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an open-label, randomised, phase 3 trial
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Health-related quality of life in patients treated with first-line pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer (KEYNOTE-177): a randomised phase 3 trial

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SUMMARY (473 of max 300 words)

Background In the open-label phase 3 KEYNOTE-177 study, pembrolizumab monotherapy provided statistically significant and clinically meaningful improvement in progression-free survival versus chemotherapy as first-line treatment in microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer. Results of the health-related quality of life (HRQoL) analyses are reported.

Methods In the randomised, open-label, phase 3 KEYNOTE-177 study conducted at 192 centres, patients aged ≥18 years with MSI-H/dMMR metastatic colorectal cancer, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and who had not received prior systemic therapy for metastatic disease were centrally randomised using an interactive voice response/integrated web response technology in the ratio of 1:1 to pembrolizumab 200 mg every 3 weeks or chemotherapy (mFOLFOX6 or FOLFIRI every 2 weeks ± bevacizumab or cetuximab). The primary end points were progression-free survival (previously reported) and overall survival (data to be reported at final analysis). HRQoL analysis was included as a prespecified exploratory end point. The analysis population included all randomised patients who received ≥1 dose of study treatment and completed ≥1 HRQoL assessment. HRQoL outcomes were change from baseline to pre-specified week 18 in EORTC QLQ-C30 and EORTC QLQ-CR29 scale/item scores, and EQ-5D-3L visual analogue scale (VAS) and health utility scores; proportion of patients with improved, stable, or deteriorated scores from baseline to pre-specified week 18 in EORTC QLQ-C30 scales/items; and time to deterioration (TTD) in EORTC QLQ-C30 global health status/quality of life (GHS/QoL), physical functioning, social functioning, and fatigue scores; and EORTC QLQ-CR29 urinary incontinence scores. The threshold for a small clinically meaningful mean difference in score for EORTC QLQ-C30 was 5-8 points.

This ongoing study is registered with ClinicalTrials.gov (NCT02563002); recruitment is closed.
**Findings** Between 11 February 2016, and 19 February 2018, 307 patients were enrolled. HRQoL analysis included 294 patients who received ≥1 dose of study treatment and completed ≥1 HRQoL assessment (pembrolizumab, n=152; chemotherapy, n=142). Median time from randomisation to data cutoff was 32.4 months (range, 24.0–48.3). Least squares mean (LSM) change from baseline to pre-specified week 18 showed clinically meaningful improvement in EORTC QLQ-C30 GHS/QoL with pembrolizumab versus chemotherapy (LSM difference: 8.96; 95% CI 4.24–13.69; two-sided nominal p=0.0002).

Pembrolizumab prolonged TTD versus chemotherapy in GHS/QoL (HR 0.61; 95% CI 0.38–0.98; one-sided nominal p=0.019), physical functioning (HR 0.50; 95% CI 0.32–0.81; one-sided nominal p=0.0016), social functioning (HR 0.53; 95% CI 0.32–0.87; one-sided nominal p=0.0050), and fatigue (HR 0.48; 95% CI 0.33–0.69; one-sided nominal p≤0.0001).

**Interpretation** Pembrolizumab monotherapy led to clinically meaningful improvements in health-related quality of life compared with chemotherapy in patients with previously untreated MSI-H/dMMR metastatic colorectal cancer. These data, along with previously reported clinical benefit, support pembrolizumab as a first-line treatment option for this patient population.

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**Panel: Research in Context**

**Evidence before this study**

We searched PubMed for clinical trials published from database inception through June 30, 2020, using the keywords (PD-1 OR PD-L1 OR MK-3475 OR pembrolizumab OR Keytruda OR BMS-936558 OR nivolumab OR Opdivo OR MPDL3280A OR atezolizumab OR Tecentriq OR MEDI4736 OR durvalumab OR Imfinzi OR MSB0010718C OR avelumab OR Bavencio) AND quality of life. No language restrictions were applied. Abstracts from the European Society for Medical Oncology Congress and the American Society of Clinical Oncology Annual Meeting were also searched using the same keywords, and the additional term “colorectal cancer.” Search results showed that monotherapy with pembrolizumab, nivolumab, or atezolizumab has shown favourable quality of life outcomes compared with chemotherapy in various tumour types, including non–small cell lung cancer, melanoma, urothelial cancer, and squamous cell carcinoma of the head and neck. Based on single-arm studies, nivolumab alone or in combination with ipilimumab has been reported to have a positive impact on health-related quality of life in patients with microsatellite instability-high (MSI-H) mismatch repair–deficient (dMMR) metastatic colorectal cancer. We found no comparative studies evaluating the effects on health-related quality of life of programmed death 1 or programmed death ligand 1 inhibitors compared with chemotherapy in colorectal cancer.

**Added value of this study**

We analysed patients’ health-related quality of life as pre-specified exploratory end points in KEYNOTE-177, an international, multicentre, open-label, randomised, phase 3 study. In patients with previously untreated MSI-H/dMMR metastatic colorectal cancer, clinically meaningful improvements in global health-related quality of life and prolonged median time to deterioration in global health-related quality of life, physical and social functioning and fatigue were observed with the use of pembrolizumab compared with chemotherapy with or without bevacizumab or cetuximab.
Implications of all the available evidence

The observed improvements in health-related quality of life with pembrolizumab over chemotherapy with or without bevacizumab or cetuximab complement the efficacy and safety results of KEYNOTE-177, which demonstrated superior progression-free survival and showed fewer treatment-related adverse events with pembrolizumab compared with standard of care chemotherapy. These findings further support pembrolizumab as a new standard of care in the first-line setting for patients with MSI-H/dMMR metastatic colorectal cancer.
INTRODUCTION

Colorectal cancers are the third most commonly diagnosed form of cancer and the second most common cause of cancer death worldwide.\(^1\) Treatment strategies for metastatic colorectal cancer have evolved rapidly over the last 10 years, leading to improvements in survival; however, treatments are not curative for most patients, and goals of treatment remain focused on prolonging survival, delaying tumour progression, managing symptoms, and improving/maintaining health-related quality of life (HRQoL).\(^2,3\)

As patients with metastatic colorectal cancer often exhibit disease-related symptoms, such as weight loss, fatigue, pain, and appetite loss, and treatment-related symptoms, such as neuropathy, HRQoL improvement is becoming an increasingly important measure in therapeutic decision-making for patients with metastatic colorectal cancer.\(^2,4,5\)

The addition of oxaliplatin or irinotecan to 5-fluorouracil and leucovorin in the first-line treatment of metastatic colorectal cancer has resulted in significant prolongation of survival with no additional impact on quality of life (QoL).\(^6,7\) When indicated, the addition of targeted therapies such as the vascular endothelial growth factor (VEGF) inhibitor bevacizumab or the epidermal growth factor receptor (EGFR) antagonists cetuximab or panitumumab can further improve survival in certain patients; however, there is little evidence that these treatment regimens provide improved HRQoL.\(^8,9\)

It has been suggested that patients with metastatic colorectal tumours that are high in microsatellite instability (MSI-H) and/or deficient in mismatch repair (dMMR) may be less responsive to conventional chemotherapy with or without VEGF inhibitors or EGFR antagonists; however, the literature to date is inconclusive and chemotherapy remains the standard of care for these patients.\(^10,11\) The clinical activity of pembrolizumab, a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1), has already been established in patients with MSI-H/dMMR metastatic colorectal cancer refractory to standard chemotherapy, and it is approved by the US Food and Drug Administration for the first-line treatment of unresectable or metastatic MSI-H/dMMR colorectal cancer.\(^12,13\) In the phase 3 KEYNOTE-177 (NCT02563002) trial, pembrolizumab monotherapy provided a statistically significant and clinically...
meaningful improvement in progression-free survival (PFS) compared with chemotherapy (mFOLOX6 or FOLFIRI) with or without bevacizumab or cetuximab as first-line therapy for MSI-H/dMMR metastatic colorectal cancer (median PFS 16.5 vs 8.2 months; hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.45–0.80; p=0.0002). Moreover, pembrolizumab monotherapy was associated with a lower incidence of grade ≥3 treatment-related adverse events (22% vs 66% of patients). These findings support the use of pembrolizumab monotherapy as an option for the first-line treatment of patients with MSI-H/dMMR metastatic colorectal cancer.

To further support the efficacy and safety findings of the KEYNOTE-177 study, health-related quality of life (HRQoL) outcomes were evaluated as pre-specified exploratory end points to assess the impact of pembrolizumab versus chemotherapy with or without bevacizumab or cetuximab on HRQoL. Results from the HRQoL analyses are presented here.

METHODS

Study design and participants

KEYNOTE-177 is a multicentre, open-label, randomised phase 3 study conducted at 192 cancer centres in 23 countries. Detailed methods along with efficacy and safety results have been reported elsewhere, and the protocol is available online. Briefly, eligible patients were aged ≥18 years, had metastatic colorectal carcinoma locally confirmed to be MSI-H by polymerase chain reaction (PCR) and/or dMMR by immunohistochemistry, had received no prior systemic therapy for metastatic disease, had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had life expectancy of ≥3 months, and had
adequate organ function. Additional eligibility criteria are provided in the appendix (p1-2) and in the protocol.

The study protocol and its amendments were approved by an independent institutional review board or ethics committee at each study site. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

**Randomisation and masking**

Patients were randomly assigned 1:1 to receive pembrolizumab monotherapy or chemotherapy. Investigator’s choice of chemotherapy (mFOLFOX6 or FOLFIRI, with or without bevacizumab or cetuximab) was determined prior to randomisation. Randomisation was performed centrally using an interactive voice response/integrated web response technology to prevent knowledge of the next assignment in the sequence. All patients were assigned a unique randomisation number, and all results were reviewed by the external Data Monitoring Committee. No stratification factors were used. The study was open-label; patients and investigators were not masked to treatment assignment.

**Procedures**

Patients received intravenous pembrolizumab 200 mg infusion over a period of 30 minutes every 3 weeks or investigator’s choice of mFOLFOX6 intravenously (oxaliplatin 85 mg/m² infusion for 2 hours on day 1, leucovorin 400 mg/m² infusion for 2 hours on day 1, 5-fluorouracil 400 mg/m² bolus on day 1 followed by a 2400 mg/m² infusion for 46–48 hours on days 1–2 every 2 weeks) or FOLFIRI intravenously (irinotecan 180 mg/m² infusion for 30–90 minutes on day 1, leucovorin 400 mg/m² infusion for 30–90 minutes on day 1, 5-fluorouracil 400 mg/m² bolus on day 1, then 2400 mg/m² infusion for 46–48 hours on days 1–2 every 2 weeks) with or without intravenous bevacizumab (5 mg/kg on day 1 every 2 weeks) or
Cetuximab (400 mg/m² infusion for 2 hours on day 1, followed by a 250 mg/m² infusion over 1 hour every week). Treatment continued until disease progression, unacceptable toxicity, patient or investigator decision to withdraw, or, for patients receiving pembrolizumab, completion of 35 cycles. Patients randomly assigned to receive chemotherapy could cross over to treatment with pembrolizumab after confirmed disease progression by blinded independent central review. Per the study protocol, no HRQoL data were planned to be collected in the crossover phase.

Microsatellite instability status was determined locally. Tumours were classified as MSI-H if at least two allelic shifts were detected among three to five microsatellite loci analysed using a polymerase-chain-reaction–based analysis. Tumours were classified as dMMR by the absence of at least one of four MMR proteins (MLH1, MSH2, MSH6, or PMS2) as determined by immunohistochemical analysis.

Three validated and commonly used HRQoL questionnaires were administered electronically by trained site personnel. The EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L) is a standardised questionnaire used to measure health outcomes using a visual analogue scale (VAS) and a descriptive system comprising five health state dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The VAS records the patient’s self-rated health status on a graduated scale from 0 (worst health you can imagine) to 100 (best health you can imagine). Each of the dimensions of the descriptive system has three levels (1, no problems; 2, some problems; 3, extreme problems) which determined the unique health state of each patient. In this analysis, these states were converted into utilities using the European algorithm. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) is a cancer-specific HRQoL questionnaire that is commonly used in colorectal cancer. The EORTC QLQ-C30 contains five functional scales (physical, social, role, cognitive, and emotional functioning), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status (GHS)/QoL scale, and six single items including symptoms commonly experienced by patients with cancer and an item to capture perceived financial impact of the disease and treatment (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and perceived financial impact).
EORTC QLQ-CR29 is a supplemental colorectal cancer-specific module with measures of CRC-associated symptoms that assesses common problems following treatment of colorectal cancer; it contains four scales (urinary frequency, blood and mucus in stool, stool frequency, and body image) and 19 single items (urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, anxiety, weight, flatulence, faecal incontinence, sore skin, embarrassment, stoma care problems, sexual interest [men], impotence, sexual interest [women], and dyspareunia). For each EORTC QLQ-C30 or QLQ-CR29 scale or item, a linear transformation was applied to standardize the score between 0 and 100. For both questionnaires, higher scores for GHS/QoL or functional scales indicate a better level of health status or functioning, while higher scores for symptom scales indicate an increased severity of symptoms. Questionnaires were administered at baseline and at weeks 2 or 3 (week 2 for the chemotherapy group and week 3 for the pembrolizumab group), 6, 9, 12, and 18, then every 9 weeks for up to 1 year or until the end of treatment (whichever came first), and at 30 days after treatment discontinuation. To minimise the impact of how patients responded to HRQoL assessments, questionnaires were completed before study drug administration, adverse event evaluation, or discussion of disease status; and in the following order at each collection: first EQ-5D-3L, then EORTC QLQ-C30, and EORTC QLQ-CR29 last.

**Outcomes**

The dual primary end points of the KEYNOTE-177 study were PFS per RECIST v1.1 by blinded independent central review and overall survival. PFS has been reported previously and overall survival data will be reported at final analysis. Secondary end points were overall response rate per RECIST v1.1 by blinded independent central review and safety. HRQoL outcomes were evaluated as pre-specified exploratory end points. HRQoL end points were mean score change from baseline to pre-specified week 18 in each scale and item of the EORTC QLQ-C30 and the EORTC QLQ-CR29, and in the EQ-5D-3L VAS and health utility scores; proportion of patients with improved, stable, or deteriorated scores from baseline to pre-specified week 18 in EORTC QLQ-C30 scores; and time to deterioration (TTD) in the
EORTC QLQ-C30 GHS/QoL, physical functioning, social functioning, and fatigue scores; and EORTC QLQ-CR29 urinary incontinence. The pre-specified week 18 time point was selected with the intention of ensuring a high number of patients would have completed the HRQoL assessment (60% completion rate; ≥80% compliance rate). In addition, at this time point it was expected that the majority of patients in both arms would not have had disease progression, allowing for meaningful comparison in HRQoL data between treatment arms. Post-baseline HRQoL scores for EORTC scales/items were classified as improved, stable, or deteriorated according to a ≥10-point change, as this is generally considered to be clinically meaningful when interpreting the results of randomised trials employing the EORTC QLQ-C30. However, more recent subscale-specific guidelines for the EORTC QLQ-C30 indicate that a mean difference of 5 to 8 points in the GHS/QoL score does represent a small clinically meaningful improvement. The threshold for a minimally important difference was 7 to 12 points for the EQ-5D-3L VAS score and 0.06 to 0.09 points for the EQ-5D-3L health utility score. TTD was defined as the time from baseline to the first onset of a ≥10-point decrease from baseline for functional scales or a ≥10-point increase for symptoms scales, with confirmation under the right-censoring rule. All available observations were used in the calculation of TTD.

Statistical analysis

Statistical methods for efficacy and safety analyses have been reported previously. Briefly, the study had 98% power to detect a hazard ratio (HR) of 0.55 for disease progression or death with a one-sided alpha of 0.25% based on 209 events of disease progression or death and 85% power to detect a HR of 0.62 for death with a one-sided alpha of 1.25% based on 190 deaths. No hypothesis testing was planned or conducted for the HRQoL end points, and there was no adjustment for multiplicity.

The HRQoL analysis population included all randomly assigned patients who received at least one dose of study treatment and completed at least one HRQoL assessment, with analysis according to allocated
treatment. Completion and compliance rates were summarised by treatment group and visit. Completion rate was defined as the number of patients in the HRQoL analysis population who completed at least one item of the HRQoL assessment divided by the number of patients in the HRQoL analysis population. Compliance rate was defined as the number of patients who completed at least one item divided by the number of eligible patients who were expected to complete the HRQoL assessment, excluding those missing by design for reasons including death, discontinuation, or translation not available. Change in least-squares mean (LSM) score from baseline to week 18 was assessed using a constrained longitudinal data analysis (cLDA) model, with HRQoL score as the response variable and treatment by study visit as a covariate. This model implicitly treats missing data as missing at random. LSM score change, 95% confidence intervals (CI), and nominal 2-sided p-values were calculated. TTD was estimated using the Kaplan–Meier method and compared between groups using a Cox proportional hazard model with Efron’s method of tie handling. HRs, 95% CIs, and one-sided p-values were calculated. P values are nominal and were not adjusted for multiplicity. Analyses were not corrected for confounders. Statistical analyses were performed using SAS (version 9-4). This study is registered with ClinicalTrials.gov (NCT02563002). Additional statistical methods are presented in the appendix (p 3-4)

Role of the funding source

The study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ, USA). The sponsor collaborated with the academic authors on study design, data collection, data analysis, and data interpretation. All authors had full access to the data. Editorial and writing assistance was provided by a professional medical writer and was funded by the sponsor. All authors were responsible for the decision to submit the manuscript for publication.

RESULTS
Between 11 February 2016 and 19 February 2018, a total of 307 patients were enrolled (appendix p11-12) and randomly assigned to receive pembrolizumab (N=153) or investigator’s choice of chemotherapy (N=154) (figure 1). All 153 patients in the pembrolizumab group received at least one dose of pembrolizumab and 143 patients in the chemotherapy group received at least one dose of study treatment. Of these patients, 152 receiving pembrolizumab and 142 receiving chemotherapy completed at least one HRQoL assessment and were included in the HRQoL analysis population (n = 294). As of 19 February 2020, median time from randomisation to data cutoff was 32·4 months (range, 24·0–48·3). Baseline characteristics of the overall HRQoL population were generally well balanced between treatment groups (appendix p13). Median age was 63·0 years in both groups. Seventy-five patients (49·3%) in the pembrolizumab group and 78 (54·9%) patients in the chemotherapy group had an ECOG performance status score of 0; 102 (67·1%) patients in the pembrolizumab group and 101 (71·1%) patients in the chemotherapy group had tumours on the right side; and 72 (47·4%) patients and 72 (50·7%) patients, respectively, had newly diagnosed metastatic disease (appendix p13).

At baseline, the EORTC QLQ-C30 was completed by 141 of 152 patients (92·8%) in the pembrolizumab group and 131 of 141 patients (92·9%) in the chemotherapy group; at week 18, the questionnaire was completed by 102 of 152 patients (67·1%) in the pembrolizumab group and 82 of 141 patients (58·2%) in the chemotherapy group (appendix p14-15). The proportion of patients completing HRQoL questionnaires declined over time, largely because of patients missing from the analysis by design (progressive disease, clinical progression, adverse events, death, or other reasons). At pre-specified week 18, 36 patients (23·7%) in the pembrolizumab group missed completing the EORTC QLQ-C30 by design, most commonly due to progressive disease or clinical progression (n=25), adverse events (n=5), or other causes including one death (n=6) (figure 1). Of the 116 (76·3%) patients in the pembrolizumab group who were expected to complete the EORTC QLQ-C30 at week 18, 14 (9·2%) patients did not complete the questionnaire due to site administrative error, patient being in hospital or hospice, patient refusal for other reasons, no records, or other reasons. At pre-specified week 18, 34 patients (24·1%) in the chemotherapy
group missed completing the EORTC QLQ-C30 by design, most commonly due to progressive disease or clinical progression (n=17), adverse events (n=5), or other causes including two deaths (n=12) (figure 1). Of the 107 (75.9%) patients in the chemotherapy group who were expected to complete the EORTC QLQ-C30 at week 18, 25 (17.7%) did not complete the questionnaire due to site administrative error, patient refusal for other reasons, no records, or other. These observations were similar for the other two questionnaires (appendix p16).

Compliance was higher than completion at all time points in both treatment arms (except at baseline) because the population for assessment of compliance excluded patients missing by design. At baseline, 141 of 152 patients (92.8%) in the pembrolizumab group and 131 of 141 patients (92.9%) in the chemotherapy group were compliant with the EORTC QLQ-C30; at week 18, 102 of 116 patients (87.9%) in the pembrolizumab group and 82 of 107 patients (76.6%) in the chemotherapy group were compliant with the EORTC QLQ-C30 (appendix p14-15). Completion and compliance rates for the EQ-5D-3L and EORTC QLQ-CR29 were almost identical to those observed for the EORTC QLQ-C30 (appendix p14-16).

At baseline, EORTC QLQ-C30 GHS/QoL scores were similar between treatment groups (table 1). Compared with baseline, EORTC QLQ-C30 GHS/QoL scores at week 18 showed slight improvement in the pembrolizumab group (LSM change 3.33; 95% CI −0.05 to 6.72) and worsened in the chemotherapy group (LSM change −5.63; 95% CI −9.32 to −1.94), with a clinically meaningful between-group LSM difference of 8.96 (95% CI 4.24−13.69; two-sided nominal p=0.0002) (table 1). EQ-5D VAS scores also showed slight improvement in the pembrolizumab group at week 18 compared with baseline (LSM change 4.50; 95% CI 1.16−7.83), whereas they showed slight worsening for the chemotherapy group (LSM change −2.88; 95% CI −6.46 to 0.69), with a between-group LSM minimally important difference of 7.38 (95% CI 2.82−11.93; two-sided nominal p=0.0016) (table 1). At week 18, the LSM change from baseline in EQ-5D health utility score was 0.04 (95% CI 0.00−0.08) in the pembrolizumab group and −0.01 (95% CI −0.05 to 0.02) in the chemotherapy group, with a small between-group LSM difference of
0.05 (95% CI 0.00–0.10; two-sided nominal p=0.031), which is not considered a minimally important difference (table 1).

EORTC QLQ-C30 GHS/QoL scores showed improvement over time (through week 45) in patients receiving pembrolizumab, and scores declined over time for patients receiving chemotherapy (figure 2 and appendix p17). Similar declines in EORTC QLQ-C30 scores were observed for physical functioning, social functioning, and fatigue for patients receiving chemotherapy (figure 2). From baseline to week 18, patients in the pembrolizumab group generally exhibited stable or improved scores in most of the EORTC QLQ-C30 and EORTC QLQ-CR29 functioning and symptom domains, while patients in the chemotherapy group generally exhibited worsening scores (figure 3 and appendix p18-19). The exceptions were in the emotional functioning domain of the EORTC QLQ-C30 and in the anxiety domain of the EORTC QLQ-CR29, in which an increase in LSM score compared with baseline was observed in both treatment arms. The domains with the largest differences between arms, all of which favoured pembrolizumab, included physical functioning, role functioning, social functioning, fatigue, pain, and appetite loss from the EORTC QLQ-C30 (figure 3) and body image, sexual interest (men), abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, and sore skin (in patients with a stoma) from the EORTC QLQ-CR29 (appendix p22-23).

Median TTD in EORTC QLQ-C30 GHS/QoL score was not reached (NR; 95% CI NR–NR) in the pembrolizumab group and not reached (95% CI NR–NR) in the chemotherapy group, with deterioration events in 30 of 141 patients (21.3%) and 39 of 131 patients (29.8%), respectively, at the time of analysis (figure 4). Median TTD was also NR in either treatment group for EORTC QLQ-C30 physical functioning (pembrolizumab, NR [95% CI NR–NR]; chemotherapy, NR [95% CI 5.2–NR]) or social functioning (pembrolizumab, NR [95% CI NR–NR]; chemotherapy, NR [95% CI NR–NR]). Median TTD for fatigue was NR (95% CI 8.5–NR) in the pembrolizumab group and was 2.1 months (95% CI 1.6–4.4) in the chemotherapy group (figure 4). Median TTD was NR (95% CI NR–NR) in the pembrolizumab group and NR (95% CI NR–NR) in the chemotherapy group for EORTC QLQ-CR29.
urinary incontinence. Compared with chemotherapy, pembrolizumab prolonged TTD in GHS/QoL (HR 0.61; 95% CI 0.38–0.98; one-sided nominal p=0.019) physical functioning (HR 0.50; 95% CI 0.32–0.81; one-sided nominal p=0.0016), social functioning (HR 0.53; 95% CI 0.32–0.87; one-sided nominal p=0.0050), and fatigue scores (HR 0.48; 95% CI 0.33–0.87; one-sided nominal p<0.0001). Prolonged TTD in urinary incontinence score was observed at later time points in the pembrolizumab group compared with the chemotherapy group (HR 0.43; 95% CI 0.14–1.31; one-sided nominal p=0.064) (figure 4).

At week 18, a greater proportion of patients in the pembrolizumab group had improved or stable EORTC QLQ-C30 GHS/QoL scores and all functioning and symptom scores (except insomnia) compared with those in the chemotherapy group (figure 5 and appendix p18-19). Additionally, a greater proportion of patients in the chemotherapy group had deteriorated EORTC QLQ-C30 GHS/QoL scores and all functioning and symptom scores compared with those in the pembrolizumab group.

**DISCUSSION**

In this analysis of pre-specified exploratory HRQoL end points from KEYNOTE-177, first-line pembrolizumab was associated with improvement in HRQoL compared with chemotherapy with or without bevacizumab or cetuximab in patients with MSI-H/dMMR metastatic colorectal cancer. At week 18, the pre-specified primary time point, a between-group LSM difference of 8.96 points (95% CI 4.24–13.69) in QLQ-C30 GHS/QoL score was observed with pembrolizumab versus chemotherapy, a difference that is considered clinically meaningful. Pembrolizumab-treated patients also consistently reported stable or improved HRQoL scores, whereas scores for patients treated with chemotherapy worsened for most HRQoL end points. The exceptions among functional scores were improvement seen in both treatment arms in emotional functioning in the EORTC QLQ-C30 and the anxiety domain of the EORTC QLQ-CR29 scale. Improvement was also seen with pembrolizumab in EQ-5D scores at week 18,
with a minimally important difference between treatment arms observed in VAS score and a small but not minimally important improvement in utility score. Pembrolizumab also prolonged TTD in multiple HRQoL measures compared with chemotherapy, including the EORTC QLQ-C30 GHS/QoL score (HR 0.61; 95% CI 0.38–0.98; p=0.019).

These findings may reflect the efficacy and safety analysis of KEYNOTE-177, where pembrolizumab showed prolonged PFS, increased overall response rate, and fewer treatment-related adverse events compared with chemotherapy. In the safety analysis, results of which have been reported elsewhere, pembrolizumab-treated patients had lower incidences of treatment-related adverse events than chemotherapy-treated patients, including diarrhoea, fatigue, nausea, vomiting, and decreased appetite; consistent with these findings, improvements were generally seen in corresponding symptom scores of the EORTC QLQ-C30 in the pembrolizumab arm. In comparison, patients in the chemotherapy arm generally exhibited worsening in symptom scores, including in fatigue, nausea and vomiting, appetite loss, and diarrhoea. The observed differences in HRQoL may also be influenced by improved convenience for patients with the pembrolizumab regimen, which involves shorter infusion times, less time in hospital for infusion, and longer intervals between treatments relative to chemotherapy.

Treatments that improve survival without negatively impacting HRQoL in patients with MSI-H/dMMR metastatic colorectal cancer are needed. The HRQoL results observed in this study align with previous studies in bladder cancer, melanoma, and non–small-cell lung cancer that demonstrated stability or improvement in HRQoL with pembrolizumab compared with chemotherapy. Improvements in HRQoL have also been demonstrated with immune checkpoint inhibitors in a non-randomised study (CheckMate 142 study) of nivolumab with or without ipilimumab in patients with MSI-H/dMMR metastatic colorectal cancer that had progressed following at least one prior treatment. Patients receiving nivolumab monotherapy exhibited statistically significant improvements in EQ-5D-3L VAS and health utility index scores from baseline through week 79 and week 61, respectively. In this cohort of heavily pre-treated patients with metastatic colorectal cancer, the LSM EORTC QLQ-C30 GHS/QoL score at
week 19 increased by 9·9 points from baseline following treatment with nivolumab. In the nivolumab plus ipilimumab cohort, most patients maintained functioning and GHS/QoL scores per EORTC QLQ-C30 from baseline, with statistically significant improvements in key HRQoL outcomes (symptoms, functioning, and GHS/QoL). However, to our knowledge, the HRQoL impact of nivolumab treatments has not been compared with that of standard chemotherapy or evaluated in the first-line setting of MSI-H/dMMR metastatic colorectal cancer.

Although the addition of cetuximab or bevacizumab to 5-fluorouracil-based chemotherapy regimens has improved overall survival in patients with metastatic colorectal cancer, there is little evidence that these treatments improve HRQoL. In the CRYSTAL study, the addition of cetuximab to first-line FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) in KRAS wild-type metastatic colorectal cancer had no significant impact on HRQoL, with stable EORTC QLQ-C30 GHS/QoL scores in both arms, regardless of early skin reactions. In the PRIME study, panitumumab plus FOLFOX4 versus FOLFOX4 alone as first-line therapy prolonged overall survival without having a negative effect on overall HRQoL in patients with metastatic colorectal cancer. Similarly, the addition of bevacizumab to 5-fluorouracil–based chemotherapy was shown to prolong survival but did not significantly improve TTD in HRQoL measures when added to 5-fluorouracil–based chemotherapy. In a prospective cohort study comparing HRQoL end points in patients with metastatic colorectal cancer treated with cetuximab- or bevacizumab-containing regimens, bevacizumab-based treatment led to a progressive positive impact on HRQoL compared with cetuximab-containing regimens. Based on the available evidence, immune checkpoint inhibitors appear to have a more favourable effect on HRQoL outcomes compared with chemotherapy-based regimens in patients with metastatic colorectal cancer, and pembrolizumab is the only agent to have shown improvement in HRQoL in a randomised trial in the first-line setting.

One of the main limitations of this study was the difference in completion and compliance rates between the treatment arms, which may have impacted the results observed. At pre-specified week 18, 67·1% of patients in the pembrolizumab arm completed the EORTC QLQ-C30 questionnaire compared with 58·2%
of patients in the chemotherapy arm, despite similar proportions of patients missing completing the questionnaire by design. Compliance was 87·9% for pembrolizumab and 76·6% for chemotherapy. Given that the study was open label, one possible explanation for the difference in compliance rates may be that patients receiving pembrolizumab were more willing to participate with study investigations due to the perceived benefit of the experimental treatment. By week 18, a slightly higher proportion of patients in the pembrolizumab arm had been excluded from the analysis due to clinical progression or progressive disease compared with the chemotherapy arm (16·4% vs 12·1%). By week 45, a substantially smaller proportion of patients in the pembrolizumab arm discontinued due to clinical progression or progressive disease compared with the chemotherapy arm (30·3% vs 44·0%). These results reflect the significant improvement in PFS with pembrolizumab reported in the KEYNOTE-177 efficacy analysis.\textsuperscript{14} However, these differences in discontinuation may also have impacted completion and compliance for HRQoL assessment and potentially altered the balance of responses received, although this would have been more prominent at week 45 than week 18 (the prespecified time point for the HRQoL analysis) given the magnitude of difference at each time point.

Additional limitations of this study include that the analyses were exploratory, no formal hypothesis testing was performed, and there was no adjustment for potential confounders such as disease progression. HRQoL data were also only collected during treatment (up to 1 year) and at the 30-day visit following discontinuation of treatment, thereby limiting analysis of HRQoL to the period during which patients remained on treatment. The impact on HRQoL beyond treatment discontinuation remains unclear, as does the impact on patients who crossed over from chemotherapy to pembrolizumab. Despite these limitations, HRQoL analyses provide essential information that is difficult to capture outside of a clinical trial. Therefore, these results contribute important information regarding the evaluation of risks and benefits of pembrolizumab in patients with MSI-H/dMMR metastatic colorectal cancer. The EQ-5D-3L, EORTC QLQ-C30, and EORTC QLQ-CR29 questionnaires were selected during study design to best cover the HRQoL impact of treatment for patients with colorectal cancer. As it is now possible to
supplement the EORTC modules with additional items specific to treatment with immune checkpoint inhibitors, their inclusion could be considered in future trials.33

Taken together with previously published efficacy and safety results,14 these data support the benefit of pembrolizumab as first-line treatment for MSI-H/dMMR metastatic colorectal cancer. The significantly prolonged PFS, lower incidence of treatment-related adverse events, and improvement in HRQoL outcomes with pembrolizumab versus chemotherapy further support that pembrolizumab should be considered an option for first-line treatment for this patient population.
**Contributors**

MA, LAD, TY, and DTL were involved in the conception, design, or planning of the study.

TA, KKS, BVJ, LHJ, CJAP, DS, RGC, IS, CDLF, FR, EE, TY, EVC, MF, and DTL acquired data for the study.

TA, MA, TY, EVC, PY, DTL, and TWK analysed the data.

TA, MA, JMN, KKS, TWK, BVJ, LHJ, CJAP, DS, RGC, IS, CDLF, FR, EE, TY, EVC, PY, and DTL interpreted the results.

TA, LAD, TY, and DTL drafted the manuscript with contribution from all authors.

TA, MA, JMN, KKS, TWK, BVJ, LHJ, CJAP, DS, RGC, IS, CDLF, FR, EE, LAD, TY, EVC, PY, MF, and DTL critically reviewed or revised the manuscript for important intellectual content.

All authors reviewed the interim drafts and the final version of the manuscript and agree with its content and submission. All authors had access to all the relevant study data and related analyses and vouch for the completeness and accuracy of the data presented. TA and DTL have accessed and can verify the underlying data. TA had final responsibility to submit this manuscript for publication.

**Declaration of interests**

TA reports consulting/advisory role and or received honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Chugai, Clovis Oncology, GlaxoSmithKline, Gritstone Oncology, HalioDx, Pierre Fabre, Roche/Ventana, Sanofi, Servier, Tesaro and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD); travel, accommodations, and expenses from Roche/Ventana, Bristol Myers Squibb, and MSD; speaker bureau fees from Bristol Myers Squibb and Servier; and research funding from MSD. TA reports participation in the scientific committee of ARCAD foundation and GERCOR group as non-renumerated activities.

MA reports employment at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and is a shareholder in Merck & Co., Inc., Kenilworth, NJ, USA.
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K-KS reports honoraria from Bristol Myers Squibb, Guardant Health, Innovent Biologics, Merck KGaA, Roche, and Servier; consulting/advisory role for Roche; research grant/funding from Amgen, Bristol Myers Squibb, Gilead, Merck KGaA, Roche, and MSD; and travel, accommodations, and expenses from Merck KGaA, Innovent Biologics, and MSD.

TWK reports research grant/funding from Merck Serono, AstraZeneca, and Pfizer.

BVJ reports research grant/funding from MSD.

LHJ’s reports research grant/funding to his institution from 2cureX, Incyte, Bristol Myers Squibb, and MSD.

CJAP reports advisory roles for Bayer, Nordic Pharma, and Servier.

DS has nothing to disclose.

RG-C has provided scientific advice, attended speakers bureau, and/or received honoraria from AAA, Advanz Pharma, Bayer, Bristol Myers Squibb, HMP, Ipsen, Merck & Co., Inc., Kenilworth, NJ, USA, Midatech Pharma, Novartis, PharmaMar, Pfizer, Pierre Fabre, Roche, Sanofi, Servier, and MSD; and has received support to his institution for the conduct of clinical trials or for molecular diagnostic platforms from ARMO Biosciences, AstraZeneca, Pfizer, Novartis, Ipsen, Roche, Pharmacyclics, Boston
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IS reports advisory/consultancy roles for Ipsen, Pfizer, Syrtex, Amgen, and Pharmamar; and speaker bureau fees from AAA, Sanofi, and Novartis.

CDLF reports advisory/consultancy roles for Roche, Pierre Fabre, Oncologie, Eisai, Bayer, and MSD; and travel, accommodations, and expenses from Amgen, Eisai, Bristol Myers Squibb, and Roche.

FR reports honoraria, advisory/consultancy roles, research grant/funding, and travel, accommodations, and expenses from Roche, Merck-Serono, Sanofi, Bristol Myers Squibb, Servier, Lilly, Amgen, Bayer, Celgene, and MSD.

EE reports personal financial interests, honoraria, advisory roles, travel grants, and research grants from Hoffman–La Roche, Sanofi, Aventis, Amgen, Merck Serono, Servier, Array Pharmaceuticals, Bristol Myers Squibb, and MSD; and institutional financial interests and honoraria from Hoffman–La Roche, Sanofi Aventis, Amgen, Merck Serono, Boehringer Ingelheim, AbbVie, Array Pharmaceuticals, Pierre Fabre, Novartis, Bristol Myers Squibb, GlaxoSmithKline, MedImmune, and MSD.
LAD is a member of the board of directors of Personal Genome Diagnostics (PGDx) and Jounce Therapeutics. He is a compensated consultant to PGDx, 4Paws (PetDx), Innovatus CP, Se’er, Kinnate, and Neophore. He is an uncompensated consultant to Merck & Co., Inc., Kenilworth, NJ, USA. He has received research support for clinical trials from Merck & Co., Inc., Kenilworth, NJ, USA. LAD is an inventor of multiple licensed patents related to technology for circulating tumor DNA analyses and mismatch repair deficiency for diagnosis and therapy from Johns Hopkins University. Some of these licenses and relationships are associated with equity or royalty payments directly to Johns Hopkins and LAD. He holds equity in PGDx, Jounce Therapeutics, Thrive Earlier Detection, Se’er, Kinnate and Neophore. His spouse holds equity in Amgen. The terms of all these arrangements are being managed by Johns Hopkins and Memorial Sloan Kettering in accordance with their conflict of interest policies.


EVC reports advisory board roles for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Halozyme, GlaxoSmithKline, Incyte, Ipsen, Lilly, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, Taiho, and MSD; and research funding from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Merck KGaA, Novartis, Roche, Servier, and MSD.

PY reports employment at MSD China Holding Co., Ltd.

MF reports reports employment at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and is a shareholder in Merck & Co., Inc., Kenilworth, NJ, USA.
DTL reports advisory board roles for MSD and Bristol Myers Squibb; research funding from MSD, Bristol Myers Squibb, Aduro Biotech, Curegenix, Medivir, and Nouscom; honoraria from MSD; and is an inventor of licensed intellectual property from Johns Hopkins University.

Data sharing statement
Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized patient-level data and clinical study reports from the company’s clinical trials for the purpose of conducting legitimate scientific research. The company is also obligated to protecting 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 process includes submission of data requests to the MSD data sharing website available at http://engagezone.msd.com/ds_documentation.php. 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 the requested data.

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**Ethics Committee Approval**

The study protocol and its amendments were approved by an independent institutional review board or ethics committee at each study site. The study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.
References


TABLES/FIGURES

Figure legends

Figure 1. CONSORT diagram for the EORTC QLQ-C30 questionnaire.

*11 patients received mFOLFOX6 only, 64 mFOLFOX6 plus bevacizumab, 5 mFOLFOX6 plus cetuximab, 16 FOLFIRI alone, 36 FOLFIRI plus bevacizumab, and 11 FOLFIRI plus cetuximab.

AE=adverse event; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30 items.

Figure 2. Mean change from baseline in EORTC QLQ-C30 scores over time

LSM change from baseline in EORTC QLQ-C30 (A) GHS/QoL, (B) physical functioning, (C) social functioning, and (D) fatigue scores by visit. Error bars indicate 95% CIs around the mean. Higher GHS/QoL and functioning scores represent better health status or functioning, and higher scores for fatigue indicate an increased symptom severity. CI=confidence interval; EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL=global health status/quality of life; LSM=least-squares mean.

Figure 3. Mean change from baseline to week 18 for EORTC QLQ-C30 scales

LSM change in (A) GHS/QoL and functional scales at week 18 and (B) in symptom scales at week 18. Error bars indicate 95% CIs around the mean. Higher GHS/QoL scores represent better GHS/QoL and higher functional subscale scores represent better functioning, whereas higher symptom subscale scores represent increased symptoms. CI=confidence interval; EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL=global health status/quality of life.
Figure 4. Kaplan–Meier curves of time to deterioration in EORTC QLQ-C30 scores

Time to deterioration in (A) GHS/QoL, (B) physical functioning, (C) social functioning, and (D) fatigue, based on relevant items in the EORTC QLQ-C30, and (E) urinary incontinence based on the relevant item in the EORTC QLQ-CR29. Time to deterioration was defined as first onset of a ≥10-point change in score from baseline. *Based on Cox regression model with treatment as a covariate. †One-sided p-value based on log-rank test. CI=confidence interval; GHS/QoL=global health status/quality of life; EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CR29=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Colorectal 29; NR=not reached.

Figure 5. Proportion of patients with improved, stable, and deteriorated EORTC QLQ-C30 scores at week 18

(A) GHS/QoL and functional scales at week 18. (B) Symptom scales at week 18. Chemo=chemotherapy; EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL=global health status/quality of life; Pembro=pembrolizumab; SOC=standard of care.
Table 1. Mean changes from baseline to week 18 in EORTC QLQ-C30 GHS/QoL, EQ-5D VAS, and EQ-5D health utility scores

<table>
<thead>
<tr>
<th></th>
<th>EORTC QLQ-C30 GHS/QoL Score</th>
<th>EQ-5D VAS Score</th>
<th>EQ-5D Health Utility Score</th>
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<tr>
<td></td>
<td>Pembrolizumab</td>
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<td>Pembrolizumab</td>
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<td><strong>Baseline</strong></td>
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<tr>
<td>Completed</td>
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<td>131</td>
<td>142</td>
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<tr>
<td>questionnaire, n</td>
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<td></td>
<td></td>
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<tr>
<td>Mean score (SD)</td>
<td>66·19 (21·03)</td>
<td>66·60 (20·74)</td>
<td>70·12 (18·86)</td>
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<td><strong>Week 18</strong></td>
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<tr>
<td>Completed</td>
<td>102</td>
<td>82</td>
<td>102</td>
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<tr>
<td>questionnaire, n</td>
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<tr>
<td>Mean score (SD)</td>
<td>72·14 (20·53)</td>
<td>62·60 (17·68)</td>
<td>76·86 (17·92)</td>
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<td>Change from baseline*</td>
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<tr>
<td>Included in analysis, n</td>
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<td>141</td>
<td>151</td>
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<tr>
<td>LSM change from baseline (95% CI)</td>
<td>3·33</td>
<td>–5·63</td>
<td>4·50</td>
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<td></td>
<td>(–0·05 to 6·72)</td>
<td>(–9·32 to –1·94)</td>
<td>(1·16–7·83)</td>
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<td>LSM difference (95% CI)</td>
<td>8.96 (4.24–13.69)</td>
<td>7.38 (2.82–11.93)</td>
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<tr>
<td>p=0.0002‡</td>
<td>p=0.0016‡</td>
<td>p=0.031‡</td>
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</table>

Data are n, mean (SD), or LSM (95% CI).

CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30 items; EQ-5D=EuroQoL 5 Dimensions; LSM=least-squares mean; SD=standard deviation; VAS=visual analogue scale.

*Based on a constrained longitudinal data analysis model with HRQoL scores as the response variable, and treatment by study visit interaction as covariates.

†Analysis using constrained longitudinal data analysis model involved patients with at least one baseline or post-baseline assessment.

‡p-values are two-sided and nominal.