive global health status and quality-of-life score over time**

	Pembrolizumab group (n=514)		Placebo group (n=505)		Difference (95% CI)	p value (Wilcoxon test)
	N	Mean (SD)	N	Mean (SD)		
Change from baseline to 2 years	491	75·1 (16·9)	485	77·3 (15·4)	–2·2 (–4·3 to –0·2)	0·042
During pembrolizumab or placebo	449	76·9 (16·0)	433	78·0 (15·4)	–1·1 (–3·2 to 0·9)	0·26
After pembrolizumab or placebo	380	75·0 (19·2)	407	77·2 (18·0)	–2·2 (–4·8 to 0·4)	0·16

Table 2: **Primary health-related quality-of-life results**

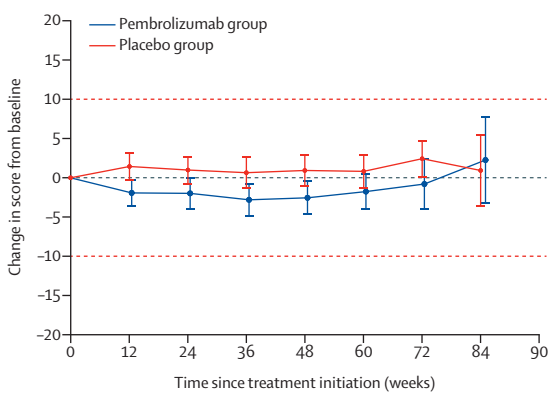
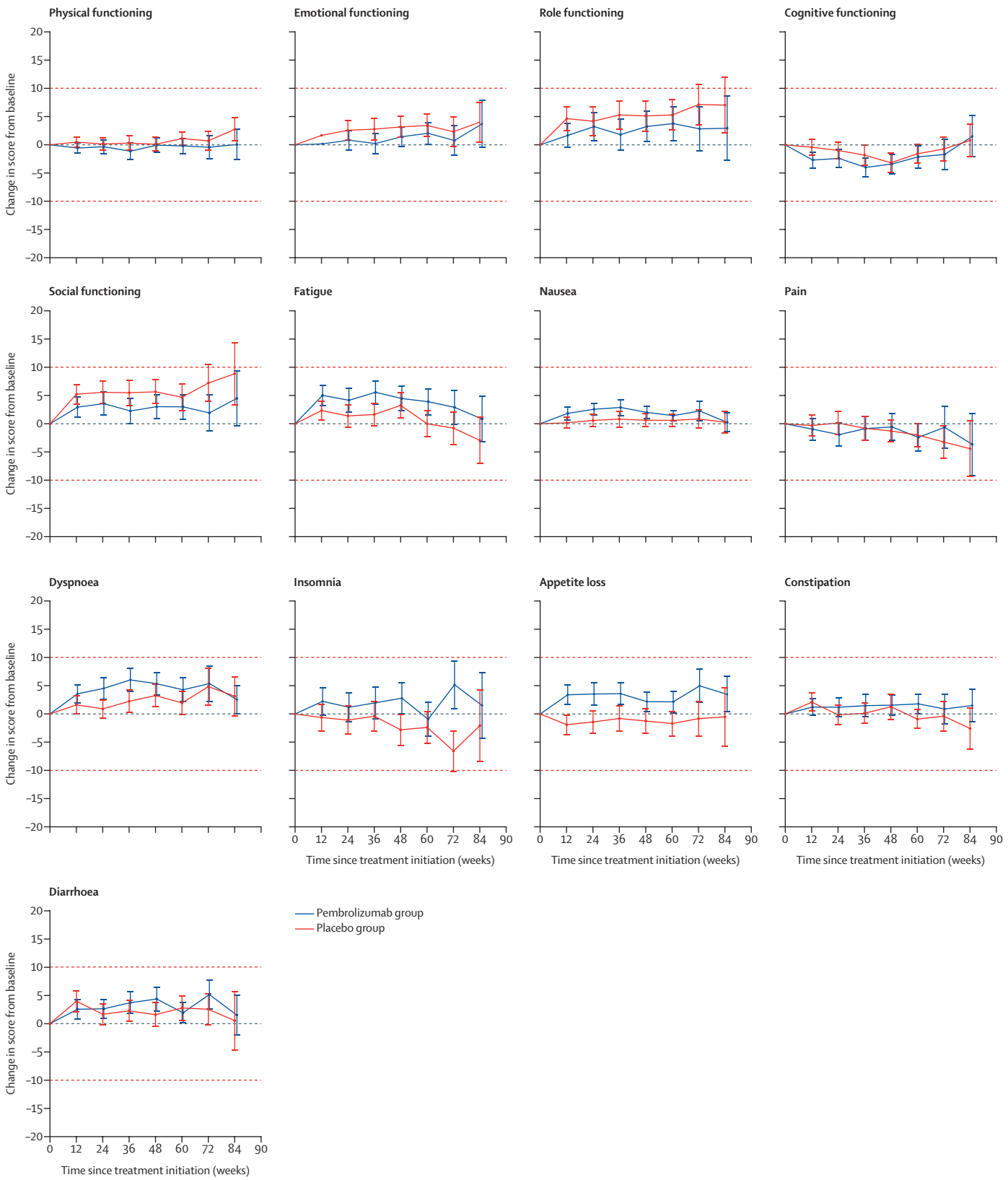


Figure 2: **Change in GHQ over time by treatment group**
Datapoints are means and error bars are 95% CIs. Horizontal dotted lines indicate the threshold for clinical relevance. GHQ=global health/quality of life.

The most commonly reported reasons for missing data were either not reported by the site (650 [44·9%] of 1448) or were an administrative error (443 [30·6%]), where either the patient or the staff forgot to complete the assessment; other reasons are in the appendix (p 1). Because these reasons are unlikely to be related to patients' health status, they can be considered as missing at random.[24]

Missing data were found to be related to time (with higher missingness at later timepoints), disease stage


Physical functioning
Emotional functioning
Role functioning
Cognitive functioning
Social functioning
Fatigue
Nausea
Pain
Dyspnoea
Insomnia
Appetite loss
Constipation
Diarrhoea
Change in score from baseline
20
15
10
5
0
−5
−10
−15
−20
0
12
24
36
48
60
72
84
90
Time since treatment initiation (weeks)
Pembrolizumab group
Placebo group

(with lower compliance for higher stage disease), and region (appendix p 3).

Sensitivity analyses yielded similar scores to the primary analysis, suggesting that the results are robust (appendix pp 5–8).

Except for GHQ scores and the financial difficulties scale, which were excluded upfront from the analysis plan as they are not generalisable because of the controlled clinical trial setting, results for all the other EORTC QLQ-C30 scales were similar between groups at most timepoints, with few statistically significant or clinically relevant differences (figure 3; appendix pp 9–13). The functional scale scores were high at baseline in both groups and remained stable, with no statistically significant or clinically relevant differences between groups over time (figure 3; appendix pp 14–15). Results for the symptom scales of the EORTC QLQ-C30 were similar to the functional scales (figure 3; appendix pp 14–15).

An additional post-hoc analysis was done to investigate the association between the reported adverse events and the QLQ-C30 outcomes. Results indicated that the occurrence of a specific side-effect did result in a HRQOL decrease on the corresponding QLQ-C30 scale (appendix pp 16–18).

Discussion

The results of our exploratory HRQOL endpoint analysis demonstrated that pembrolizumab had no clinically relevant effect on the GHQ scale compared with placebo, showing that prolonged recurrence-free survival does not necessarily come at the price of reduced HRQOL. Furthermore, various sensitivity analyses using different populations, methods, or outcomes supported the primary analysis, showing that overall, patients had a high level of GHQ.[25] Although statistically significant differences between pembrolizumab and placebo were noted for the overall effect of treatment on GHQ, this study was designed to detect an improvement in recurrence-free survival. Therefore, this study was overpowered for the exploratory HRQOL endpoint, resulting in small HRQOL treatment differences being statistically significant. We have mitigated this by using an absolute 10-point difference as benchmark to declare clinically relevant treatment effects.[7] Studies observed that thresholds for some scales could be much lower or even much higher, thus the 10-points change might not be relevant for all the scales.[26] However, this threshold has recently been revised and a difference as low as 5 points might still be considered clinically meaningful. This does not change the interpretation of the results, because the observed differences in HRQOL GHQ were within the 5-point clinical relevance threshold. Similar patterns were also observed with secondary scales—most differences between the treatment groups were neither statistically nor clinically significant (did not reach the prespecified 10-point threshold).

Furthermore, the results showed a good level of functioning in both treatment groups with higher or similar functioning scores as well as lower or similar symptom scores (fewer symptoms) compared with the general population.[25] Although the incidence of treatment-related adverse events grade 3 or higher was greater in the pembrolizumab group than the placebo group,[15,16] these effects were not reflected in the HRQOL scales. Exploratory analyses showed that adverse events are consistently reported by the patients in their corresponding QLQ-C30 scale. However, these reduced scores in QLQ-C30 scales are not substantial enough to result in relevant changes on the population level or for the overall GHQ scale. Adverse events not being reflected in the patient-reported outcomes can be a consequence of the masking of the treatment, whereby patients have treatment side-effects as indicators of the activity of the drug.

Comparing our results to the reference data for a similar population of patients with stage III or IV melanoma,[25] the baseline GHQ data obtained in this study are significantly higher for both groups (77·55 in the pembrolizumab group and 76·54 in the placebo group *vs* 69·7 in the reference data).[25] Similar results are seen in normative data obtained from a healthy population sample.[27] Indeed, the normative values present scores of 71·2.[25] These results show that patients included in the EORTC 1325-MG/KEYNOTE-054 trial have similar baseline GHQ to the general population. This could be explained by the selection criteria for the clinical trial, which required patients to be disease-free after complete resection with good performance status (ECOG 0–1) and a completely healed surgical wound.

A previous literature review compared HRQOL outcomes in patients with advanced solid tumours receiving PD-(L)1 inhibitors to patients who had had traditional cytotoxic therapy. The patients receiving PD-(L)1 inhibitors reported better quality of life than those who did not receive PD-(L)1 inhibitors.[28] The KEYNOTE-002 melanoma trial showed that in addition to a prolonged progression-free survival, GHQ scores were significantly higher in the pembrolizumab group than in the chemotherapy group.[29] Moreover, the KEYNOTE-006 advanced melanoma trial, which showed a prolonged progression-free survival and overall survival,[30] reported some additional benefits on HRQOL, and more specifically a more stable GHQ and a longer time to deterioration of HRQOL, in the pembrolizumab group than in the ipilimumab group.[31] The results of our study and those of previous studies in metastatic melanoma have demonstrated that pembrolizumab in the adjuvant setting improves survival outcomes

Figure 3: **Change in functioning and symptom scales over time by treatment group**

Datapoints are means and error bars are 95% CIs. Horizontal dotted lines indicate the threshold for clinical relevance.

(recurrence-free survival, progression-free survival, and overall survival), but has little effect on GHQ.

Published results of the EORTC 1325-MG/KEYNOTE-054 showed that in patients treated with pembrolizumab as an adjuvant therapy, 75 (14·7%) of 509 had treatment-related adverse events of grade 3 or worse.[15] Pembrolizumab appears to be less toxic than ipilimumab, with which 196 (41·6%) of 471 patients had treatment-related adverse events of grade 3 or worse.[14,15] One (0·2%) of 509 patients in the pembrolizumab group and five (1·1%) of 471 in the ipilimumab group had deaths related to study treatment. However, both pembrolizumab and ipilimumab treatments resulted in small or non-significant impairment in HRQOL, despite the number of reported grade 3 or worse adverse events with pembrolizumab being lower than with ipilimumab.

A common challenge to HRQOL in randomised, controlled trials, and a limitation in this study, is missing data. Compliance in this trial was good at baseline assessments and despite a decrease, remained within acceptable limits to allow the analyses to be performed as intended. Sensitivity analyses confirmed the results and an investigation into the causes of missing data showed no systematic bias. However, bias due to selective missing data can never be ruled out completely. In addition, it is important to note that no module was used to assess the specific symptoms seen in patients with resected, high-risk stage III melanoma, and that some symptoms or HRQOL issues could be better assessed with a specific instrument.

In summary, to the best of our knowledge, this trial is the first to show longer recurrence-free survival with adjuvant pembrolizumab than with placebo, without any significant impairment on patients' HRQOL, supporting the clinical use of the immune PD-1 inhibitor in resected, high-risk stage III melanoma. These results provide important information that pembrolizumab in the adjuvant setting does not result in a clinically significant decrease in the HRQOL compared with placebo. They will aid future clinical decision making by providing a comprehensive picture of the effect of pembrolizumab in patients with stage III melanoma after complete resection.

Contributors

AB, CC, SSu contributed to the study design, data interpretation, data analysis, data verification, and manuscript writing. AMME contributed to study design, data collection, data interpretation, and manuscript writing. AMH, AJMvdE, AMDG, ACJvA, CUB, CR, MSC, PR, PAA, SM, RG, RJ, SD, JL, LH-A, SP, AM, SSa, and RK contributed to data collection, data interpretation, and manuscript synthesis. JM contributed to data analysis. GVL contributed to data collection, data interpretation, and manuscript writing. MM, AK, DS, J-JG, and PCL contributed to data collection. VGA contributed to data collection and interpretation. MK contributed to data analysis and interpretation of the results. CK and IN contributed to study design and interpretation of the results. All authors reviewed the manuscript and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AMME reports non-financial support from Bristol Myers Squibb (BMS) and Merck & Co during the conduct of the study; personal fees from Biocad, BioInvent, BMS, CatalYm, GSK, IO Biotech, ISA pharmaceuticals, Merck, Novartis, Regeneron, Sellas, SkylineDx, Novartis, and Pfizer, outside the submitted work. AMH reports personal fees from Merck Sharp and Dohme (MSD); and personal fees from Novartis and BMS, outside the submitted work. AJMvdE reports grants and personal fees from BMS; grants from Roche and Idera; and personal fees from MSD, Amgen, Pierre Fabre, and Novartis, outside the submitted work. AM reports personal fees from Lilly Pharma, AstraZeneca Pharmaceuticals, Merck, BMS, and Sanofi-Aventis Group, outside the submitted work AMDG reports advisor or consultant roles from BMS, Pierre Fabre, Sanofi, and MSD, outside the submitted work. ACJvA reports grants and personal fees from Amgen and Merck-Pfizer; and personal fees from BMS, Novartis, MSD-Merck, Sanofi, Sirius Medical, and 4SC, outside the submitted work. CUB reports grants and personal fees from BMS and Novartis; personal fees from Roche, MSD, Pfizer, Lilly, Pierre Fabre, and GenMAb; grants from NanoString and Third Rock Ventures; stock ownership of Unity Cars; and is a cofounder of Immagene, outside the submitted work. CR participated in advisory boards for Roche, Pierre Fabre, Merck, Novartis, Amgen, BMS, Novartis, MSD, Sanofi, Biothera, and Ultimovacs. DS reports personal fees consulting or advisory role, honorarium, speakers bureau, travel, accommodations, and expenses from MSD during the conduct of the study; personal fees and non-financial support from Roche/Genentech, Merck Serono, and Merck; grants, personal fees, non-financial support, consulting or advisory role, honoraria, speakers bureau, travel, accommodations, expenses, and research funding from Novartis and Amgen; grants, personal fees, consulting or advisory role, honoraria, speakers bureau, travel, accommodations, expenses, and research funding from BMS; and personal fees from Immunocore, Incyte, 4SC, Pierre Fabre, Sanofi, Array BioPharma, Pfizer, Philogen, Regeneron, Nektar, and Sandoz, outside the submitted work. GVL reports personal fees from Aduro Biotech, Amgen, Array Biopharma, Boehringer Ingelheim, BMS, Highlight Therapeutics, MSD, Novartis Pharma, QBiotics, Rhegeneron Pharmaceuticals, and SkylineDX, outside the submitted work. NI and CK report personal fees from Merck & Co during the conduct of the study. J-JG reports personal fees from BMS, MSD, Novartis, Roche, Amgen, Pierre Fabre, and Sanofi; and personal fees from Merck and Pfizer, outside the submitted work. JL reports grants and personal fees from BMS, MSD, Pfizer, Novartis, Roche, Immunocore, Achilles therapeutics, and Nektar; personal fees from Eisai, GSK, Kymab, Secarna, AstraZeneca, Boston Biomedical, EUSA Pharma, Ipsen, Imugene, Incyte, iOnctura, Merck Serono, Pierre Fabre, Vitaccess, and Covance; and grants from Aveo and Pharmacyclics, outside the submitted work. LH-A reports personal fees from Merck during the conduct of the study; and personal fees from BMS, Merck, Amgen, Roche, Regeneron, Novartis, Immunocore, Merck-EMD, Corvus, Polynoma, and Genentech, outside the submitted work. MM reports grants from BMS, MSD, and Roche; and advisory board from Pierre Fabre, BMS, and MSD, outside the submitted work. MSC reports personal fees from MSD, BMS, Novartis, Roche, Pierre Fabre, and Sanofi; and personal fees from Merck Serono, Nektar, Eisia, and Ideaya, outside the submitted work. PAA reports grants and personal fees from BMS, Roche-Genentech, and Array; personal fees, advisory or consultant role, and travel support from MSD; personal fees from Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, NewLink Genetics, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, and Boehringer Ingelheim, outside the submitted work. PCL reports personal fees and advisory, speaker, and trials roles for BMS, Novartis, Amgen, GSK, and Chugai; and personal fees from Merck, outside the submitted work. PR reports personal fees from MSD, BMS, Novartis, Pierre Fabre, Blueprint Medicines, and Pfizer outside the submitted work. RG reports documentation fees to institution from MSD during the conduct of the study; personal fees and non-financial support from BMS, Roche Pharma, Merck Serono, Pierre Fabre, and Sanofi Regeneron; fees from MSD, Almirall Hermal, SUN Pharma, and 4SC; grants, personal fees, and non-financial support from Amgen and Novartis; grants and personal fees from Pfizer; and grants from Johnson & Johnson, outside the submitted work. RJ reports grants, fees paid to institution for the conduct of studies in melanoma, and grant for Investigator Initiated Trial in metastatic melanoma from BMS during the conduct of the study;

grants, per patients fees paid to the institution for the conduct of the study, and grant for Investigator Initiated Trial in metastatic melanoma from Merck; fees paid to the institution for the conduct of studies in melanoma from Roche/Genentech, GSK, AstraZeneca, and Novartis; and grants from Iovance, outside the submitted work; and has acted as a presenter or as a consultant in advisory boards for both BMS and Merck but has not received any monetary compensation for those roles. SD acts as principal investigator in clinical trials promoted by BMS and MSD and has received institutional research grants from BMS and MSD. SP reports grants from Leo Pharma, Almirall, Castle Bioscience, AMLO Bioscience, and Melagenics; personal fees from Amirall, Leo Pharma, Isdin, Sanofi, La Roche Posay, Regeneron, and Pfizer; speaker bureau from La Roche Posay, Roche, Pierre Fabre, BMS, Bioderma, and Sanofi, outside the submitted work. SSa reports personal fees from BMS and MSD outside the submitted work. SSu, MK, CC, and AK report grants from MSD during the conduct of the study. VGA reports personal fees and non-financial support from BMS; personal fees from Merck, MSD, Novartis, Pierre Fabre, Roche, and Nektar; and travel support from Onco-sec, outside the submitted work. All other authors declare no competing interests.

Data sharing

MSD, a subsidiary of Merck & Co (Kenilworth, NJ, USA) 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 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 assessing and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD 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 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 USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country-specific 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.

Acknowledgments

We are grateful to Merck & Co for supporting this independent EORTC study. We thank the investigators who participated to this study (appendix pp 16–20). We warmly thank all EORTC headquarters team members who have not been included among the co-author list of this publication, and who contributed to the study success (Sven Janssen, Robby Louis, Nathalie Elaut, Leen Wijnen, Gaetan de Schaetzen, Nitish Jha, Sandrine Rivrain, Monika Turek, and Abigirl Machingura) and Merck & Co team members (Veronica Rivas, Rachel Kloss Silverman, and Scott Diede). We thank the patients and their families for participating in this study.

References

1 Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med* 2017; **377:** 1813–23.

2 Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014; **384:** 1109–17.

3 Bottomley A, Pe M, Sloan J, et al. Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials. *Clin Trials* 2018; **15:** 624–30.

4 Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol* 2016; **17:** e510–14.

5 Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; **29:** 89–96.

6 Schadendorf D, Larkin J, Wolchok J, et al. Health-related quality of life results from the phase III CheckMate 067 study. *Eur J Cancer* 2017; **82:** 80–91.

7 US Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006; **4:** 79.

8 Eggermont AMM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet* 2008; **372:** 117–26.

9 Bottomley A, Coens C, Suciu S, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol* 2009; **27:** 2916–23.

10 Kilbridge KL, Cole BF, Kirkwood JM, et al. Quality-of-life-adjusted survival analysis of high-dose adjuvant interferon alpha-2b for high-risk melanoma patients using intergroup clinical trial data. *J Clin Oncol* 2002; **20:** 1311–18.

11 Eggermont AM, Chiarion-Sileni V, Grob J-J, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015; **16:** 522–30.

12 Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016; **375:** 1845–55.

13 Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. *Eur J Cancer* 2019; **119:** 1–10.

14 Coens C, Suciu S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2017; **18:** 393–403.

15 Eggermont AMM, Blank CU, Mandalà M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018; **378:** 1789–801.

16 Eggermont AMM, Blank CU, Mandalà M, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 trial. *J Clin Oncol* 2020; **38:** 3925–36.

17 Eggermont AMM, Blank CU, Mandalà M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a randomised, controlled, double-blind, phase 3 trial. *Lancet Oncol* 2021; published online April 12. https://doi.org/10.1016/S1470-2045(21)00065-6.

18 Young T, de Haes H, Curran D, et al. Guidelines for assessing quality of life in EORTC clinical trials. 2002. https://www.eortc.org/app/uploads/sites/2/2018/02/clinical_trials__guidelines_qol.pdf (accessed March 30, 2021).

19 Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 scoring manual (3rd edition). 2001. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf (accessed March 29, 2021).

20 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

For more on **MSD data sharing** see http://engagezone.msd.com/ds_documentation.php

21 Long GV, Atkinson V, Ascierto PA, et al. Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: results from the phase III CheckMate 066 study. *Ann Oncol* 2016; **27:** 1940–46.

22 Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol* 2020; **21:** e83–96.

23 Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013; **309:** 814–22.

24 Rubin DB. Inference and missing data. *Biometrika* 1976; **63:** 581–92.

25 Scott NW, Fayers PM, Aaronson NK, et al. EORTC QLQ-C30 reference values. July 2008. https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf (accessed March 29, 2021).

26 Musoro JZ, Bottomley A, Coens C, et al. Interpreting European Organisation for Research and Treatment for Cancer Quality of life Questionnaire core 30 scores as minimally importantly different for patients with malignant melanoma. *Eur J Cancer* 2018; **104:** 169–81.

27 Nolte S, Liegl G, Petersen MA, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *Eur J Cancer* 2019; **107:** 153–63.

28 Abdel-Rahman O, Oweira H, Giryes A. Health-related quality of life in cancer patients treated with PD-(L)1 inhibitors: a systematic review. *Expert Rev Anticancer Ther* 2018; **18:** 1231–39.

29 Schadendorf D, Dummer R, Hauschild A, et al. Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. *Eur J Cancer* 2016; **67:** 46–54.

30 Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015; **372:** 2521–32.

31 Petrella TM, Robert C, Richtig E, et al. Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma. *Eur J Cancer* 2017; **86:** 115–24.