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Health-related quality of life with pembrolizumab monotherapy in patients with previously treated advanced microsatellite instability high/mismatch repair deficient endometrial cancer in the KEYNOTE-158 study

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HIGHLIGHTS

- In KEYNOTE-158, ORR was 48% with pembrolizumab for previously treated advanced MSI-H/dMMR endometrial cancer (EC).
- Pre-specified analyses in KEYNOTE-158 included health-related quality of life (HRQoL) assessments from baseline to week 9.
- Changes from baseline in EORTC QLQ-C30 scores showed pembrolizumab improved or preserved HRQoL in this patient population.
- HRQoL improvements from baseline were greatest in patients who achieved an objective response.
- Combined with efficacy and safety data, these HRQoL data support pembrolizumab for previously treated, advanced MSI-H/dMMR EC.

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ABSTRACT

Objective. Pembrolizumab demonstrated a clinically meaningful objective response rate in patients with previously treated, advanced MSI-H/dMMR endometrial cancer in the multicohort phase 2 KEYNOTE-158 study (ClinicalTrials.gov, NCT02628067). We present health-related quality of life (HRQoL) results for these patients.

Methods. This analysis included patients from cohorts D (endometrial cancer with any MSI status) and K (any MSI-H/dMMR solid tumor except colorectal) who had previously treated, advanced MSI-H/dMMR endometrial cancer. Patients received pembrolizumab 200 mg Q3W for 35 cycles. EORTC QLQ-C30 and EQ-5D-3L questionnaires were administered at baseline, at regular intervals during treatment, and 30 days after treatment discontinuation. Pre-specified exploratory analyses included changes from baseline to week 9 in QLQ-C30 global health status (GHS)/QoL and EQ-5D-3L visual analog scale (VAS) score for all patients and by best overall response.

Results. 84 of 90 enrolled patients completed ≥1 HRQoL questionnaire and were included in the analysis. QLQ-C30 and EQ-5D-3L compliance rates were 90% and 94%, respectively, at baseline, and 92% and 93% at week 9. Mean (95% CI) QLQ-C30 GHS/QoL scores improved from baseline to week 9 by 6.08 (0.71–11.46) points in the overall population, with greater improvement in patients who achieved complete or partial response

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(11.67 [5.33–18.00]-point increase). Mean (95% CI) EQ-5D-3L VAS scores improved by 6.00 (2.25–9.75) points in the overall population and 9.11 (5.24–12.98) points in patients with CR/PR.

Conclusions. Pembrolizumab maintained or improved HRQoL in patients with previously treated, advanced MSI-H/dMMR endometrial cancer, further supporting efficacy and safety results from KEYNOTE-158 and pembrolizumab use in this setting.

1. Introduction

Endometrial cancer, the second most common form of gynecologic cancer among women worldwide [1], has been increasing in incidence, particularly in developed countries [1–3]. Although endometrial cancer is often diagnosed at an early stage with good prognosis [2], the 5-year relative survival rate for patients with metastatic disease was recently reported to be 17% [4], and better treatment options are needed. Standard first-line systemic therapy for recurrent or metastatic endometrial cancer is chemotherapy with carboplatin and paclitaxel [5]; however, many patients ultimately experience disease progression or recurrence after platinum-based chemotherapy, with limited subsequent treatment options [6]. Newer treatment strategies for advanced disease that consider mechanisms of oncogenesis and immune surveillance are emerging.

Microsatellite instability (MSI), which is caused by DNA mismatch repair deficiency (dMMR), results in high mutational burden and increased cancer risk [7,8]. Approximately 25% to 31% of patients diagnosed with endometrial cancer have high levels of microsatellite instability (MSI-H) and dMMR [7,9]. The immune checkpoint receptor programmed death 1 (PD-1) and its ligand PD-L1 are often upregulated in MSI-H tumors, both on tumor cells and infiltrating lymphocytes [10]. MSI-H/dMMR status is therefore a biomarker of interest for identifying patients likely to experience treatment response with immunotherapy. The phase 2 KEYNOTE-158 study (ClinicalTrials.gov, NCT02628067) is a nonrandomized, open-label, multicohort study of the anti–PD-1 immunotherapy pembrolizumab across multiple types of advanced (unresectable and/or metastatic) rare cancers that progressed on prior therapy. Efficacy analyses from KEYNOTE-158 among patients with previously treated advanced MSI-H/dMMR endometrial cancer from cohort D, which enrolled patients with endometrial cancer irrespective of MSI status, and cohort K, which enrolled patients with any MSI-H/dMMR advanced solid tumor except colorectal cancer, have previously been reported [11], with pembrolizumab demonstrating an objective response rate of 48% (95% CI, 37%–60%), including 11 patients (14%) with a complete response (CR), and median duration of response that was not reached (range, 2.9 to 49.7+ months).

Patients with endometrial cancer have reported an adverse impact on health-related quality of life (HRQoL) from both the disease and standard treatments, and improving QoL with efficacious and well-tolerated treatments is an important goal [2,12,13]. Among cancer survivors in general, symptoms that reduce QoL include pain, fatigue, anxiety, distress, and depression [12]. Additional disease and treatment effects that can reduce QoL specifically in patients with endometrial cancer include vaginal bleeding, lymphedema, urinary and bowel symptoms, and peripheral neuropathy [14,15]. The Gynecologic Cancer InterGroup has highlighted the increasing role that patients play in treatment selection and that QoL concerns may impact their decisions, underscoring the importance of assessing HRQoL in clinical trials [16]. Patient-reported outcomes (PROs) were assessed as pre-specified exploratory endpoints in KEYNOTE-158 [11]. Here we present results from the HRQoL analyses among patients with previously treated advanced MSI-H/dMMR endometrial cancer.

2. Methods

2.1. Study design and patient eligibility

In the open-label, multicohort, nonrandomized phase 2 KEYNOTE-158 study (ClinicalTrials.gov, NCT02628067), patients with advanced endometrial cancer were enrolled into 1 of 2 cohorts: cohort D, which included patients with advanced endometrial cancer regardless of MSI/MMR status (sarcomas and mesenchymal tumors excluded), and cohort K, which opened for enrollment later than cohort D and included patients with any MSI-H/dMMR advanced solid tumor except colorectal cancer. Patients with MSI-H/dMMR disease were preferentially enrolled into cohort K once it opened. In addition, eligible patients were aged ≥18 years and had histologically or cytologically documented metastatic and/or unresectable, incurable disease, with progression on or intolerance to prior standard therapy; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (per independent central radiologic review); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate organ function based on laboratory assessments. Patients were excluded if they had a diagnosis of immunodeficiency or had received systemic steroids within 7 days before the study or had active autoimmune disease requiring systemic treatment within 2 years before the study; if they had previously received an anticancer monoclonal antibody within 4 weeks, or prior chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks before study treatment; or had not recovered from an adverse event (AE) of any grade due to these therapies. Additional exclusions included active central nervous system metastases (previously treated brain metastases permitted, if stable) or carcinomatous meningitis; current pneumonitis or a history of noninfectious pneumonitis requiring steroid therapy; or any active infection requiring systemic treatment.

This study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent before participating in the study. The protocol and all amendments were approved by the institutional review board or ethics committee at each participating institution.

2.2. Study treatment

Patients received pembrolizumab 200 mg intravenously every 3 weeks for 35 cycles (approximately 2 years) or until documented disease progression, unacceptable toxicity, intercurrent illness preventing further treatment, investigator decision, or patient withdrawal of consent.

2.3. Assessments

As previously described, tumor MSI/MMR status was assessed retrospectively by a central laboratory in cohort D using polymerase chain reaction (PCR)–based assays, and was assessed prospectively at local laboratories in cohort K using PCR and/or immunohistochemistry (IHC). MSI/MMR status was determined by immunohistochemistry

based on loss of protein expression for enzymes MLH1, MSH2, MSH6, or PMS2; or by PCR–based assays assessing tumor microsatellite loci (either mononucleotide loci [BAT25, BAT26, NR21, NR24, Mono27] or mixed mononucleotide and dinucleotide loci [BAT25, BAT26, Di 5S346, Di 2S123, Di17S250]). MSI-H/dMMR was defined as the absence of ≥1 of the 4 MMR proteins by IHC or ≥ 2 allelic loci size shifts among the 5 microsatellite markers analyzed by PCR.

Computed tomography (preferred) or magnetic resonance imaging was performed at baseline, then every 9 weeks for the first year of study treatment, and every 12 weeks thereafter to assess tumor response.

Patient-reported outcomes were assessed using 2 HRQoL questionnaires administered at each cycle from cycles 1 to 4, then every 3 cycles through 9 months, and every 4 cycles thereafter until disease progression or treatment discontinuation, and 30 days after treatment stopped (or at the 30-day safety follow-up visit). The first questionnaire administered at these visits was the EuroQol 5-Dimensions 3-Level (EQ-5D-3L) [17], which assesses the 5 health state dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on patient ratings from 1 (extreme problem) to 3 (no problem). Patient ratings on these dimensions were used to generate a utility index score ranging from 0 (death) to 1 (perfect health), with higher scores indicating higher health utility [18]. Patients also rate their current health status using a visual analog scale (VAS), with grading from 0 (worst imaginable health state) to 100 (best imaginable health state). The second questionnaire administered at the pre-specified visits was the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) [19], which assesses QoL based on patient ratings from 1 (no difficulty) to 4 (great difficulty) across 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea/vomiting, pain), and 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties). This questionnaire also assesses global health status (GHS)/QoL based on patient responses to 2 questions, which are scored from 1 (very poor) to 7 (excellent). Trained site personnel administered these PRO questionnaires electronically at the pre-specified visits before pembrolizumab dosing, AE evaluation, or tumor imaging.

2.4. Study endpoints

The primary efficacy endpoint in KEYNOTE-158 was objective response rate per RECIST v1.1 by independent central radiologic review. PROs were assessed as pre-specified exploratory endpoints, with week 9 defined as the primary time point of interest. Changes from baseline in QLQ-C30 GHS/QoL and EQ-5D-3L utility index score were assessed overall and by best overall response (CR, partial response [PR], stable disease [SD], or progressive disease [PD]). Additional PRO endpoints for the QLQ-C30 were change from baseline to week 9 in each of the 5 functional scales, 3 symptom scales, and 6 single items; and proportion of patients at week 9 with scores that deteriorated (≥10-point decrease), remained stable (<10-point change), or improved (≥10-point increase) from baseline. Changes from baseline to week 9 in EQ-5D-3L VAS score were also assessed.

2.5. Statistical analyses

The present analysis includes patients from cohorts D and K who had MSI-H/dMMR advanced endometrial cancer. All patients who received ≥1 pembrolizumab dose and completed ≥1 PRO assessment were included in PRO analyses. Completion rates were calculated as the percentage of patients in the analysis population at each time point who completed ≥1 item on a questionnaire. Rates of compliance with PRO questionnaires were calculated as the percentage of patients among those expected to complete the questionnaire at each time point (ie, patients remaining on study with a scheduled visit) who completed the PRO questionnaire, excluding patients whose PRO assessments were missing by design (eg, translation not available). Patients who completed ≥1 item on a questionnaire were considered to have completed the PRO questionnaire. Scores for specific scales were calculated based on the average score for completed items; if more than half of the items within a scale were missing, the scale was considered to be missing.

Summary statistics were calculated for QLQ-C30 GHS/QoL mean scores by visit and the proportions of patients at week 9 with deteriorated, stable, or improved GHS/QoL scores. Changes in scores from baseline to week 9 were analyzed using a repeated measures model based on the missing at random assumption.

3. Results

3.1. Patients

Ninety patients in total with previously treated MSI-H advanced endometrial cancer were enrolled into either cohort D or cohort K between February 1, 2016, and September 23, 2020. As reported in detail elsewhere [11], the median age of these patients was 64 years (range, 42–86 years), 61% had an ECOG performance status of 1, 48% had received ≥2 prior lines of systemic therapy, and 68% had received prior radiation therapy. As of the data cutoff date (October 5, 2020), 52 patients (58%) had discontinued treatment, 18 (20%) had completed 35 cycles of pembrolizumab, and 20 (22%) remained on treatment. A total of 84 patients met criteria for the PRO analysis population. At the time of data cutoff, median time from first dose to the date of death or database cutoff for these patients was 14.2 months (range, 0.5–56.1 months) and PRO data were available through week 111.

3.2. PRO questionnaire completion and compliance

Of 84 patients in the PRO analysis population, 76 patients completed the QLQ-C30 and 79 completed the EQ-5D-3L at baseline, representing compliance rates of 90% and 94%, respectively (Table 1). Compliance rates for both questionnaires were similarly high at week 9 (92% and 93%, respectively) and were > 50% across all study visits through week 111.

3.3. QLQ-C30

Among all patients in the PRO analysis population, scores on the QLQ-C30 GHS/QoL scale improved from baseline at all time points through week 111, with the exception of week 39 (Fig. 1A). Notably, at week 39, 2 patients experienced a sudden decrease in GHS/QoL, with changes from baseline of −100 points in a patient who died approximately 3 months later and −75 points in a second patient who, in the timeframe of week 39, experienced grade 1 AEs of arthralgia, asthenia, costal pain (right side), difficulty swallowing, fever, hypogastrium discomfort, gingivitis (multiple events), and nausea, none of which were considered treatment related. Scores improved by a mean (95% CI) of 6.08 (0.71 to 11.46) points from baseline to week 9 (Table 2). When analyzed by best overall response, mean (95% CI) score changes from baseline to week 9 were 11.67 (5.33 to 18.00) for patients who achieved a CR or PR, 0.69 (−8.46 to 9.85) for patients with SD, and −2.08 (−17.08 to 12.91) for patients with PD.

For the overall analysis population, mean (95% CI) scores remained stable from baseline to week 9 across all QLQ-C30 functional scales (Fig. 2A), with no change in physical functioning, role functioning,

Table 1
Compliance and completion rates for EORTC QLQ-C30 and EQ-5D-3L assessments by week.

	EORTC QLQ-C30 ($N = 84$)	EQ-5D-3L (N = 84)
Baseline		
Completion[a]	76 (90)	79 (94)
Compliance[b]	76/84 (90)	79/84 (94)
Week 3		
Completion[a]	66 (79)	68 (81)
Compliance[b]	66/80 (83)	68/80 (85)
Week 6		
Completion[a]	68 (81)	68 (81)
Compliance[b]	68/77 (88)	68/77 (88)
Week 9		
Completion[a]	68 (81)	69 (82)
Compliance[b]	68/74 (92)	69/74 (93)
Week 18		
Completion[a]	55 (65)	55 (65)
Compliance[b]	55/69 (80)	55/69 (80)
Week 27		
Completion[a]	43 (51)	45 (54)
Compliance[b]	43/55 (78)	45/55 (82)
Week 39		
Completion[a]	33 (39)	33 (40)
Compliance[b]	33/51 (65)	33/51 (65)
Week 51		
Completion[a]	27 (32)	28 (33)
Compliance[b]	27/35 (77)	28/35 (80)
Week 63		
Completion[a]	18 (21)	19 (23)
Compliance[b]	18/34 (53)	19/34 (56)
Week 75		
Completion[a]	20 (24)	21 (25)
Compliance[b]	20/29 (69)	21/29 (72)
Week 87		
Completion[a]	13 (15)	13 (15)
Compliance[b]	13/25 (52)	13/25 (52)
Week 99		
Completion[a]	18 (21)	18 (21)
Compliance[b]	18/23 (78)	18/23 (78)
Week 111		
Completion[a]	11 (13)	11 (13)
Compliance[b]	11/20 (55)	11/20 (55)

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-3L, EuroQol 5-Dimensions 3-Level; PRO, patient-reported outcomes.

[a] Data are number (%) of patients who completed questionnaire. Completion rates were calculated as the percentage of patients in the analysis population at each time point who completed ≥1 item.

[b] Data are number (%) of patients who completed/number of patients expected to complete questionnaire. Compliance rates were calculated as the percentage of patients among those expected to complete the questionnaire at each time point (ie, patients remaining on study with a scheduled visit) who completed the PRO questionnaire, excluding those missing by design (eg, translation not available).

emotional functioning, cognitive functioning, or social functioning. Among patients with a CR or PR, mean scores improved for physical functioning, role functioning, emotional functioning, and social functioning, whereas cognitive functioning remained stable. For patients with SD, mean scores remained stable for physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, although 95% CIs were wide for some scales. Among patients with PD, mean change in functioning scale scores remained stable.

On the QLQ-C30 symptom scales, where negative scores represent improvement, mean (95% CI) scores in the overall analysis population improved from baseline to week 9 for pain and insomnia, while scores remained stable for fatigue, nausea and vomiting, dyspnea, appetite loss, constipation, diarrhea, and financial difficulties (Fig. 2B). For patients with a CR or PR, mean scores improved for fatigue, pain, insomnia, appetite loss, and constipation and remained stable for nausea and vomiting, dyspnea, diarrhea, and financial difficulties. Among patients with SD, mean scores remained stable across all symptom scales. Patients with PD had mean scores that worsened for nausea and vomiting; scores for the other symptom scales remained stable, although with wide 95% CIs for some scales. In the overall cohort, 54 of 84 (64%) of patients experienced either improved (≥10-point improvement in score from baseline) or stable (<10-point change from baseline) scores at week 9 for GHS/QoL (improved, $n = 24$ [29%]; stable, $n = 30$ [36%]; deteriorated, $n = 9$ [11%]).

3.4. EQ-5D-3L

Mean scores on the EQ-5D-3L VAS improved from baseline to week 9 among patients in the overall cohort by a mean (95% CI) of 6.00 (2.25 to 9.75) points (Table 2) and subsequently improved or remained stable relative to baseline through week 111 (Fig. 1B). For patients with a CR or PR, VAS score improved from baseline to week 9 by a mean (95% CI) of 9.11 (5.24 to 12.98) points (Table 2). Among patients with SD and patients with PD, mean (95% CI) changes from baseline to week 9 were 6.25 (−3.06 to 15.56) and −0.76 (−11.19 to 9.66), respectively.

Among patients in the overall cohort, mean (standard deviation) baseline utility index score on the EQ-5D-3L was 0.72 (0.18) and remained stable from baseline to week 9, with a mean (95% CI) change of 0.04 (−0.01 to 0.08) (Table 2). Mean (standard deviation) baseline scores by response status were 0.73 (0.17) for patients with CR or PR, 0.79 (0.13) for patients with SD, and 0.63 (0.20) for patients with PD; mean (95% CI) changes in score for these groups were 0.08 (0.03 to 0.13), −0.00 (−0.10 to 0.10), and −0.03 (−0.18 to −0.11), respectively, indicating improvement only among patients with an objective response.

4. Discussion

Results from this pre-specified exploratory analysis among patients with previously treated, advanced MSI-H/dMMR endometrial cancer enrolled in the KEYNOTE-158 study show that pembrolizumab maintained or improved HRQoL, with greater improvements in patients with a confirmed objective response (CR or PR) per RECIST v1.1 by blinded independent central review. In the overall population, QLQ-C30 GHS/QoL scores improved from baseline to week 9 by a mean (95% CI) of 6.08 (0.71 to 11.46) points, with the most profound changes seen in patients with best overall response of CR or PR whose scores improved by 11.67 (5.33 to 18.00) points. In contrast, mean GHS/QoL scores did not improve overall among the patient groups with a best overall response of SD or PD. Similar results were observed for the QLQ-C30 functional and symptom scales.

Notably, an increase of approximately 3 points on the QLQ-C30 GHS/QoL scale has been previously reported as the minimal clinically important difference that represents perceived improvement among patients receiving medical oncology care [20]. In patients with endometrial cancer, a > 5-point difference has been previously used to define the minimal clinically important difference in QLQ-C30 scores [21]. The changes in QLC-C30 GHS/QoL scores we observed among patients with previously treated advanced MSI-H/dMMR endometrial cancer, both in the overall population and in patients who achieved an objective response, exceeded this threshold and therefore represent a clinically meaningful magnitude of benefit.

A similar pattern of results was observed for the EQ-5D-3L VAS and utility index score. On the VAS, mean scores improved from baseline to week 9 in the overall population by a mean of 6.00 points and in patients with CR/PR by 9.11 points but did not change in patients with SD or PD. Mean utility index scores improved from baseline to week 9 only for patients with a confirmed CR or PR and remained stable for the overall population and among patients with SD or PD; notably, the mean change in score of 0.08 from baseline to week 9 among patients with a confirmed response was within the range of 0.06 to 0.16, which has previously been defined as a minimally important difference for cancer patients with ECOG performance status of 0 to 3, including women with gynecological cancer [22].

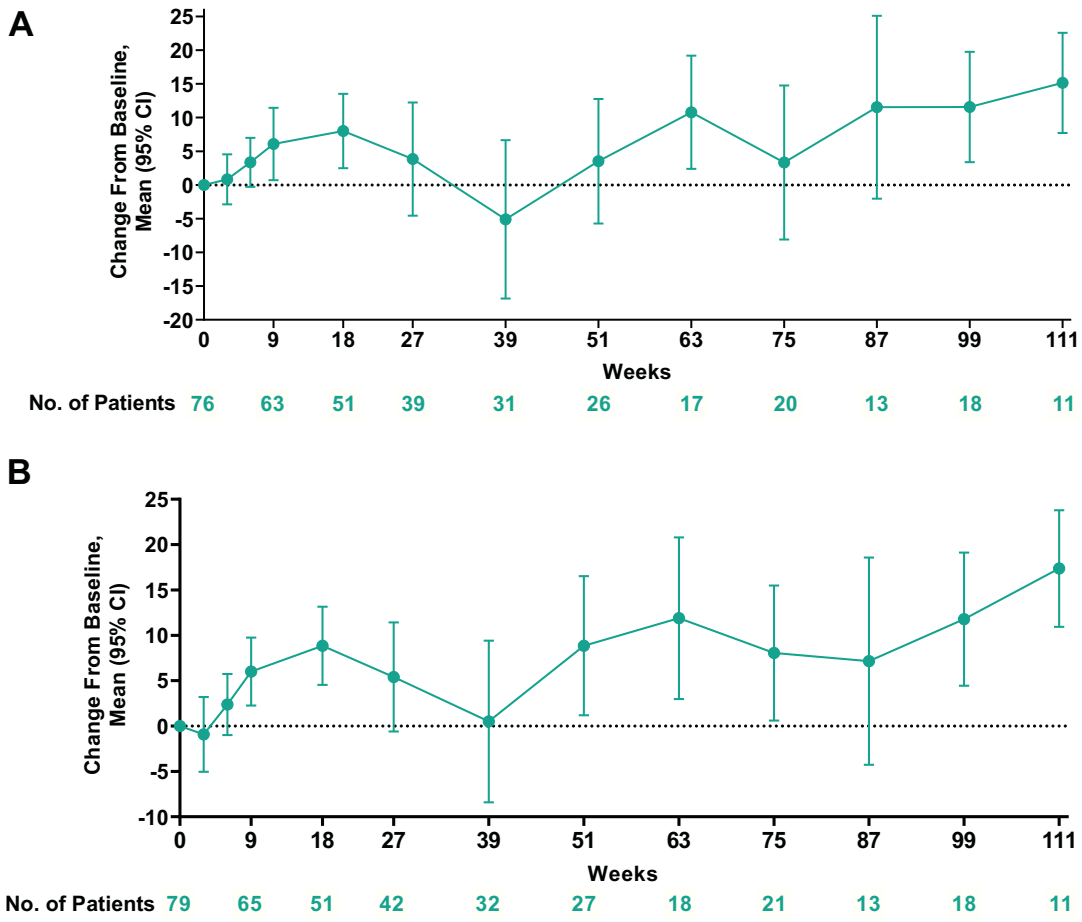


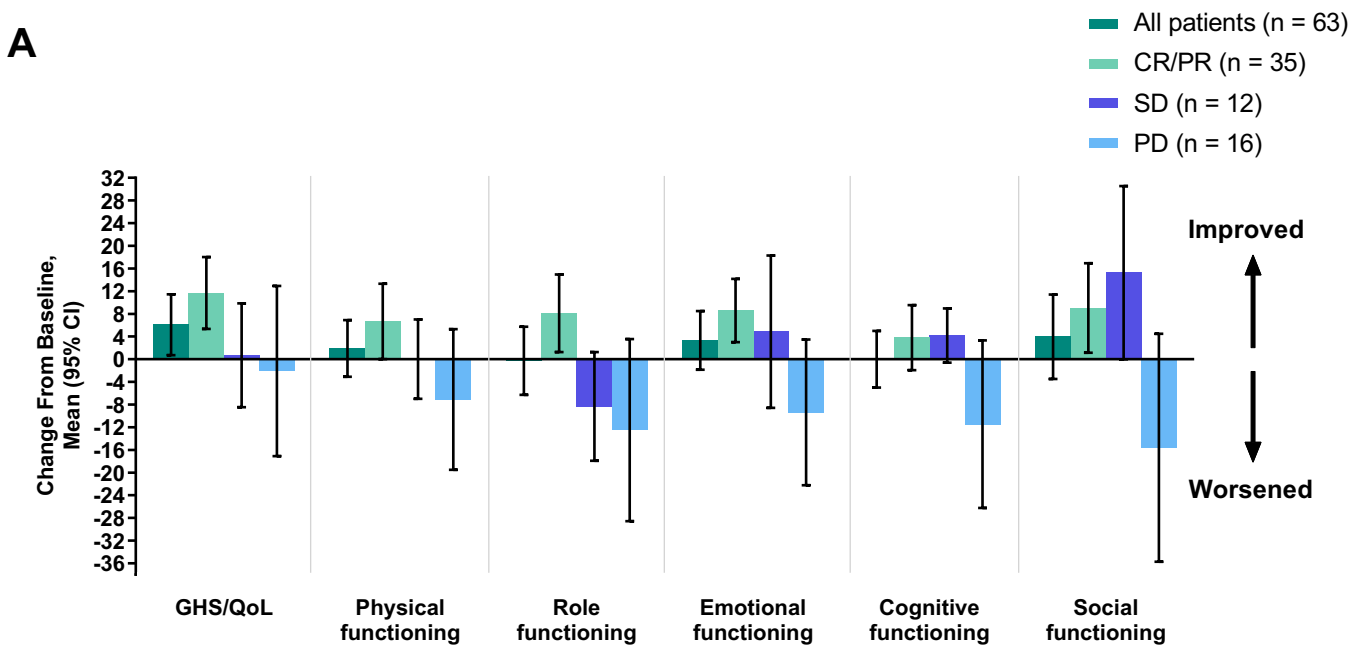
Fig. 1. Mean change from baseline by study visit over time for (A) EORTC QLQ-C30 GHS/QoL[a] and (B) EQ-5D-3L Visual Analog Scale. [a]Two patients experienced a sudden decrease in EORTC QLQ-C30 GHS/QoL at week 39: changes from baseline were −100 (patient died ~3 months later) and −75. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-3L, EuroQol 5-Dimensions 3-Level questionnaire; GHS/QoL, global health status/quality of life.

Fatigue, pain, and psychological distress are common cancer-related symptoms that can affect QoL [12]. In our analysis, patients with an objective response had improvements of >5 points in each of these domains (8.25-point, 18.57-point, and 8.57-point improvement in fatigue, pain, and emotional functioning, respectively), contributing to improved GHS/QoL scores. Importantly, endometrial cancer is commonly diagnosed in older women [23], and cancer can uniquely affect the QoL of older patients [13]. A prospective longitudinal study that evaluated changes in the QoL of older patients after a cancer diagnosis found that bodily pain and role limitations worsened among patients with endometrial cancer, with declines in the latter exceeding the minimally important difference [13]. Recognizing the impact that pain and role limitations may have on the QoL of older patients with endometrial cancer, and considering that the median age of patients with MSI-H/dMMR advanced endometrial cancer in KEYNOTE-158 was 64 years (range, 42–86 years) [11], the greater improvements in these domains

Table 2
Change from baseline to week 9 in EORTC QLQ-C30 GHS/QoL and EQ-5D-3L visual analog scale and utility index score overall and by best overall response.

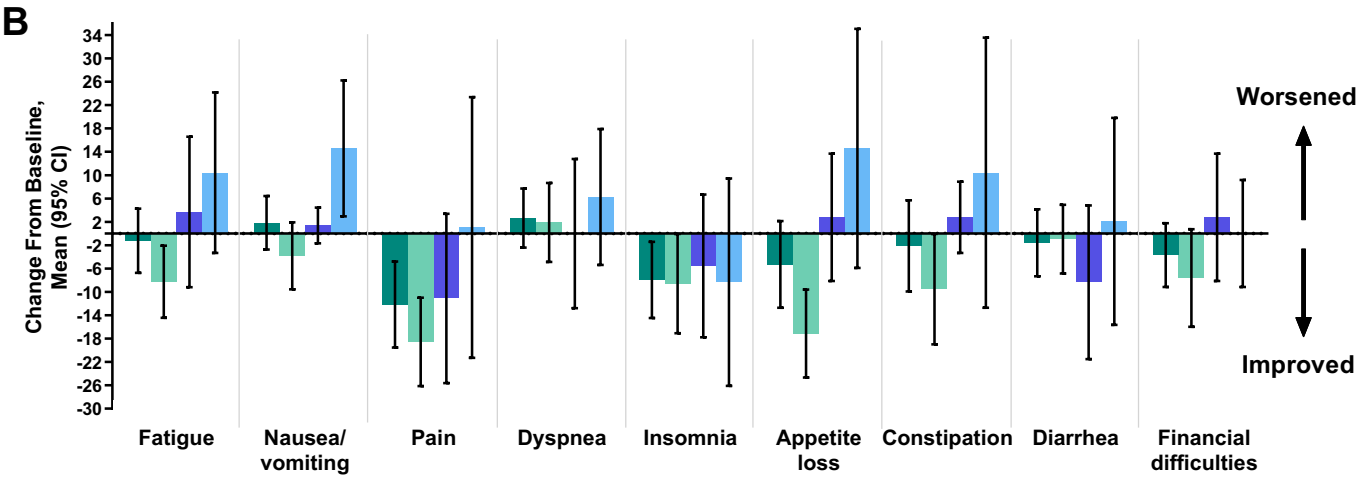
	Overall Cohort	Best Overall Response		
		CR/PR	SD	PD
QLQ-C30 GHS/QoL Scale				
Patients, n[a]	63	35	12	16
Baseline, mean score (standard deviation)	65.61 (20.11)	65.48 (20.12)	74.31 (13.04)	59.38 (22.95)
Change from baseline, mean change (95% CI)	6.08 (0.71 to 11.46)	11.67 (5.33 to 18.00)	0.69 (−8.46 to 9.85)	−2.08 (−17.08 to 12.91)
EQ-5D-3L Visual Analog Scale				
Patients, n[a]	65	36	12	17
Baseline, mean score (standard deviation)	69.68 (18.28)	72.58 (16.68)	73.25 (15.20)	61.00 (21.45)
Change from baseline, mean change (95% CI)	6.00 (2.25 to 9.75)	9.11 (5.24 to 12.98)	6.25 (−3.06 to 15.56)	−0.76 (−11.19 to 9.66)
EQ-5D-3L Health Utility Index				
Patients, n[a]	65	36	12	17
Baseline, mean score (standard deviation)	0.72 (0.18)	0.73 (0.17)	0.79 (0.13)	0.63 (0.20)
Change from baseline, mean change (95% CI)	0.04 (−0.01 to 0.08)	0.08 (0.03 to 0.13)	−0.00 (−0.10 to 0.10)	−0.03 (−0.18 to 0.11)

CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-3L, EuroQol 5-Dimensions 3-Level questionnaire; GHS/QoL, global health status/quality of life; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Number of patients with available data for change from baseline to week 9.



Mean (95% CI) change from baseline

All patients	6.08 (0.71 to 11.46)	1.90 (−3.08 to 6.89)	−0.26 (−6.27 to 5.74)	3.31 (−1.87 to 8.48)	−0.00 (−5.00 to 5.00)	3.97 (−3.48 to 11.42)
CR/PR	11.67 (5.33 to 18.00)	6.67 (0.02 to 13.31)	8.10 (1.24 to 14.95)	8.57 (3.00 to 14.15)	3.81 (−1.93 to 9.55)	9.05 (1.15 to 16.94)
SD	0.69 (−8.46 to 9.85)	0.00 (−7.00 to 7.00)	−8.33 (−17.91 to 1.25)	4.86 (−8.58 to 18.30)	4.17 (−0.62 to 8.96)	15.28 (−0.01 to 30.56)
PD	−2.08 (−17.08 to 12.91)	−7.08 (−19.49 to 5.32)	−12.50 (−28.55 to 3.55)	−9.38 (−22.23 to 3.48)	−11.46 (−26.22 to 3.30)	−15.63 (−35.74 to 4.49)



Mean (95% CI) change from baseline

All patients	−1.23 (−6.74 to 4.27)	1.85 (−2.74 to 6.44)	−12.17 (−19.53 to −4.81)	2.65 (−2.42 to 7.71)	−7.94 (−14.46 to −1.41)	−5.29 (−12.71 to 2.13)	−2.12 (−9.93 to 5.70)	−1.59 (−7.31 to 4.14)	−3.70 (−9.16 to 1.76)
CR/PR	−8.25 (−14.42 to −2.09)	−3.81 (−9.55 to 1.93)	−18.57 (−26.15 to −10.99)	1.90 (−4.87 to 8.67)	−8.57 (−17.06 to −0.08)	−17.14 (−24.68 to −9.60)	−9.52 (−18.97 to −0.08)	−0.95 (−6.83 to 4.93)	−7.62 (−15.99 to 0.75)
SD	3.70 (−9.19 to 16.59)	1.39 (−1.67 to 4.45)	−11.11 (−25.63 to 3.40)	0.00 (−12.77 to 12.77)	−5.56 (−17.78 to 6.67)	2.78 (−8.13 to 13.68)	2.78 (−3.34 to 8.89)	−8.33 (−21.50 to 4.83)	2.78 (−8.13 to 13.68)
PD	10.42 (−3.34 to 24.17)	14.58 (2.95 to 26.22)	1.04 (−21.30 to 23.38)	6.25 (−5.39 to 17.89)	−8.33 (−26.10 to 9.43)	14.58 (−5.89 to 35.06)	10.42 (−12.71 to 33.55)	2.08 (−15.64 to 19.81)	0.00 (−9.17 to 9.17)

Fig. 2. Mean change from baseline to week 9 in EORTC QLQ-C30 (A) GHS/QoL and functional scales and (B) symptom scales. For GHS/QoL score and functional scales, a higher score indicates better health or function. For symptom scales, a higher score denotes worse symptoms. Numbers in the legend represent the number of patients in the PRO analysis population in each group. CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS/QoL, global health status/quality of life; PD, progressive disease; PR, partial response; PRO, patient-reported outcomes; SD, stable disease.

among patients with a confirmed objective response in our analysis (18.57-point and 8.10-point improvement in pain and role functioning, respectively) may have further contributed to the clinically meaningful improvements in GHS/QoL we observed. In contrast and as expected, there were no improvements across most functional and symptom scales nor in GHS/QoL scores among patients in our analysis with SD or PD. Our finding that the greatest improvements in HRQoL among patients with an objective response occurred in certain functional domains and symptoms scales (as opposed to a more generalized improvement across all domains and scales) suggests that these improvements were likely the result of a treatment effect with resulting improvement in symptoms that impact QoL in cancer patients (such as pain) rather than solely due to a better outlook regarding disease prognosis as a consequence of an assessment of objective response. Moreover, there was a trend toward improved GHS/QoL before the first assessment of response at week 9 (ie, before patients were aware of their treatment response).

Results of this analysis are generally consistent with those observed for the overall MSI-H patient population in KEYNOTE-158, which showed a mean improvement in GHS/QoL score of 3.07 points with pembrolizumab monotherapy overall, irrespective of tumor type, with a greater improvement of 10.85 points among patients who achieved an objective response [24]. Importantly, the present analysis contributes to limited existing PRO data in endometrial cancer [2,14,25–27]. Although cross-trial comparisons can be challenging due to differences in patient populations, study designs, and questionnaires used, prior randomized phase 3 studies have demonstrated effects of standard treatments on HRQoL [14,28]. Results from the phase 3 PORTEC-3 study showed that patients with high-risk endometrial cancer had scores on the QLQ-C30 GHS/QoL, physical, role, and social functioning scales that were 10 to 20 points lower during treatment with chemoradiotherapy than with radiotherapy alone [28]. In the phase 3 Gynecologic Oncology Group 122 study, which assessed PROs using symptom-specific questionnaires and the Functional Assessment of Cancer Therapy–General questionnaire, patients with advanced endometrial cancer had worsening fatigue, increased urinary and bowel symptoms, and decreased physical well-being following whole abdominal irradiation, as well as worsened peripheral neuropathy at least 6 months following doxorubicin-cisplatin chemotherapy [14], highlighting the potential for long-lasting adverse QoL outcomes with standard therapies. Notably, PROs among patients with advanced endometrial cancer in the phase 3 Study 309/KEYNOTE-775 (ClinicalTrials.gov, NCT03517449) showed no difference between treatment groups (lenvatinib plus pembrolizumab versus the treatment of physician's choice) in change from baseline to week 12 QLQ-C30 GHS/QoL scores, with mean scores that changed by <10 points from baseline in each treatment group, supporting an overall favorable benefit/risk profile with lenvatinib plus pembrolizumab when considered along with results demonstrating significantly prolonged progression-free survival (HRs in the MMR-proficient and all-comer populations, respectively: 0.60 and 0.56) and overall survival (HRs in the MMR-proficient and all-comer populations: 0.68 and 0.62) in addition to manageable safety with lenvatinib plus pembrolizumab [27]. Consistent with findings in the present study, results from a PRO analysis among patients with MSI-H/dMMR advanced endometrial cancer in the phase 1 GARNET study showed improvements in QoL with the anti–PD-1 monoclonal antibody dostarlimab, with increases from baseline in QLQ-C30 scores for physical functioning beginning at cycle 4 and for disease-related symptoms of pain and fatigue beginning at cycles 1 and 3, respectively [26]. PROs will additionally be assessed as secondary endpoints in the phase 3 KEYNOTE-C93/GOG-3064/ENGOT-en15 study (ClinicalTrials.gov, NCT05173987) evaluating pembrolizumab monotherapy versus carboplatin plus paclitaxel in patients with previously untreated dMMR advanced or recurrent endometrial carcinoma [29].

A primary limitation of our analysis was the single-arm design of KEYNOTE-158, which was inherently required due to the multiple cohorts included, the requirement that patients have a previously treated advanced solid tumor with no remaining standard treatment options, and the lack of a treatment option for comparison across histologies. By assessing changes in QoL scores from baseline according to best overall response, we showed that disease control, with the most impactful outcome being disease regression, was a key factor in improving PROs in patients with previously treated, advanced MSI-H/dMMR endometrial cancer, underscoring the need for treatments such as pembrolizumab that provide durable responses in a clinically meaningful number of patients and a manageable safety profile. Incorporation of disease-specific HRQoL questionnaires in our study was also not feasible due to the multicohort design; therefore, we did not include the EORTC QLQ-EN24 module developed to assess disease and treatment PROs in endometrial cancer [30]; however, the QLQ-C30 questionnaire utilized in this study is widely used in clinical trials, including studies in advanced endometrial cancer [2], and a benchmark for determining clinically meaningful changes from pretreatment scores has been previously established for this questionnaire [20]. Additionally, previous reports have shown that standard treatments for endometrial cancer can be associated with long-term adverse effects [2,31]; therefore, patients included in this analysis could have had residual symptoms from prior therapy that affected their QoL. However, it is unlikely that this influenced our results given that unresolved AEs of any grade associated with prior treatment were an exclusion criterion and posttreatment PROs were compared with baseline.

In conclusion, our findings demonstrate that pembrolizumab monotherapy improved or maintained HRQoL in patients with previously treated, advanced MSI-H/dMMR endometrial cancer, with the greatest benefit observed in patients with a confirmed objective response. From the patient's perspective, the impact of a therapy on QoL reflects the balance between risk and benefit associated with that treatment [32] and is an important consideration in treatment selection. Our findings, together with the durable and clinically meaningful responses observed in efficacy analyses from KEYNOTE-158 [11], provide support for the use of pembrolizumab monotherapy in patients with previously treated, advanced MSI-H/dMMR endometrial cancer.

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Data sharing statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical

analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Trial registration

ClinicalTrials.gov, NCT02628067

CRediT authorship contribution statement

D.M. O'Malley: Resources, Visualization, Writing – original draft, Writing – review & editing. **G.M. Bariani:** Resources, Writing – review & editing. **P.A. Cassier:** Resources, Visualization, Writing – review & editing. **A. Marabelle:** Resources, Visualization, Writing – review & editing. **A.R. Hansen:** Resources, Visualization, Writing – review & editing. **A. De Jesus Acosta:** Resources, Visualization, Writing – review & editing. **W.H. Miller:** Resources, Visualization, Writing – review & editing. **T. Safra:** Resources, Visualization, Writing – review & editing. **A. Italiano:** Resources, Visualization, Writing – review & editing. **L. Mileshkin:** Resources, Visualization, Writing – review & editing. **M. Amonkar:** Formal analysis, Visualization, Writing – review & editing. **L. Yao:** Formal analysis, Writing – review & editing. **F. Jin:** Writing – review & editing. **K. Norwood:** Writing – review & editing. **M. Maio:** Resources, Visualization, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary data

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