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Original Research

EMPOWER CERVICAL-1: Effects of cemiplimab versus chemotherapy on patient-reported quality of life, functioning and symptoms among women with recurrent cervical cancer☆

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KEYWORDS
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Abstract ***Background:*** In a phase III, randomised, active-controlled study (EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9; R2810-ONC-1676; NCT03257267) and cemiplimab significantly improved survival versus investigator's choice of chemotherapy among patients with recurrent cervical cancer who had progressed on platinum-based therapy. Here we report patient-reported outcomes in this pivotal study.
Methods: Patients were randomised 1:1 to open-label cemiplimab (350 mg intravenously every 3 weeks) or investigator's choice of chemotherapy in 6-week cycles. Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 during cycles 1–16. Least-squares mean changes from baseline in global health status (GHS)/quality of life (QoL) and physical functioning (PF) were secondary end-points in the statistical hierarchy.
Results: Of 608 patients (304/arm), 77.8% patients had squamous cell carcinoma and 22.2% patients had adenocarcinoma. Questionnaire completion rates were ~90% throughout. In the squamous cell carcinoma population, overall between-group differences statistically significantly favoured cemiplimab in GHS/QoL (8.49; 95% confidence interval [CI]: 3.77–13.21; $P = 0.0003$) and PF (8.35; 95% CI: 4.08–12.62; $P < 0.0001$). Treatment differences favoured cemiplimab in both histologic populations by cycle 2. Overall changes from baseline in most functioning and symptom scales favoured cemiplimab, with clinically meaningful treatment differences in role functioning, appetite loss and pain in both populations. The sensitivity analyses, responder analyses and time to definitive deterioration favoured cemiplimab in both populations.
Conclusions: Cemiplimab conferred favourable differences in GHS/QoL and PF compared with chemotherapy among patients with recurrent cervical cancer, with benefits in PF by cycle 2, and clinically meaningful differences favouring cemiplimab in role functioning, appetite loss, and pain.

1. Introduction

Cervical cancer is a leading cause of cancer-related death among women [1]. Survival for patients with cervical cancer has improved in high-income countries with better prevention and detection, as well as more effective treatments [2]. Worldwide, there is no current standard of care for recurrent or metastatic cervical cancer after first-line treatment failure, and significant impairments of quality of life (QoL), functioning and symptoms remain [3,4]. In patients with advanced cancer, physical well-being is significantly associated with overall survival, with a 3.7% decrease in risk of death for each unit of improvement in physical well-being [5].

Patient-reported outcomes (PROs) are used by clinicians and patients to assess treatment choices and shape guidelines and by regulatory authorities and policy makers to evaluate risk–benefit profiles of medicines [6]. Measuring what matters to patients is of critical importance in cancer clinical trials [7] and developing new treatments that improve survival must be contextualised with their effects on PROs.

Cemiplimab is a human immunoglobulin G4 monoclonal antibody to the programmed cell death-1 receptor. In an international, phase III, randomised, active-controlled study of patients with recurrent or metastatic cervical cancer after first-line platinum-based chemotherapy (EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9; R2810-ONC-1676; NCT03257267), cemiplimab significantly improved overall survival compared with investigator's choice of chemotherapy. This report describes PRO results in this pivotal study.

2. Methods

2.1. Study design

The study design was described previously in full [8]. Briefly, 608 patients from approximately 100 sites globally were randomised 1:1 to either the experimental or the control group and received open-label study treatment for up to 96 weeks in 6-week treatment cycles. In the experimental group, cemiplimab 350 mg was administered intravenously every 3 weeks. In the control group, the investigator chose chemotherapy from the following: antifolate, topoisomerase 1 inhibitor, nucleoside analogue and vinca alkaloid (Supplementary Fig. 1).

All patients had relapsed or metastatic cervical cancer (squamous cell carcinoma [SCC] or adenocarcinoma/adenosquamous carcinoma [AC]) that had progressed after first-line platinum-based chemotherapy. Randomisation was stratified by histology (SCC versus AC), geographic region (North America versus Asia versus rest of world), prior use of bevacizumab (yes versus no) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1). All patients provided written informed consent. An institutional review board or ethics committee reviewed and approved the study protocol and informed consent form for each site.

2.2. PROs

Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) at baseline and on day 1 of each 6-week treatment cycle, up to cycle 16 or disease progression, and then at two post-treatment follow-up visits, with a recall period for each question of 'during the past week.' Scores on each EORTC QLQ-C30 scale range from 0 to 100; higher scores for global health status (GHS)/QoL and functioning scales indicate better health status and function, and higher scores for symptom scales indicate more symptoms [9]. A 10-point threshold for clinically meaningful differences [10–12] was used to assess changes from baseline (within patient or within group) and differences between treatment groups.

2.3. Statistical analysis

Analyses were performed on the full analysis set, defined as all randomised patients, using SAS version 9.4 (SAS Institute, Cary, NC, USA). Longitudinal analyses included patients in the full analysis set with EORTC QLQ-C30 assessments at baseline and at least once after the baseline visit.

Instrument completion rate at each timepoint was summarised. Mixed models for repeated measures (MMRM) were used to estimate least-squares (LS) mean changes from baseline. The following covariates were included as fixed effects: treatment arm, timepoint, baseline PRO score, geographic region, histology (for the overall population only), interaction of baseline PRO score and timepoint, and interaction of treatment arm and timepoint. In each population (SCC, AC and overall), MMRM analyses did not include cycles when the sample size dropped below 10 patients in either treatment group.

The statistical hierarchy (Supplementary Table 1) included MMRM analysis of GHS/QoL and physical functioning, in the SCC and overall populations, for overall change from baseline and change from baseline to cycle 2 (week 6). In another advanced cervical cancer trial, median times to response and progression were approximately 2 months [13], suggesting that cycle 2 was the best opportunity to understand clinical benefit in this study. Secondary end-points in the statistical hierarchy were assessed for statistically significant differences at a one-sided P value of 0.025, with multiplicity adjustment. After the first end-point in the hierarchy failed this test, subsequent comparisons were not tested formally. End-points not in the statistical hierarchy were tested at a two-sided P value of 0.05, without multiplicity adjustment. P values after the break of hierarchy were nominal. Other statistical methods are described in the Supplementary Methods.

3. Results

3.1. Baseline characteristics and disposition

Of 608 patients randomised (304 in each group), 300 received at least one dose of cemiplimab and 290 received at least one dose of chemotherapy. The treatment groups were similar at baseline (Table 1). Most patients had SCC histology (77.8%) and metastatic disease (94.4%).

At baseline, study participants had a low-to-moderate disease burden for GHS/QoL and functioning scores compared with normative values in the general population (Supplementary Fig. 2) [14]. Baseline GHS/QoL and functioning scores among study participants were slightly lower than reference values for patients with any cancer or cervical cancer (where available) [15]. Baseline symptom scale scores in the SCC population were also generally similar between the treatment groups, except for higher pain scores with cemiplimab, and were consistent with reference values for patients with any cancer or cervical cancer.

Patients progressively discontinued the study due to disease progression, death or other reasons (e.g. lost to follow-up, patient or physician decision, withdrawal of consent). The number of expected PRO assessments, therefore, decreased during the study for both the SCC

Table 1
Patient characteristics (reprinted from Tewari *et al.* [8]).

	Cemiplimab (n = 304)	Chemotherapy (n = 304)	Overall (N = 608)
Age, years			
Mean (SD)	51.1 (11.59)	51.2 (11.77)	51.1 (11.67)
Range	22–81	24–87	22–87
≥65–<75, *n* (%)	30 (9.9)	29 (9.5)	59 (9.7)
≥75, *n* (%)	5 (1.6)	11 (3.6)	16 (2.6)
Race, *n* (%)			
White	193 (63.5)	192 (63.2)	385 (63.3)
Asian	88 (28.9)	88 (28.9)	176 (28.9)
Black or African American	9 (3.0)	12 (3.9)	21 (3.5)
Other or not reported	14 (4.6)	12 (3.9)	26 (4.3)
Geographic region, *n* (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of world	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance status, *n* (%)			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)
Histology/cytology, *n* (%)			
SCC	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma	54 (17.8)	62 (20.4)	116 (19.1)
Adenosquamous cell carcinoma	10 (3.3)	9 (3.0)	19 (3.1)
Extent of disease, *n* (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent	20 (6.6)	14 (4.6)	34 (5.6)

ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; SD, standard deviation.

population (Supplementary Fig. 3A) and the overall population (Supplementary Fig. 3B). Among patients still on study, >95% completed at least one PRO scale at baseline and approximately 90% completed at least one PRO scale at each subsequent assessment.

Results were evaluable for ≥10 patients in each treatment group through cycle 7 in the SCC population (at cycle 8: cemiplimab, n = 49; chemotherapy, n = 8), through cycle 8 in the overall population (at cycle 9: cemiplimab, n = 54; chemotherapy, n = 8) and through cycle 4 in the AC population (at cycle 5: cemiplimab, n = 23; chemotherapy, n = 6). Due to the limited PRO sample and follow-up for the AC population, results are presented herein only for the SCC and overall populations.

3.2. GHS/QoL

MMRM results for GHS/QoL showed that at each post-baseline visit LS mean scores were generally maintained or improved with cemiplimab, while those for chemotherapy generally worsened (95% confidence intervals [CIs] did not include null) at cycles 2–4, both in the SCC population (Fig. 1A) and in the overall population (Fig. 1B). The overall LS mean difference between treatment groups in GHS/QoL change from baseline was statistically significant in favour of cemiplimab in the SCC population (8.49; 95% CI: 3.77–13.21; P = 0.0003) (Fig. 2A). The LS mean difference between treatment groups in change from baseline for GHS/QoL at cycle 2 was 4.14 (95% CI: −0.21, 8.50; P = 0.031) in the SCC population, but the P value was >0.025; per the statistical hierarchy (Supplementary Table 1), all subsequent comparisons were nominal. LS mean changes from baseline favoured cemiplimab in the overall population (7.81; 95% CI: 3.30–12.33; P = 0.0004) (Fig. 2B). The LS mean difference between the cemiplimab and chemotherapy groups in change from baseline for GHS/QoL at cycle 2 in the overall population was 3.25 (95% CI: −0.54, 7.03; P = 0.046).

Sensitivity analysis using a pattern-mixture model (PMM) showed clinically meaningful (i.e. ≥10 points) differences favouring cemiplimab across multiple delta values in both populations (Supplementary Fig. 4A and 4B). The proportion of responders (i.e. patients who improved by ≥ 10 points from baseline) was higher and the proportion of non-responders (i.e. patients who worsened by ≥ 10 points from baseline) was lower for cemiplimab versus chemotherapy at cycle 7 in the SCC population (Fig. 3A) and at cycle 8 in the overall population (Fig. 3B). The median time to definitive deterioration of GHS/QoL was longer with cemiplimab than with chemotherapy in both populations (Fig. 4A and B).

3.3. Physical functioning

MMRM results for physical functioning showed that at each cycle, LS mean scores were generally maintained or improved with cemiplimab, while those for chemotherapy generally worsened (95% CIs did not include null) in both populations (Fig. 1C and D). In the SCC population, the overall LS mean difference between

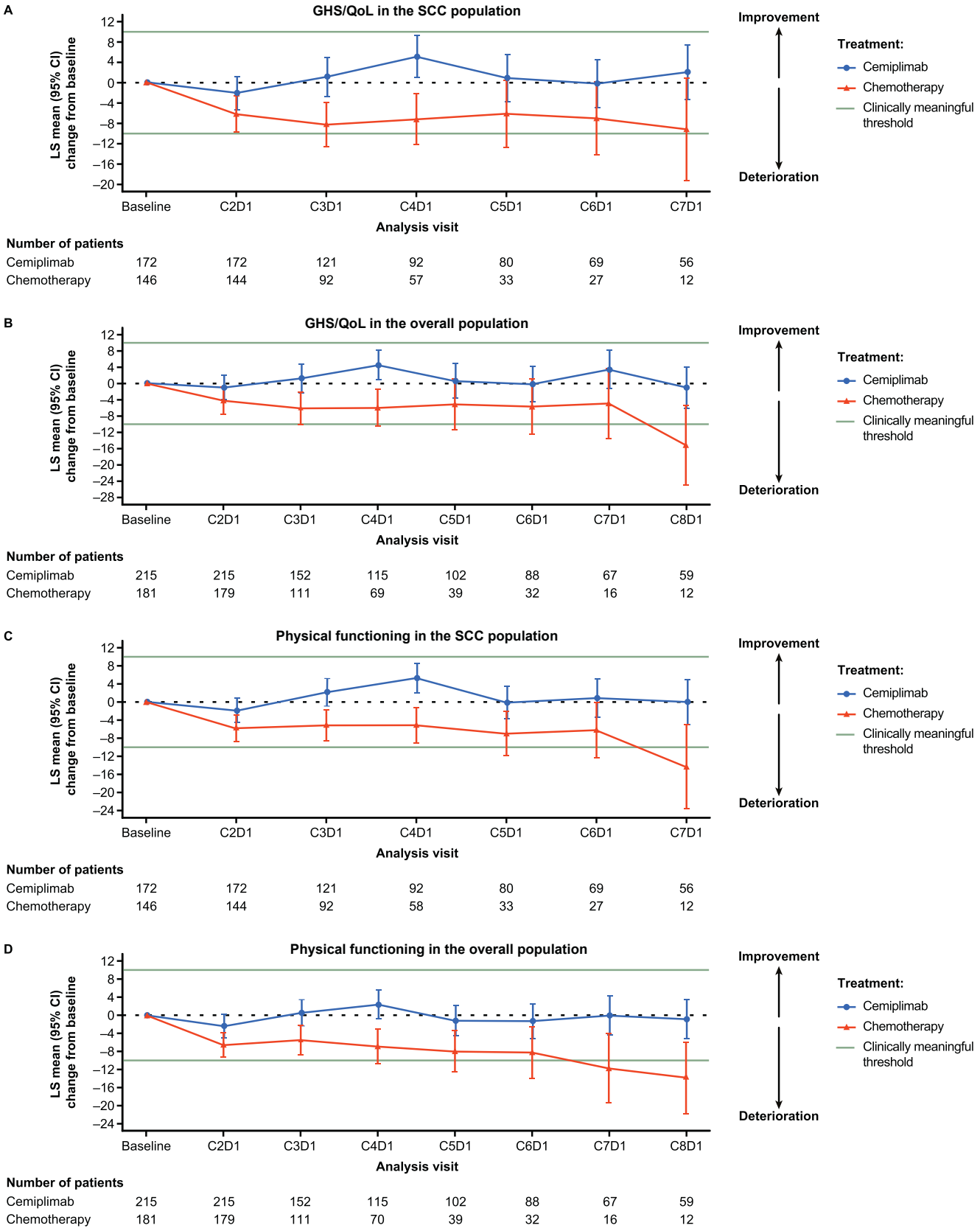
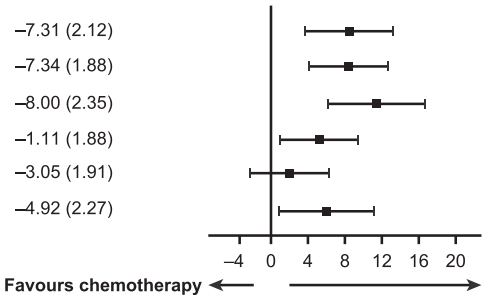


Fig. 1. **Change from baseline to each visit for pre-specified secondary endpoints**. GHS/QoL in (A) the SCC population and (B) the overall population. Physical functioning in (C) the SCC population and (D) the overall population. Scheduled visits with <10 patients in either arm, unscheduled visits and off-treatment visits were not included in the analysis. C, cycle; CI, confidence interval; D, day; GHS, global health status; LS, least squares; QoL, quality of life; SCC, squamous cell carcinoma.

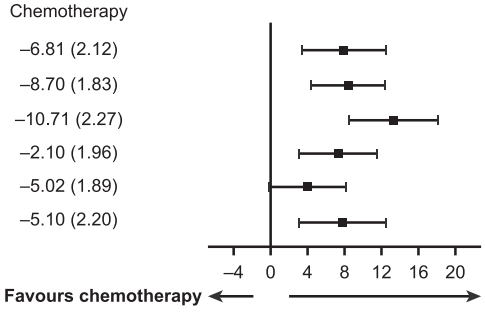
A GHS/QoL and functioning in the SCC population

Domain	LS mean (SE) overall		Contrast cemiplimab vs chemotherapy (95% CI), *P* value
	Cemiplimab	Chemotherapy	
GHS/QoL	1.18 (1.60)	–7.31 (2.12)	8.49 (3.77, 13.21), 0.0003
Physical functioning	1.01 (1.46)	–7.34 (1.88)	8.35 (4.08, 12.62), <0.0001
Role functioning	3.44 (1.80)	–8.00 (2.35)	11.44 (6.26, 16.62), <0.0001
Emotional functioning	4.15 (1.40)	–1.11 (1.88)	5.26 (1.11, 9.41), 0.0133
Cognitive functioning	–0.97 (1.48)	–3.05 (1.91)	2.08 (–2.20, 6.36), 0.3386
Social functioning	1.14 (1.84)	–4.92 (2.27)	6.06 (0.98, 11.15), 0.0197



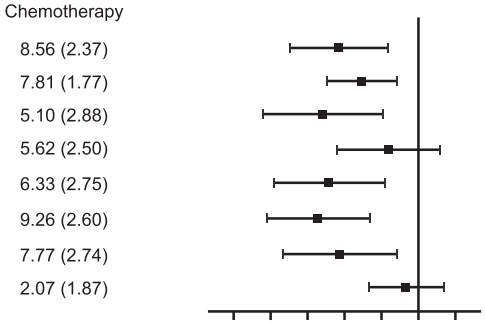
B GHS/QoL and functioning in the overall population

Domain	LS mean (SE) overall		Contrast cemiplimab vs chemotherapy (95% CI), *P* value
	Cemiplimab	Chemotherapy	
GHS/QoL	1.01 (1.54)	–6.81 (2.12)	7.81 (3.30, 12.33), 0.0004
Physical functioning	–0.45 (1.39)	–8.70 (1.83)	8.26 (4.29, 12.22), <0.0001
Role functioning	2.39 (1.73)	–10.71 (2.27)	13.10 (8.26, 17.93), <0.0001
Emotional functioning	5.10 (1.41)	–2.10 (1.96)	7.20 (3.01, 11.39), 0.0008
Cognitive functioning	–1.08 (1.43)	–5.02 (1.89)	3.95 (–0.13, 8.02), 0.0574
Social functioning	2.54 (1.77)	–5.10 (2.20)	7.64 (2.96, 12.32), 0.0015



C Symptoms in the SCC population

Domain	LS mean (SE) overall		Contrast cemiplimab vs chemotherapy (95% CI), *P* value
	Cemiplimab	Chemotherapy	
Fatigue	–0.06 (1.83)	8.56 (2.37)	–8.62 (–13.97, –3.28), 0.0017
Nausea/vomiting	1.69 (1.35)	7.81 (1.77)	–6.12 (–10.01, –2.24), 0.0022
Pain	–5.25 (2.23)	5.10 (2.88)	–10.35 (–16.87, –3.82), 0.0021
Dyspnoea	2.39 (1.95)	5.62 (2.50)	–3.22 (–8.88, 2.43), 0.2619
Insomnia	–3.33 (2.16)	6.33 (2.75)	–9.66 (–15.79, –3.53), 0.0022
Appetite loss	–1.63 (1.92)	9.26 (2.60)	–10.89 (–16.55, –5.22), 0.0002
Constipation	–0.71 (2.22)	7.77 (2.74)	–8.48 (–14.70, –2.26), 0.0078
Diarrhoea	0.72 (1.36)	2.07 (1.87)	–1.34 (–5.50, 2.82), 0.5246



D Symptoms in the overall population

Domain	LS mean (SE) overall		Contrast cemiplimab vs chemotherapy (95% CI), *P* value
	Cemiplimab	Chemotherapy	
Fatigue	1.51 (1.74)	10.55 (2.31)	–9.05 (–14.05, –4.04), 0.0004
Nausea/vomiting	0.84 (1.24)	7.89 (1.70)	–7.04 (–10.61, –3.48), 0.0001
Pain	–4.73 (2.08)	5.51 (2.77)	–10.23 (–16.20, –4.26), 0.0009
Dyspnoea	1.11 (1.69)	5.07 (2.22)	–3.96 (–8.73, 0.80), 0.1023
Insomnia	–2.43 (2.14)	6.39 (2.76)	–8.82 (–14.71, –2.93), 0.0035
Appetite loss	–3.14 (1.83)	8.15 (2.50)	–11.30 (–16.58, –6.02), <0.0001
Constipation	–0.95 (2.13)	5.33 (2.67)	–6.28 (–11.96, –0.60), 0.0303
Diarrhoea	0.06 (1.32)	0.50 (1.79)	–0.44 (–4.30, 3.42), 0.8231

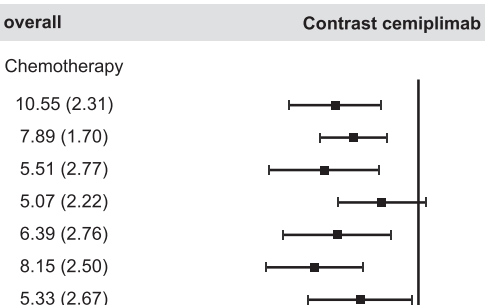


Fig. 2. **Overall changes from baseline and differences between treatment groups**. GHS/QoL and functioning scales in (A) the SCC population and (B) the overall population. Symptoms in (C) the SCC population and (D) the overall population. CI, confidence interval; GHS, global health status; LS, least squares; QoL, quality of life; SCC, squamous cell carcinoma; SE, standard error.

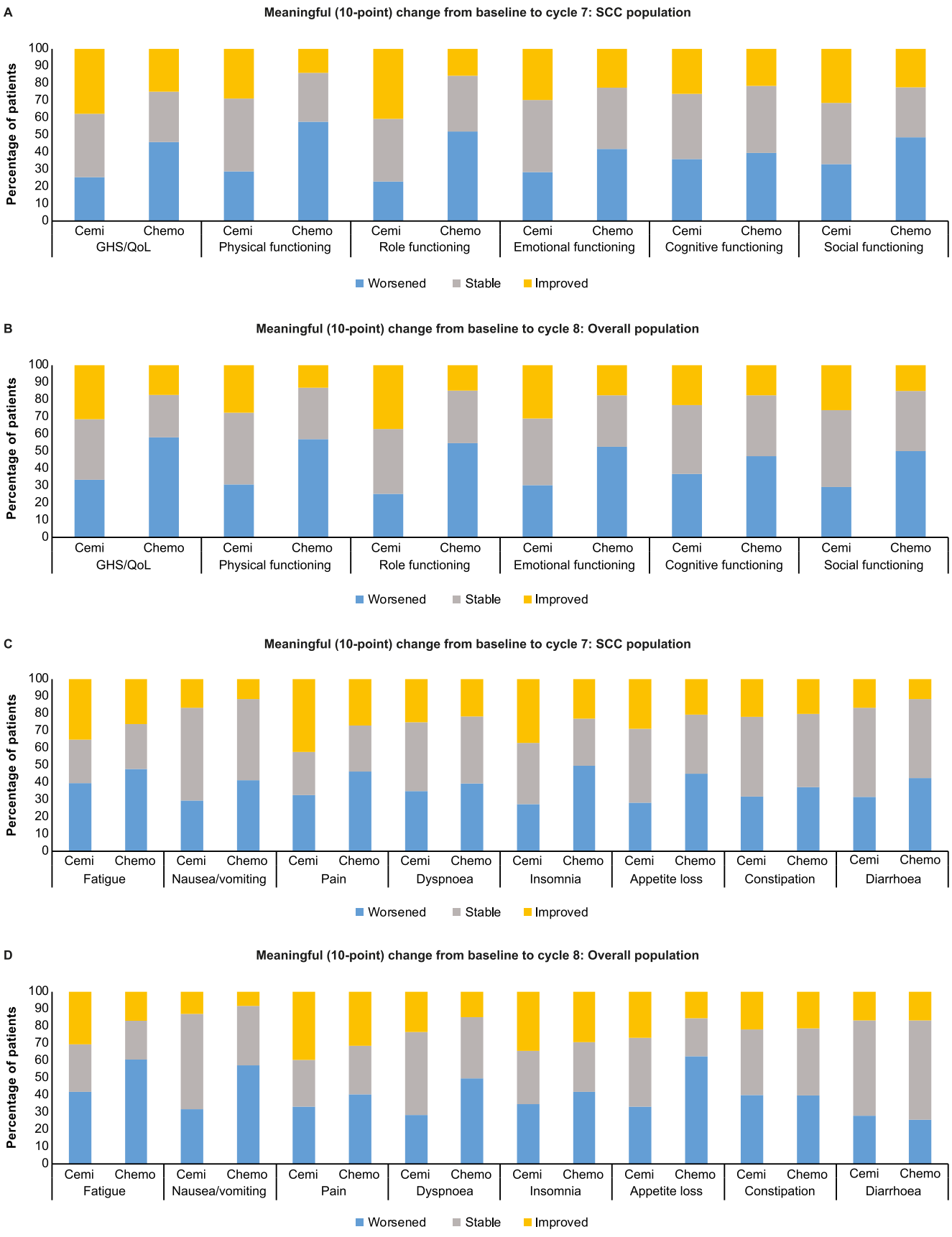


Fig. 3. **Responder analyses, using missing-at-random imputation**. GHS/QoL and functioning scales in (A) the SCC population at cycle 7 and (B) the overall population at cycle 8. Symptoms in (C) the SCC population at cycle 7 and (D) the overall population at cycle 8. Cemi, cemiplimab; Chemo, chemotherapy; GHS, global health status; QoL, quality of life; SCC, squamous cell carcinoma.

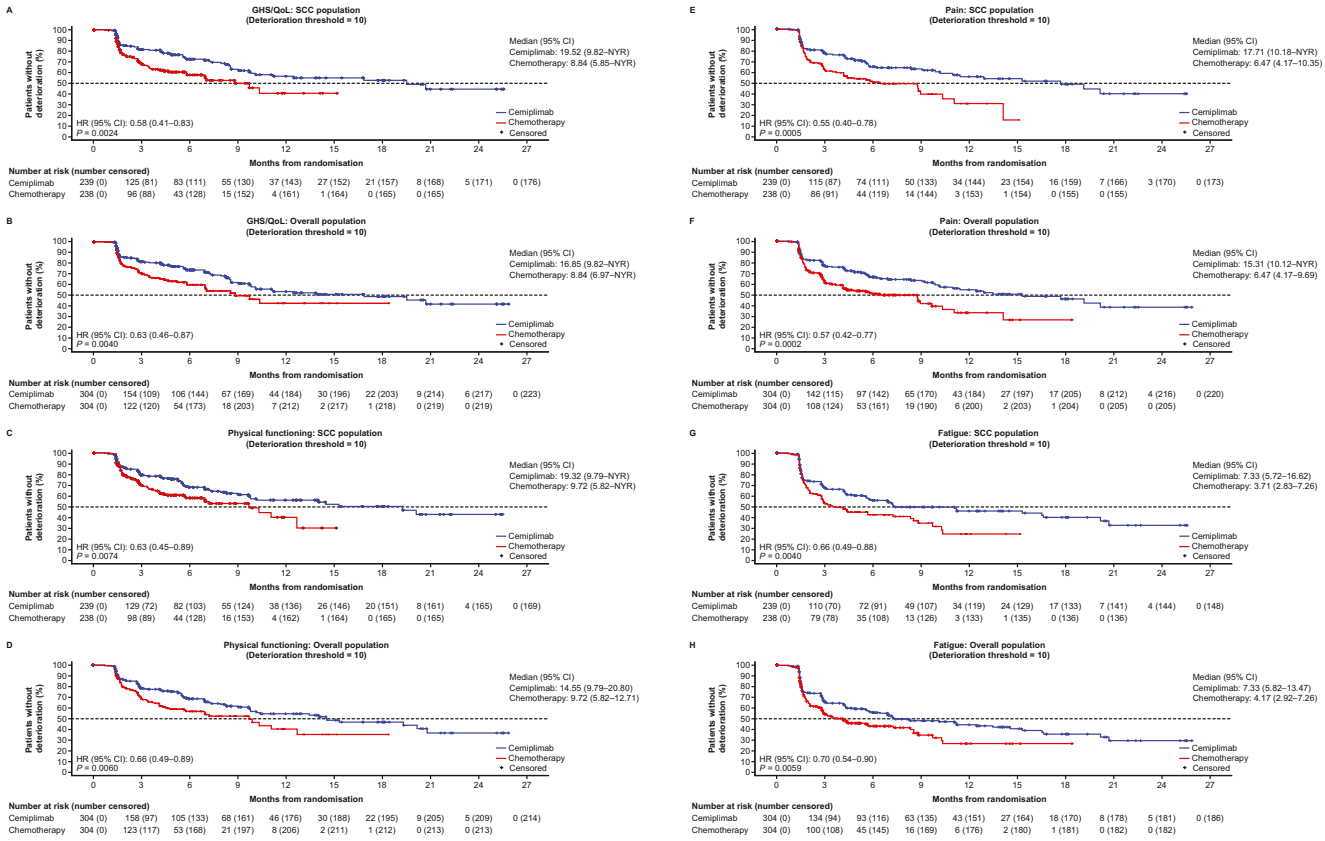


Fig. 4. **Time to definitive deterioration**. GHS/QoL in (A) the SCC population and (B) the overall population. Physical functioning in (C) the SCC population and (D) the overall population. Pain in (E) the SCC population and (F) the overall population. Fatigue in (G) the SCC population and (H) the overall population. CI, confidence interval; GHS, global health status; HR, hazard ratio; NYR, not yet reached; QoL, quality of life; SCC, squamous cell carcinoma.

treatment groups in change from baseline for physical functioning was statistically significant in favour of cemiplimab (8.35; 95% CI: 4.08−12.62; $P < 0.0001$; Fig. 2A). The treatment difference at cycle 2 favoured cemiplimab (4.09; 95% CI: 0.54−7.64; $P = 0.012$). In the overall population, treatment differences favoured cemiplimab for overall change from baseline (8.26; 95% CI: 4.29−12.22; $P < 0.0001$) (Fig. 2B) and at cycle 2 (4.16; 95% CI: 1.08−7.23; $P = 0.0041$).

Sensitivity analysis using PMM showed clinically meaningful LS mean differences between treatment arms in favour of cemiplimab across multiple delta values in both populations (Supplementary Fig. 4A and 4B). The proportion of responders was higher and the proportion of non-responders was lower for cemiplimab compared with chemotherapy in the SCC population at cycle 7 (Fig. 3A) and in the overall population at cycle 8 (Fig. 3B). The median time to definitive deterioration of physical functioning was longer with cemiplimab than with chemotherapy in both populations (Fig. 4C and D).

3.4. Other functioning scales

Differences between treatment groups in overall LS mean changes from baseline favoured cemiplimab for role functioning, emotional functioning and social functioning in both populations (Figs. 2A and B). Treatment differences for role functioning exceeded the clinically meaningful threshold of 10 points in each population. Treatment differences favoured cemiplimab for all functioning scales in PMM sensitivity analyses, with clinically meaningful differences for role functioning in the SCC population (Supplementary Fig. 4A) and for role functioning, emotional functioning and social functioning in the overall population (Supplementary Fig. 4B). The proportion of responders was higher (Fig. 3A and B) and the median time to definitive deterioration was longer with cemiplimab than with chemotherapy (Supplementary Figs. 5A and 5B) for all functioning scales in both populations.

3.5. Symptoms

Treatment differences for fatigue, nausea/vomiting, pain, insomnia, appetite loss and constipation all favoured cemiplimab in both populations (Figs. 2C and D). Differences in appetite loss and pain exceeded the clinically meaningful threshold. In PMM sensitivity analyses, treatment differences favoured cemiplimab

for the same symptom scales in the SCC population (Supplementary Fig. 4C) and the same scales plus dyspnoea in the overall population (Supplementary Fig. 4D). The proportion of responders generally was higher for cemiplimab versus chemotherapy for these symptoms in the SCC population through cycle 7 (Fig. 3C) and in the overall population through cycle 8 (Fig. 3D). The median time to definitive deterioration was longer with cemiplimab than with chemotherapy in both populations for pain (Figs. 4E and F), fatigue (Figs. 4G and H) and nausea/vomiting, dyspnoea (overall population only), insomnia, appetite loss and constipation (Supplementary Figs. 5C and 5D).

4. Discussion

The primary analysis of Study R2810-ONC-1676 (EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9) demonstrated significant improvement in clinical endpoints for cemiplimab versus chemotherapy in patients with recurrent or metastatic cervical cancer, including significant reduction in the risk of death and disease progression in both the SCC and overall populations [8]. In this analysis, patients showed low-to-moderate symptom burden at baseline, with functioning scores that were lower than normative values in the general population [14] and slightly lower than reference values for patients with cancer.

Cemiplimab provided statistically significant benefit versus chemotherapy in the SCC population for overall changes from baseline in GHS/QoL and physical functioning. Treatment differences also favoured cemiplimab over chemotherapy for changes from baseline in GHS/QoL and physical functioning in the overall population. Early benefits of cemiplimab over chemotherapy were seen at cycle 2 in both populations, but the statistical hierarchy broke with the evaluation of changes from baseline to cycle 2 for GHS/QoL. Separation was seen by cycle 3 or 4, suggesting that comparisons at cycle 2 may have been premature. The proportion of patients who reported a ≥10-point GHS/QoL or physical functioning improvement (a clinically meaningful within-patient change on the EORTC QLQ-C30 scale [10–12]) was higher, and the proportion with ≥10-point worsening was lower, with cemiplimab compared with chemotherapy. The median time to definitive deterioration (≥10-point sustained worsening) was longer with cemiplimab than with chemotherapy for both GHS/QoL and physical functioning.

Other functioning scales showed treatment differences favouring cemiplimab for role functioning, emotional functioning and social functioning in both populations (SCC and overall), including a clinically meaningful benefit for role functioning. Symptom scores favoured cemiplimab for fatigue, nausea/vomiting, pain, insomnia, appetite loss and constipation. Time to definitive deterioration also favoured cemiplimab for fatigue, pain, nausea/vomiting, insomnia, appetite loss and constipation. The reported treatment differences for pain and appetite loss exceeded the clinically meaningful threshold. QoL, physical functioning, role functioning and disease-related symptoms such as pain are recommended by regulatory authorities as core outcomes for clinical trials of treatment for cancer [16,17].

Study R2810-ONC-1676 is the largest phase III randomised, controlled clinical trial of second-line treatment for recurrent or metastatic cervical cancer and the first such study to examine PROs. A single-arm study reported that PROs were stable after 9 weeks of nivolumab treatment in 19 women with cervical cancer [18] but that study lacked a control arm or long-term monitoring of changes.

Some limitations should be considered. EORTC QLQ-C30 was designed as a generic cancer instrument and may not capture all pertinent symptoms or components of QoL for patients with cervical cancer. It has nonetheless shown adequate psychometric measurement properties in cervical cancer [19] and is one of the most commonly used PRO instruments in cancer research. Future research should continue to examine the effects of cemiplimab and other new treatments on PROs by also using questionnaires that are specifically designed for use in this patient population. Study treatment was administered open-label but several studies have shown that the potential for bias in PROs may be less prominent in open-label studies than is commonly assumed [20,21]. PRO completion rates in this study were high and similar in both treatment arms, suggesting low bias. There was a higher dropout rate in the chemotherapy arm due to differences in progression and survival in favour of cemiplimab. Per the PRO statistical analysis plan, between-group comparisons of PRO data were limited to on-treatment analyses. Continued comparison of PROs after the discontinuation of study treatment would have limited generalisability because it would be confounded by the effects of subsequent treatments on QoL and symptoms. Sensitivity analysis with PMM partly addressed this concern by showing that differences also favoured cemiplimab when data were assumed to be missing-not-at-random. A 10-point threshold was used for clinically meaningful differences, based on prior research in other cancer types [10–12], but it has not been specifically established for use in patients with cervical cancer. Other analyses that were beyond the scope of this study should be considered for future research of PROs in patients with cervical cancer who receive cemiplimab or other immunotherapy, such as PROs by PD-L1 status and other patient subgroups, or the application of analytical methods such as quality-adjusted time without symptoms or toxicity (Q-TWIST) [22] or quality-adjusted progression-free survival [23].

In this international, randomised controlled study, treatment with cemiplimab resulted in a statistically significant benefit versus chemotherapy in the SCC population for GHS/QoL and physical functioning. Consistent benefits over chemotherapy were observed across most functioning and symptom scales, meeting the clinically meaningful threshold for between-group differences in role functioning, appetite loss and pain. The primary analysis showed that cemiplimab significantly improved overall survival, and this analysis showed that PROs further supported the favourable benefit–risk profile of cemiplimab compared with chemotherapy in patients with recurrent or metastatic cervical cancer.

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Role of the funding source

The funder participated in study design, data analysis and interpretation, and manuscript writing, and maintained the study database. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Data sharing

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymised participant data will be considered for sharing once the product and indication have been approved by major health authorities (e.g. Food and Drug Administration, European Medicines Agency), if there is legal authority to share the data, and there is not a reasonable likelihood of participant re-identification. Requests should be submitted to https://vivli.org/.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **A.O.** reports serving on advisory boards for Roche, AstraZeneca, MSD/Merck, PharmaMar, Clovis Oncology, Tesaro, Immunogen, Genmab, Mersana Therapeutic, GSK, SUTRO, AGENUS and Deciphera Pharmaceuticals; and support for travel or accommodation from Roche, AstraZeneca and PharmaMar.

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C.I. and **M.R.** report employment at IQVIA and institutional research funding from Regeneron Pharmaceuticals, Inc.

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Appendix A. Supplementary data

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