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Original Research

Health-related quality of life in patients treated with pembrolizumab for microsatellite instability–high/mismatch repair–deficient advanced solid tumours: Results from the KEYNOTE-158 study

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KEYWORDS
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Health-related quality of life;
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Abstract ***Background:*** In the KEYNOTE-158 study (NCT02628067), pembrolizumab showed a high objective response rate and durable clinical benefit for patients with previously treated, unresectable/metastatic microsatellite instability–high (MSI-H)/mismatch repair–deficient (dMMR) non-colorectal solid tumours. We present health-related quality of life (HRQoL) results from the MSI-H/dMMR population (cohort K).

Patients and methods: Eligible patients had previously treated MSI-H/dMMR advanced non-colorectal solid tumours, measurable disease per RECIST v1.1, and ECOG performance status ≤1. Patients received pembrolizumab 200 mg Q3W for 35 cycles (2 years). The EORTC Quality of Life Questionnaire (QLQ-C30) and EQ-5D-3L were administered at baseline, at regular intervals throughout treatment, and 30 days after treatment discontinuation. Prespecified analyses (exploratory endpoints) included the magnitude of change from baseline to post-baseline timepoints in all patients and by the best overall response for QLQ-C30 global health status (GHS)/QoL, QLQ-C30 functional/symptom scales/items, and EQ-5D-3L visual analogue scale (VAS) score.

Results: At data cutoff (October 5, 2020), 351 patients were enrolled, of whom 311 and 315 completed baseline QLQ-C30 and EQ-5D-3L questionnaires, respectively. QLQ-C30 GHS/QoL scores improved from baseline to week 9 (mean [95% CI] change, 3.07 [0.19–5.94]), then remained stable or improved by week 111, with greater improvements observed in patients with a best response of complete response (CR) or partial response (PR) (10.85 [6.36–15.35]). Patients with CR/PR showed improvements in physical (5.58 [1.91–9.25]), role (9.88 [3.80–15.97]), emotional (5.62 [1.56–9.68]), and social (8.33 [2.70–13.97]) functioning, and stable cognitive functioning (1.74 [−1.45 to 4.94]).

Conclusions: Pembrolizumab generally improved or preserved HRQoL in patients with previously treated MSI-H/dMMR advanced non-colorectal solid tumours.

1. Introduction

Microsatellite instability (MSI), which is caused by DNA mismatch repair deficiency (dMMR), is a strong mutator phenotype observed in some cancers [1–3]. Tumours with high levels of MSI (MSI-H)/dMMR are at increased risk of further DNA mutations relative to other tumours [3,4]. Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) are often upregulated in MSI-H tumours, both on tumour cells and in infiltrating lymphocytes [1]. MSI-H/dMMR status has subsequently emerged as a biomarker that can be employed to identify patients likely to respond to treatment with certain immune checkpoint inhibitors [1].

Pembrolizumab, an anti–PD-1 monoclonal antibody, has demonstrated efficacy in the treatment of patients with unresectable or metastatic MSI-H/dMMR solid tumours in the ongoing phase 2, open-label, multicohort KEYNOTE-158 study (NCT02628067) [5]. One cohort of KEYNOTE-158 (cohort K) enrolled patients with MSI-H/dMMR tumours irrespective of the anatomic site [5]. Among patients in cohort K, the objective response rate (complete or partial response [CR/PR]) was 30.8%, with 70.1% of responders maintaining an objective response for ≥36 months [6]. Stable disease (SD) was observed for 19.0% of patients, and progressive disease (PD) for 40.8%. Median PFS and OS were 3.5 (95% CI, 2.3–4.2) months and 20.1 (14.1–27.1) months, respectively.

Assessment of patient-reported outcomes (PROs), such as health-related quality of life (HRQoL), represents an important endpoint in the evaluation of cancer treatments [7,8]. Changes in PROs can be associated with objective outcome measures and augment the understanding of treatment effects [9]. Factors assessed by PROs may influence a patient's assessment of the risk-benefit associated with treatment [10]. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) is perhaps the most widely used PRO instrument in the oncology setting [9,11]. The EuroQol 5-Dimensions 3-Level (EQ-5D-3L) questionnaire, which is not cancer-specific, is sensitive to HRQoL changes in patients with cancer [12,13]. Characterization of PROs using the EORTC QLQ-C30 and the EQ-5D-3L questionnaires was included as a prespecified exploratory objective in the KEYNOTE-158 study, both overall and according to subgroups defined by patients' best overall response. We present the results from these PRO endpoints for patients with MSI-H/dMMR tumours in cohort K.

2. Methods

2.1. Study design and patient eligibility

KEYNOTE-158 is a phase 2, multicentre, multicohort, single-arm, open-label study of pembrolizumab

monotherapy [5]. The study protocol was approved by the institutional review board or independent ethics committee at each study site prior to enrolling the first patient. Patients provided written informed consent before participating.

As previously described [6], patients were eligible to enrol in cohort K if they were ≥18 years old, had histologic or cytologic documentation of an advanced (metastatic or unresectable), incurable solid tumour that was MSI-H or dMMR (assessed as described below), and had disease progression on or intolerance to prior standard treatment. Patients had measurable disease per RECIST v1.1, confirmed by blinded independent central radiologic review; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of ≥3 months; and adequate organ function.

2.2. Study treatment

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

2.3. Assessments

At screening, MSI/MMR status was prospectively assessed at local laboratories using tumour tissue samples and immunohistochemistry (IHC) or polymerase chain reaction (PCR). MSI/MMR status was determined as previously described [6].

Tumour imaging was performed by computed tomography (preferred modality) or magnetic resonance imaging at baseline, every 9 weeks during treatment for the first year, and every 12 weeks thereafter.

Two patient-reported outcomes instruments were administered: the EORTC QLQ-C30 [11] and the EQ-5D-3L [13]. Questionnaires were administered by trained site personnel at baseline, regular intervals throughout treatment (cycles 1, 2, 3, 4, 7, 10, 14, and every subsequent fourth cycle until disease progression or treatment discontinuation), and 30 days after treatment discontinuation (or the time of the mandatory safety follow-up visit). At each time point, the EQ-5D-3L questionnaire was administered first, followed by the EORTC QLQ-C30; questionnaires were administered before dosing, before AEs were evaluated, and before tumour imaging was done.

2.4. Endpoints and statistical analyses

The primary study objective was the objective response rate per RECIST v1.1 by independent central radiologic review. A prespecified exploratory objective was the change between baseline and post-baseline time points in QLQ-C30 and EQ-5D-3L scores, both overall and according to the best overall response (i.e. CR, PR, stable disease [SD], progressive disease [PD]). Additional PRO endpoints included QLQ-C30 global health status (GHS)/QoL scores; change from baseline to week 9 in QLQ-C30 GHS/QoL, functional scales, symptom scales, and single items and the EQ-5D-3L utility score and visual analogue scale (VAS); and the proportion of patients whose QLQ-C30 scores deteriorated (≤10-point reduction), remained stable (<10-point change), or improved (≥10-point improvement).

PRO analyses included all patients who received ≥1 pembrolizumab dose and completed ≥1 questionnaire. Patients were considered to have completed a questionnaire if they completed ≥1 item on the PRO instrument. Completion rates were calculated as the percentage of patients who completed a PRO instrument at each time point divided by the total number of patients in the analysis population. PRO compliance was calculated as the percentage of patients who completed the questionnaire among those who were expected to complete the questionnaire at each time point (i.e. patients who remained on treatment and had a scheduled study visit), excluding those missing by design.

QLQ-C30 GHS/QoL scores were analyzed using summary statistics. Changes in QLQ-C30 and EQ-5D-3L scores from baseline to week 9 were analyzed using a repeated measures model based on the missing at random assumption. Changes from baseline were also analyzed through week 111, the last time point that PRO data were collected before the data cutoff date. Summary statistics were used to analyze the proportion of patients whose QLQ-C30 scores deteriorated, remained stable, or improved.

3. Results

3.1. Patients

At data cutoff (October 5, 2020), 351 patients in cohort K had received pembrolizumab treatment. Of these, 58 (16.5%) had completed treatment, 237 (67.5%) had discontinued, and 56 (16.0%) remained on study treatment. Discontinuations were due to radiographic or clinical progression (n = 179), AE (n = 38), patient withdrawal (n = 10), CR (n = 5), physician decision (n = 3), and excluded medication (n = 2). Median (range) age was 60.0 (20–89) years and 80.9% of patients were White. Most had stage IV disease (96.9%) and had received ≥2 lines of prior systemic therapy (55.6%). The most common tumour types were endometrial (22.5%), gastric (14.5%), small intestine (7.4%), ovarian (7.1%), cholangiocarcinoma/biliary tract (6.3%), pancreatic (6.3%) and brain (6.0%). No other cancer type accounted for more than 4.0% of the cohort.

3.2. PRO instrument completion and compliance

Of the 334 patients who were expected to complete questionnaires at baseline, 311 completed the QLQ-C30 and 315 completed the EQ-5D-3L, reflecting compliance rates of 93.1% and 94.3%, respectively (Table 1). Compliance rates remained high at the primary analysis time point of week 9 (87.5% and 87.8%, respectively) and throughout the remainder of the follow-up period through week 111.

3.3. QLQ-C30

In the overall cohort, QLQ-C30 GHS/QoL scores improved by a mean (95% CI) of 3.07 (0.19–5.94) points from baseline to week 9, then remained stable or continued to improve through week 111 (Fig. 1A, Table 2). When analyzed by the best overall response, mean (95% CI) changes from baseline to week 9 were 10.85 (6.36–15.35) for patients who achieved CR/PR, 2.36 (−2.48 to 7.20) for patients with SD, and −3.70 (−8.49 to 1.08) for patients with PD.

Among all patients, mean (95% CI) improvements were observed from baseline to week 9 for the QLQ-C30 role functioning scale (4.26 [0.61–7.90]), whereas scores were stable for social (1.88 [−1.67 to 5.42]), emotional (1.19 [−1.28 to 3.66]), physical (−0.06 [−2.54 to 2.42]), and cognitive functioning (−2.09 [−4.44 to 0.25]; Fig. 2A). Patients with CR/PR showed improvements from baseline to week 9 in role (9.88 [3.80–15.97]), physical (5.58 [1.91–9.25]), emotional (5.62 [1.56–9.68]), and social functioning (8.33 [2.70–13.97]) but had no change in cognitive functioning (1.74 [−1.45 to 4.94]). Patients with SD had improvements in role functioning (7.86 [0.91–14.82]), with no change in physical (0.63 [−2.87 to 4.13]), emotional (2.99 [−2.27 to 8.24]), cognitive (−0.31 [−4.39 to 3.76]) or social functioning (3.77 [−2.38 to 9.93]) scores. For patients with PD, no change was observed in role (−2.59 [−8.35 to 3.16]) or social functioning (−5.00 [−11.22 to 1.22]) scores, but scores worsened for physical (−5.41 [−9.87 to −0.94]), emotional (−4.17 [−7.99 to −0.35]), and cognitive functioning (−6.48 [−11.00 to −1.96]).

Improvements from baseline to week 9 were observed for the overall cohort for the QLQ-C30 symptom scales of pain (mean [95% CI], −4.69 [−8.46 to −0.92]), insomnia (−4.76 [−8.52 to −1.00]), and appetite loss (−4.47 [−8.15 to −0.79]; Fig. 2B). For patients with CR/PR, scores improved for fatigue (−7.36 [−12.32 to −2.41]), nausea and vomiting (−3.49 [−6.64 to −0.33]), pain (−11.82 [−17.51 to −6.13]), appetite loss (−13.95 [−18.91 to −8.99]), and financial difficulties (−12.79 [−19.10 to −6.48]); scores were unchanged for dyspnea (−2.33 [−6.95 to 2.30]), insomnia (−3.88 [−9.51 to 1.76]), constipation (−4.65 [−10.04 to 0.74]), and diarrhoea (2.71 [−1.27 to 6.70]). For patients with SD, symptom scores improved for dyspnea (−8.18 [−15.13 to −1.22]), and insomnia (−10.69 [−18.90 to −2.48]); scores were unchanged for nausea and vomiting (0.63 [−3.40 to 4.65]), fatigue (−2.31 [−7.12 to 2.51]), pain (−5.35 [−13.03 to 2.34]), appetite loss (−1.89 [−7.42 to 3.64]), constipation (−1.26 [−6.95 to 4.43]), diarrhoea (−4.40 [−10.91 to 2.10]), and financial difficulties (0.00 [−8.26 to 8.26]). For patients with PD, scores were unchanged for symptoms of nausea and vomiting (4.26 [−0.50 to 9.01]), pain (3.15 [−3.19 to 9.49]), dyspnea

Table 1
Compliance and completion rates for quality-of-life assessments.

	EQ-5D-3L (N = 334)	EORTC QLQ-C30 (N = 334)
Baseline		
Completion[a]	315 (94.3)	311 (93.1)
Compliance[b]	315/334 (94.3)	311/334 (93.1)
Week 3		
Completion[a]	269 (80.5)	261 (78.1)
Compliance[b]	269/309 (87.1)	261/309 (84.5)
Week 6		
Completion[a]	252 (75.4)	249 (74.6)
Compliance[b]	252/293 (86.0)	249/293 (85.0)
Week 9		
Completion[a]	245 (73.4)	244 (73.1)
Compliance[b]	245/279 (87.8)	244/279 (87.5)
Week 18		
Completion[a]	182 (54.5)	181 (54.2)
Compliance[b]	182/229 (79.5)	181/229 (79.0)
Week 27		
Completion[a]	147 (44.0)	145 (43.4)
Compliance[b]	147/179 (82.1)	145/179 (81.0)
Week 39		
Completion[a]	120 (35.9)	120 (35.9)
Compliance[b]	120/154 (77.9)	120/154 (77.9)
Week 51		
Completion[a]	93 (27.8)	91 (27.2)
Compliance[b]	93/116 (80.2)	91/116 (78.4)
Week 63		
Completion[a]	72 (21.6)	71 (21.3)
Compliance[b]	72/107 (67.3)	71/107 (66.4)
Week 75		
Completion[a]	65 (19.5)	64 (19.2)
Compliance[b]	65/88 (73.9)	64/88 (72.7)
Week 87		
Completion[a]	54 (16.2)	55 (16.5)
Compliance[b]	54/76 (71.1)	55/76 (72.4)
Week 99		
Completion[a]	52 (15.6)	52 (15.6)
Compliance[b]	52/66 (78.8)	52/66 (78.8)
Week 111		
Completion[a]	44 (13.2)	44 (13.2)
Compliance[b]	44/55 (80.0)	44/55 (80.0)

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.

[a] Completion rates were calculated as the percentage of patients who completed a PRO instrument (i.e. completed at least one item) at each time point divided by the total number of patients in the analysis population.

[b] Compliance rates were calculated as the percentage of patients who completed the questionnaire among those who were expected to complete the questionnaire at each time point (i.e. patients who remained on treatment and had a scheduled study visit), excluding those missing by design.

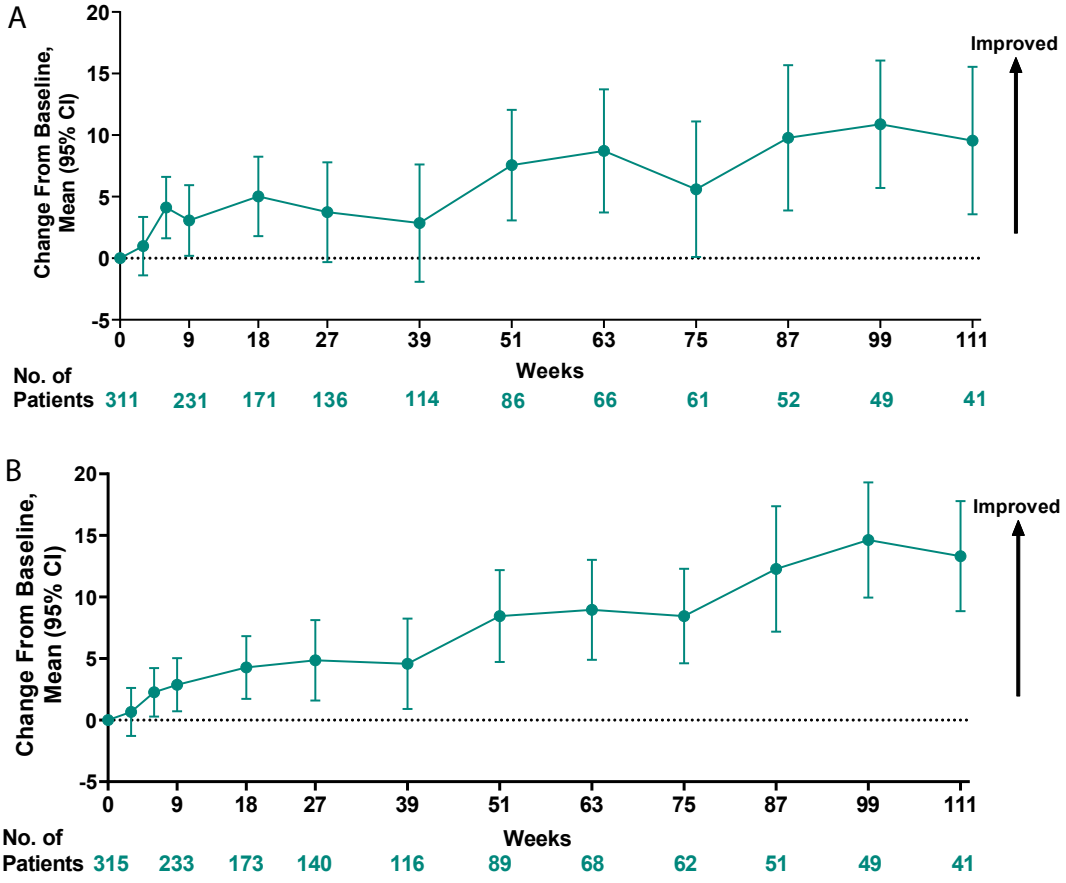

Fig. 1. Change from baseline in (A) EORTC QLQ-C30 GHS/QoL scores and (B) EQ-5D-3L visual analogue scale scores. EORTC QLQ-C30. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L, EuroQol 5-Dimensions 5-Level questionnaire; GHS/QoL, global health status/quality of life.

(5.56 [−0.29 to 11.41]), insomnia (−1.11 [−7.25 to 5.03]), appetite loss (3.33 [−3.85 to 10.51]), constipation (1.48 [−4.96 to 7.93]), diarrhoea (−1.85 [−5.95 to 2.25]), and financial difficulties (−0.37 [−5.33 to 4.59]), but worsened for fatigue (5.19 [0.29 to 10.08]).

In the overall cohort, more than 75% 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, 32.0%; stable, 45.9%) and all functional and symptom

Table 2
Changes from baseline to week 9 in the QLQ-C30 GHS/QoL scale and in the EQ-5D-3L Utility Scale and Visual Analogue Scale.

	Overall cohort	Best Objective Response[a]		
		Patients with CR/PR	Patients with SD	Patients with PD
QLQ-C30 GHS/QoL scale				
N	231	86	53	90
Baseline	65.22 (19.93)	66.67 (20.21)	70.28 (18.74)	61.30 (19.65)
Change, baseline to week 9	3.07 (0.19–5.94)	10.85 (6.36–15.35)	2.36 (−2.48 to 7.20)	−3.70 (−8.49 to 1.08)
EQ-5D-3L Utility Scale				
N	233	87	53	91
Baseline	0.73 (0.21)	0.75 (0.19)	0.79 (0.16)	0.67 (0.24)
Change, baseline to week 9	−0.00 (−0.03 to 0.02)	0.08 (0.04–0.11)	−0.01 (−0.06 to 0.04)	−0.08 (−0.12 to −0.03)
EQ-5D-3L Visual Analogue Scale				
N	233	87	53	91
Baseline	70.37 (18.45)	73.78 (16.14)	72.47 (18.60)	66.18 (19.80)
Change, baseline to week 9	2.88 (0.72–5.03)	6.74 (3.51–9.96)	4.40 (0.25–8.54)	−1.88 (−5.62 to 1.86)

CR, complete response; QLQ-C30, 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] One patient had the best overall confirmed response that was not CR, PR, SD, or PD. For that patient, baseline and change from baseline to week 9 scores were as follows: QLQ-C30 GHS/QoL, 33.3 and 33.3; EQ-5D-3L utility scale, 0.64 and 0.12, respectively; EQ-5D-3L VAS, 50.00 and 30.00, respectively.

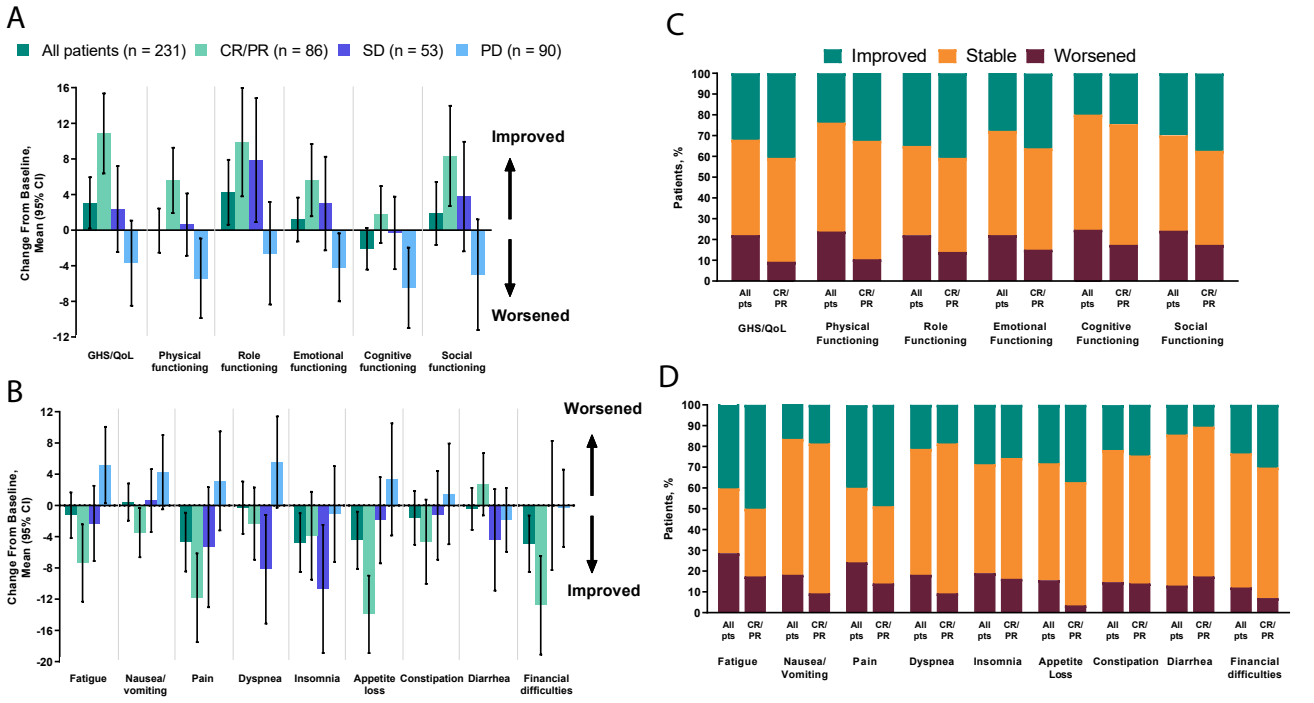

Fig. 2. Mean change from baseline to week 9 in the (A) QLQ-C30 GHS/QoL and functional scales and (B) QLQ-C30 symptom scales and proportion of patients with QLQ-C30 improved/stable/worsened scores on the (C) QLQ-C30 GHS/QoL and functional scales and (D) QLQ-C30 symptom scales. CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PD, progressive disease; PR, partial response; SD, stable disease.

scales/items (Fig. 2C and D). The largest improvements were seen for functional scales of role (35.1%) and social (29.9%) functioning and symptom scales/items of fatigue (40.3%), pain (39.8%), insomnia (28.6%), and appetite loss (28.1%). Across all functional scales and most symptom scales, patients with CR/PR accounted for the largest proportion of improved scores at week 9.

3.4. EQ-5D-3L

In the overall cohort, the mean (standard deviation) baseline EQ-5D-3L utility score was 0.73 (0.21) (Table 2). At week 9, the mean EQ-5D-3L utility score was unchanged from baseline (0.00 [95% CI, −0.03 to 0.02]). Patients with a best objective response of CR/PR, SD, or PD had mean (standard deviation) baseline scores of 0.75 (0.19), 0.79 (0.16), and 0.67 (0.24), respectively. At week 9, mean (95% CI) changes from baseline were 0.08 (0.04−0.11), −0.01 (−0.06 to 0.04), and −0.08 (−0.12 to −0.03), respectively.

The mean (standard deviation) baseline EQ-5D-3L VAS score for the overall cohort was 70.37 (18.45). The VAS score increased by a mean (95% CI) of 2.88 (0.72−5.03) points by week 9 (Fig. 1B) and then remained stable or further improved from week 9 through week 111. In analyses according to best objective response, patients with CR/PR, SD, and PD had mean (standard deviation) baseline EQ-5D-3L VAS scores of 73.78 (16.14), 72.47 (18.60), and 66.18 (19.80), respectively. At week 9, mean (95% CI) changes from baseline were 6.74 (3.51−9.96), 4.40 (0.25−8.54), and −1.88 (−5.62 to 1.86), respectively.

4. Discussion

In this prespecified exploratory PRO analysis from the KEYNOTE-158 study, HRQoL was generally improved or preserved in patients with previously treated MSI-H/dMMR advanced non-colorectal solid tumours who received pembrolizumab monotherapy. In the overall study population, QLQ-C30 GHS/QoL scores increased (improved) from baseline to week 9. GHS/QoL scores were maintained or further increased through week 111. Moreover, we found that achievement of an objective radiologic response was associated with improvements in GHS/QoL. Patients who attained CR/PR per RECIST v1.1 per independent radiologic review had larger increases in the QLQ-C30 GHS/QoL scale (mean, 10.85 points) than those with SD (2.36 points) or PD (−3.70 points). Notably, the mean change in GHS/QoL score at week 9 among patients with an objective response exceeded the minimal clinically important difference in the QLQ-C30 GHS/QoL score reported in the literature [14], supporting the clinical relevance of this outcome. The finding of patients who attained CR/PR reporting greater improvements than those with SD or PD was consistent across all QLQ-C30 functioning domains and most symptom scales.

The analysis assessed rates of improvement, stability, or deterioration in QLQ-C30 scores using a 10-point change as the threshold for improvement or deterioration. This magnitude of change is generally considered by patients to reflect a moderate or large change in HRQoL [15] and can be considered clinically meaningful [16,17]. Using this 10-point threshold, approximately one-third of patients had clinically meaningful improvements in GHS/QoL from baseline to week 9, and more than three-quarters of patients had improved or stable GHS/QoL scores. Again, the subgroup of patients with CR/PR had the highest proportion (41%) of patients with clinically meaningful improvement; scores remained stable (i.e. less than 10-point change) for an additional 50% of patients. Similar findings were observed across QLQ-C30 functioning domains and symptom scores, for which most patients with CR/PR had clinically meaningful improvement or stability in scores. Although a majority of patients with SD had improvement or stability across QLQ-C30 domains, the percentages were numerically lower than observed in the subgroup with CR/PR. Stability or deterioration in QLQ-C30 scores from baseline to week 9 was observed for most patients with PD.

Changes in EQ-5D-3L VAS scores were consistent with the QLQ-C30 results. The analysis by best overall response was also consistent with the QLQ-C30 results, with the greatest increases observed for patients with CR/PR, smaller increases observed for those with SD, and no change for those with PD.

The principal limitation of our study was its single-arm design, which was necessitated by the enrollment of a patient population for whom all standard therapies had been ineffective and, for cohort K, the lack of a single standard therapy for patients with MSI-H/dMMR tumours that could be administered in a control arm. Nonetheless, our findings are consistent with randomised controlled studies that evaluated HRQoL with pembrolizumab or other immune checkpoint inhibitors and enrolled patients according to the anatomic origin of the tumour. In the KEYNOTE-024 study of pembrolizumab versus platinum-based chemotherapy in patients with non–small-cell lung cancer with PD-L1 tumour proportion score $\geq$50%, patients treated with pembrolizumab had a least-squares mean 6.9-point increase from baseline to week 15 in the QLQ-C30 GHS/QoL score, a significant improvement compared with patients who received chemotherapy (−0.9-point reduction; between-group difference, 7.8 points, $P = 0.002$) [18]. In the KEYNOTE-006 study of pembrolizumab Q2W or Q3W versus ipilimumab in patients with advanced melanoma, smaller deteriorations in QLQ-C30 GHS/QoL scores were observed at treatment week 12 for the pembrolizumab doses (reductions of −1.9 and −2.5, respectively) than for ipilimumab (reduction of −10.0; $P < 0.001$ vs both pembrolizumab doses) [19]. In KEYNOTE-177, PRO data were provided by 294 patients with metastatic MSI-H/dMMR colorectal cancer who received pembrolizumab (n = 152) or chemotherapy (n = 142) [20]. For the QLQ-C30 GHS/QoL scale, the 8.96-point (95% CI, 4.24–13.69) least-squares mean difference between groups favoured pembrolizumab. The pembrolizumab group also had longer median times to deterioration in GHS/QoL, physical and social functioning, and fatigue scores. PROs were also reported for 74 heavily pretreated patients with MSI-H/dMMR colorectal cancer who received nivolumab in the CheckMate 142 study [21]. For those patients, QLQ-C30 scores improved by treatment week 13 for the GHS/QoL scale (an increase of 8.7 points) and subscales of social and emotional functioning (12.5 and 9.1 points, respectively). Scores for the symptoms of pain, insomnia, and fatigue also improved (reductions of 16.2, 10.5, and 9.6 points, respectively) by week 13, and the EQ-5D-3L VAS score increased by 13.9 points.

To our knowledge, this is the first report of PRO data for a PD-1/PD-L1 inhibitor in a tumour-agnostic population. Given the large size of cohort K and enrollment of patients with MSI-H/dMMR tumours irrespective of primary anatomic site, the current analysis provides broad insight into HRQoL changes experienced by such patients during pembrolizumab monotherapy. Compliance rates remained high through week 111 (limiting the potential for selection bias), although completion rates for PRO instruments declined as patients discontinued treatment. We are aware of one other study that assessed PROs for patients with non-colorectal MSI-H/dMMR tumours treated with an immune checkpoint inhibitor. In the GARNET study of the anti–PD-1 monoclonal antibody dostarlimab in patients with MSI-H/dMMR advanced endometrial cancer, there were increases over 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 [22]. In GARNET, compliance rates declined over time, from 100% at baseline to 45% at cycle 7.

In summary, pembrolizumab monotherapy was associated with improved or stable HRQoL for many patients with advanced MSI-H/dMMR non-colorectal solid tumours. The improvements became apparent by treatment week 9, were maintained throughout the remainder of the study, and were clinically meaningful for a substantial proportion of patients, particularly those who achieved an objective radiologic response during treatment. These PRO analyses support the efficacy and safety results for pembrolizumab in this population [6].

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Role of the funding source

The sponsor was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) 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 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.

Author contributions

M. Maio had full access to all the data in the study and has taken responsibility for the integrity and accuracy of the data analysis. Conception, design, or planning of the study: J.M. Norquist, T. Doi, M. Gottfried, K. Norwood, Acquisition, analysis, or interpretation of the data: M. Maio, M.M. Amonkar, J.M. Norquist, P.A. Ascierto, L. Manzyuk, D. Motola-Kuba, N. Penel, P.A. Cassier, G.M. Bariani, A.D.J. Acosta, T. Doi, F. Longo, W.H. Miller, Jr., D.-Y. Oh, R. Wang, K. Norwood, A. Marabelle, Provision of study materials/patients: M. Maio, P.A. Ascierto, L. Manzyuk, N. Penel, P.A. Cassier, G.M. Bariani, A.D.J. Acosta, W.H. Miller, Jr., M. Gottfried, A. Marabelle, Drafting of the manuscript: G.M. Bariani, T. Doi, D.-Y. Oh, K. Norwood.

Conflict of Interest Statement

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

Michele Maio: study funding to the institution from Merck Sharp & Dohme LLC, and Merck & Co., Inc., Rahway, NJ, USA, to support study conduct; honoraria for serving as a speaker from MSD, Roche, Bristol Myers Squibb (BMS), Sanofi, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, GlaxoSmithKline (GSK), Sciclone, Alfasigma, and Merck Serono; personal fees for advisory boards from Merck Sharp & Dohme LLC, Roche, BMS, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, Sanofi, GSK, Alfasigma, and Merck Serono; stockholder in Epigen Therapeutics and Theravance.

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Appendix A. Supplementary data

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