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Cemiplimab in recurrent cervical cancer: Final analysis of overall survival in the phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial

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ABSTRACT

Aim: Cemiplimab has demonstrated significantly longer survival than physician's choice of chemotherapy in patients with recurrent cervical cancer after first-line platinum-containing chemotherapy. We report the final survival analysis from the phase III randomized study (EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9).

Methods: Cemiplimab (n = 304) or chemotherapy (n = 304) were administered every 3 weeks. The primary endpoint was overall survival (OS). Patients were included regardless of programmed cell death-ligand 1 (PD-L1) status.

Results: At a median follow-up of 47.3 months (data cut-off: April 20, 2023), median OS was 11.7 versus 8.5 months for patients treated with cemiplimab and chemotherapy, respectively (hazard ratio 0.67, 95 % confidence interval 0.56–0.80, p < .00001). OS benefit was seen in PD-L1 positive and negative populations, even though more patients with PD-L1 < 1 % (n = 92), had poor performance status in the cemiplimab arm than the chemotherapy arm (61.4 % vs 47.9 %).

Conclusion: This final analysis confirms that cemiplimab maintains survival benefit compared with chemotherapy in recurrent cervical cancer after progression on first-line platinum therapy, regardless of PD-L1 expression. The safety profile was consistent with published data; incidences of adverse events were similar between cemiplimab and chemotherapy groups. These results support the use of second-line cemiplimab for patients with recurrent cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer among women, and causes considerable morbidity and mortality [1]. Approximately 600,000 new cases and 350,000 deaths occur due to cervical cancer globally each year [2], with almost all cases caused by infection with high-risk types of human papillomavirus (HPV) [3]. If diagnosed early, treatment options are available; however, cervical cancer is usually slow-growing with few symptoms of early disease, so screening programs are imperative to detecting early abnormalities and pre-invasive disease [4].

Current treatment for locally advanced cervical cancer is chemoradiation and high dose-rate intracavitary brachytherapy [5]. Still, approximately a third of patients experience disease recurrence [6]. Newer approaches include the addition of immunotherapy to chemoradiation regimens, such as pembrolizumab, an anti-programmed cell death 1 (PD-1) agent, which improved progression-free survival (PFS) versus concurrent chemoradiotherapy alone [7]. Induction chemotherapy followed by chemoradiation alone also improved PFS and overall survival (OS) in patients with locally advanced cervical cancer [8]. At the time of this study, available data supported platinum-based chemotherapy with or without bevacizumab as the standard first-line therapy for patients with persistent or recurrent cervical cancer [9–11]; however, most patients progress after existing first-line platinum-containing therapy [12]. Although approved for the treatment of advanced cervical cancer in the USA in 2014 and Europe in 2015, optional bevacizumab therapy was not widely prescribed during enrollment of this study [13,14]. Alternative options for first-line therapy in these patients may include the addition of pembrolizumab [15] or atezolizumab [16] to chemotherapy with or without bevacizumab, both of which have demonstrated improved PFS and OS. However, there remain limited treatment options for these patients and no standard of care for second-line therapy [12,17], highlighting an unmet need for effective second-line treatments for recurrent cervical cancer.

Based on preliminary evidence in cervical cancer trials, as well as activity in other HPV-associated cancers, blockade of PD-1 warranted investigation in cervical cancer [18,19]. Cemiplimab, an anti-PD-1 inhibitor, was the first immunotherapy to demonstrate a survival benefit in second-line treatment of cervical cancer and was approved in November 2022 as monotherapy in Europe for adults with recurrent cervical cancer and disease progression on or after platinum-based chemotherapy [20]. It is also approved for recurrent cervical cancer in Brazil, Canada, and Japan.

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 is an open-label, randomized, phase III study of cemiplimab versus investigator's choice of chemotherapy in patients with recurrent cervical carcinoma following progression on platinum-containing chemotherapy, regardless of programmed cell death-ligand 1 (PD-L1) tumor expression. Results from the second interim analysis demonstrated significantly improved OS in patients with cervical cancer receiving cemiplimab monotherapy [21]. Per protocol, the final analysis for OS was the occurrence of 340 events in patients with squamous cell carcinoma (SCC). Here, we report the final survival analysis of the 608 patients enrolled in EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9, after a median follow-up of 47 months.

2. Material and methods

The study design and methods of the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 (NCT03257267) trial have previously been reported [21], and the protocol is available online at https://clinicaltrials.gov/study/NCT03257267.

Briefly, 608 adult female patients with recurrent and/or persistent cervical cancer were recruited. Key inclusion criteria included cervical cancer that had progressed on or after platinum-containing chemotherapy. Patients must have had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1.

Patients were randomized 1:1 to receive cemiplimab 350 mg (n = 304) or investigator's choice of chemotherapy (n = 304). Chemotherapy agents used belonged to one of four classes: antifolate (eg, pemetrexed [n = 111]), topoisomerase 1 inhibitor (topotecan [n = 21], irinotecan [n = 19]), nucleoside analogue (gemcitabine [n = 121]), or vinca alkaloid (vinorelbine [n = 32]) [21]. Treatment in both arms continued for ≤ 96 weeks or until disease progression or unacceptable toxicity. Post-treatment follow-up included safety, progression events, and OS. After the post-treatment follow-up, patients were followed further for survival.

The primary endpoint of this analysis was OS; secondary endpoints included objective response rate (ORR) and safety. OS based on PD-L1 score was assessed through exploratory analyses. Safety was assessed for all study drugs; information regarding adverse events (AEs) was reported at each patient contact. PD-L1 expression status was retrospectively assessed as the tumor proportion score (ie, the percentage of tumor cells expressing PD-L1 in archived [pre-treatment] tumor samples) and was categorized as either ≥ 1 % or < 1 % [21].

The statistical analysis plan is available within the supplementary material associated with the primary publication, at NEJM.org [21]. Primary and secondary endpoints were analyzed using the intention-to-treat principle, with patients grouped according to randomized treatment assignment, regardless of adherence [21]. The final survival analysis, estimated using the Kaplan–Meier method, was planned to be conducted after approximately 340 observed OS events in

approximately 460 enrolled patients with SCC to provide 90 % power to detect at least a 30 % lower risk of death in the cemiplimab group [21]. The odds of committing a Type I error were reduced by first assessing OS in the SCC population [21]; if these results were significant, OS was then analyzed in the entire study population [21].

Safety was evaluated in all patients who received at least one dose of the assigned treatment [21]. Assessments included treatment-related AEs occurring at any time and AEs reported until 90 days after the last treatment dose or 1 day before the initiation of post-treatment therapy, whichever was first [21].

3. Results

Of the 752 patients screened, 608 were recruited between July 2017 and August 2020 (Supplementary Figure 1). At baseline, 87.7 % of patients were < 65 years of age, 94.4 % had metastatic disease, and 5.6 % had locoregional recurrence only. Histologic distribution was consistent with real-world distribution: 77.8 % of patients had SCC, 19.1 % had adenocarcinoma, and 3.1 % had adenosquamous cell carcinoma. Baseline characteristics were well balanced between treatment arms (Table 1).

In the overall population, at a median follow-up of 47.3 months, median OS was 11.7 months versus 8.5 months for cemiplimab-treated patients (n = 304) versus chemotherapy (n = 304; hazard ratio [HR] 0.67, 95 % confidence interval [CI] 0.56–0.80, one-sided p < .00001) (Figure 1 and Supplementary Table 1). In patients with SCC histology, median OS was 10.9 months versus 8.8 months for cemiplimab-treated patients (n = 239) versus those receiving chemotherapy (n = 238; HR 0.70, 95 % CI 0.57–0.86, one-sided p = .00024), respectively (Supplementary Figure 2A). In an exploratory analysis in patients with adenocarcinoma or adenosquamous carcinoma histology, median OS was 13.5 months for cemiplimab (n = 65) versus 7.0 months for chemotherapy (n = 66) (HR 0.55, 95 % CI 0.37–0.82; Supplementary Figure 2B). In a pre-defined subgroup analysis, OS was longer for patients treated with cemiplimab in all subgroups, except for Japanese patients (Supplementary Figure 3).

In the PD-L1 tested population (n = 254), cemiplimab significantly improved OS versus chemotherapy regardless of PD-L1 data availability (Supplementary Figure 4). In patients with PD-L1 < 1 % (n = 92), there were more with poor ECOG PS (of 1) in the cemiplimab than in the chemotherapy arm (61.4 % vs 47.9 %) (Table 1).

In the exploratory analysis assessing OS by PD-L1 expression adjusted by ECOG PS, in the PD-L1 < 1 % subgroup OS was 8.2 months for cemiplimab versus 6.7 months for chemotherapy (HR=0.76) (Table 2).

In cemiplimab-treated patients, ORR was higher versus chemotherapy regardless of PD-L1 status. In the overall population, ORR was 17.1 % (95 % CI 13.0–21.8) with cemiplimab versus 6.3 % (95 % CI 3.8–9.6) with chemotherapy (Supplementary Table 2).

In the cemiplimab group, AEs of any grade occurred in 89.7 % of patients versus 91.7 % of patients in the chemotherapy group; the most commonly reported were nausea, vomiting, and anemia (Supplementary Table 3). A total of 57.3 % and 81.7 % of patients in the cemiplimab group and the chemotherapy group, respectively, had treatment-related AEs (the most commonly reported were nausea, 9.3 % vs 30.3 %; fatigue, 10.7 % vs 13.4 %; anemia, 7.7 % vs 36.9 %, respectively). In the cemiplimab and chemotherapy arms, 9.0 % and 5.2 % of patients discontinued treatment due to AEs, and there were zero and two treatment-related AEs leading to death, respectively. No chemotherapy-treated patients reported an AE of special interest (AESI) compared with 36 cemiplimab-treated patients (12 %); 12 patients (4 %) discontinued cemiplimab due to an AESI (Supplementary Table 3).

Table 1
Baseline characteristics in the overall trial population.

N (%)	Cemiplimab (n = 304)	Chemotherapy (n = 304)	Total (N = 608)
Age group, years			
<65	269 (88.5)	264 (86.8)	533 (87.7)
≥65	35 (11.5)	40 (13.2)	75 (12.3)
Race			
White	193 (63.5)	192 (63.2)	385 (63.3)
Black or African American	9 (3.0)	12 (3.9)	21 (3.5)
Asian	88 (28.9)	88 (28.9)	176 (28.9)
American Indian or Alaska Native	2 (0.7)	1 (0.3)	3 (0.5)
Other	8 (2.6)	4 (1.3)	12 (2.0)
Unknown/not reported	4 (1.3)	7 (2.3)	11 (1.8)
ECOG PS			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)
ECOG PS (PD-L1 ≥1 %, n = 162)			
0	34 (41.5)	34 (42.5)	68 (42.0)
1	48 (58.5)	46 (57.5)	94 (58.0)
ECOG PS (PD-L1 <1 %, n = 92)			
0	17 (38.6)	25 (52.1)	42 (45.7)
1	27 (61.4)	23 (47.9)	50 (54.3)
Histology/cytology			
Squamous cell carcinoma	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			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent	20 (6.6)	14 (4.6)	34 (5.6)
Prior bevacizumab use			
Yes	148 (48.7)	149 (49.0)	297 (48.8)
No	156 (51.3)	155 (51.0)	311 (51.2)
Number of prior lines of systemic therapy for recurrent or metastatic disease[a]			
1	177 (58.2)	169 (55.6)	346 (56.9)
>1	124 (40.8)	135 (44.4)	259 (42.6)
With PD-L1 expression	126 (41.4)	128 (42.1)	254 (41.8)
PD-L1 expression per TC method			
TC ≥ 1 %	82 (27.0)	80 (26.3)	162 (26.6)
TC < 1 %	44 (14.5)	48 (15.8)	92 (15.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; TC, tumor cell.

[a] n = 301 for cemiplimab, as three patients did not receive prior systemic therapy for recurrent or metastatic disease.

4. Discussion

Cemiplimab is the first immunotherapy agent to show significant and clinically meaningful OS benefit as second-line monotherapy for patients with recurrent cervical cancer previously treated with platinum-based chemotherapy [21]. Based on prior results from the phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study, cemiplimab monotherapy was approved by multiple health authorities for the treatment of adults with recurrent cervical cancer and disease progression on or after platinum-based chemotherapy [20]. In this final analysis from the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study, cemiplimab continued to demonstrate superior survival for recurrent cervical cancer compared with investigator's choice of chemotherapy. At a median follow-up of 47.3 months, cemiplimab demonstrated a sustained and long-lasting survival benefit, regardless of histology and PD-L1 expression level.

Regarding the population in which cemiplimab was studied, during the clinical trial enrolment period, the standard of care for persistent, recurrent or metastatic cervical cancer was platinum-based chemotherapy with or without bevacizumab [22]. Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, was an optional therapy before enrolment since many patients are not eligible for bevacizumab due to risk of recto-vaginal fistula. In our study approximately 50 % had received bevacizumab and indeed, this figure is quite aligned with the published data on the KN826 where only 60 % of the population received bevacizumab as part of the first-line regimen [23]. We therefore considered that our treated population is aligned with the real-world population. Indeed, our data are further supported by real-world evidence, which has demonstrated the efficacy of

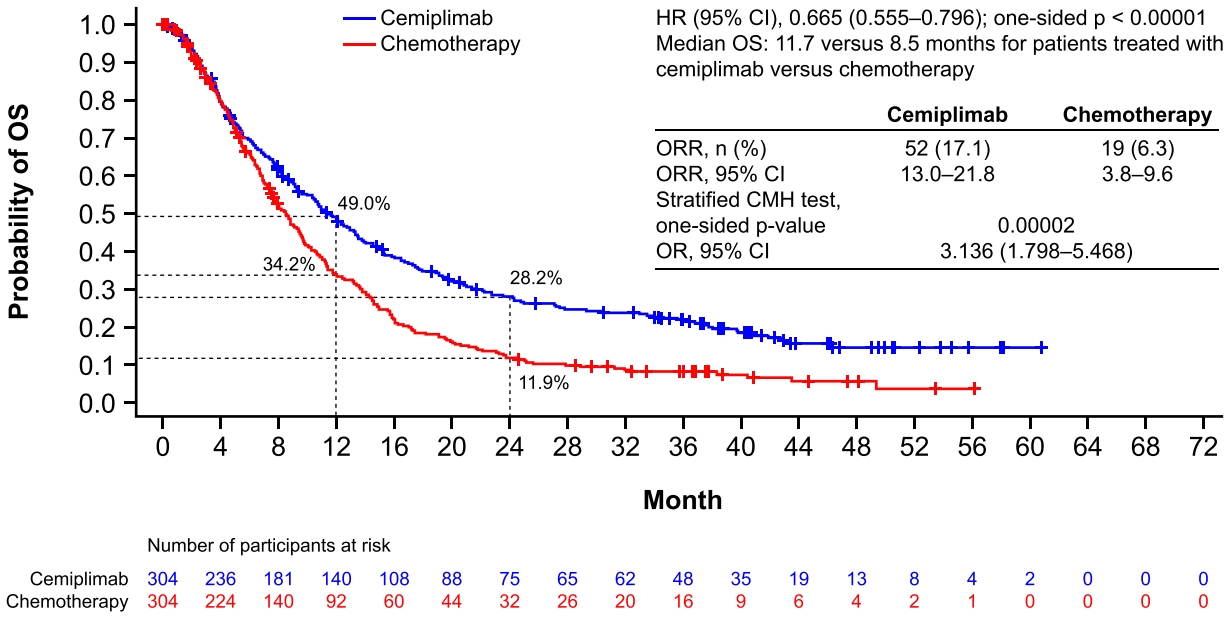

Fig. 1. OS in the overall trial population. CI, confidence interval; CMH, Cochran-Mantel-Haenszel; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival.

Table 2
OS by PD-L1 expression.

	Cemiplimab (n = 304)		Chemotherapy (n = 304)		HR (95 % CI)[b]	HR (95 % CI)[c] adjusted by ECOG PS
	Event/total (%)	Median time, months (95 % CI)[a]	Event/total (%)	Median time, months (95 % CI)[a]		
All patients	237/304 (78.0)	11.7 (9.6–13.4)	256/304 (84.2)	8.5 (7.5–9.6)	0.67 (0.56–0.80)	0.66 (0.55–0.79)
PD-L1 unknown	138/178 (77.5)	11.7 (9.2–13.5)	145/176 (82.4)	8.7 (7.4–9.7)	0.66 (0.52–0.83)	0.64 (0.50–0.82)
PD-L1 known	99/126 (78.6)	12.0 (8.1–14.9)	111/128 (86.7)	8.2 (6.7–11.0)	0.75 (0.56–0.99)	0.72 (0.55–0.96)
TC ≥ 1 %	62/82 (75.6)	13.9 (9.6–17.4)	67/80 (83.8)	9.3 (7.0–11.4)	0.72 (0.50–1.0)	0.69 (0.49–0.99)
TC < 1 %	37/44 (84.1)	8.2 (4.3–12.3)	44/48 (91.7)	6.7 (3.9–11.8)	0.86 (0.54–1.37)	0.76 (0.47–1.24)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1; TC, tumor cell.
Cut-slide sample stability for assessment of PD-L1 expression in cervical cancer specimens was determined to be 6 months. The validity of results obtained from cut-slides > 6 months in age cannot be assured.
[a] Based on the Kaplan–Meier method.
[b] Based on geographic region (North America vs Asia vs rest of world) and histology (squamous cell carcinoma vs adenocarcinoma).
[c] Based on geographic region (North America vs Asia vs rest of world), histology (squamous cell carcinoma vs adenocarcinoma), and ECOG (0 vs 1), stratified by a proportional hazards model (cemiplimab vs chemotherapy).

cemiplimab for (n = 135) patients with recurrent cervical cancer in a nominal use program in Italy [24].

Although cemiplimab demonstrated significant survival benefits both in patients with SCC and adenocarcinoma histology, there was a numerically greater reduction in the risk of death in patients with adenocarcinoma histology than in those with SCC histology (HR [95 % CI], 0.552 [0.372–0.819] vs 0.698 [0.570–0.855]). PD-L1 expression is reported to be higher in patients with SCC histology than in adenocarcinoma histology [25,26], and this may partially account for the observed differences in survival outcomes seen between these two histology subtypes [25].

ECOG PS is a known predictor of survival for patients with cancer [27], and this was therefore used as a randomization factor for the total population. An exploratory analysis also assessed OS based on PD-L1 expression. However, in the cemiplimab arm, ECOG PS was imbalanced between the PD-L1 negative and PD-L1 positive participants, therefore the survival benefit in the cemiplimab arm may have been underestimated in patients with PD-L1 < 1 %. (Table 1). Initial results for the PD-L1 negative participants had a higher proportion of poor performance status (ie, a higher ECOG PS); as such, their median survival was underestimated (Table 2). A covariance-adjusted analysis was subsequently performed to correct this imbalance and better estimate the true treatment effect; in the PD-L1 < 1 % subgroup, cemiplimab reduced the risk of death by 25 % over chemotherapy in the ECOG PS-adjusted analysis (HR=0.76) (Table 2). A previous analysis of this study at 30 months follow-up used a larger sample of patients with PD-L1 status data (n = 371). In this PD-L1-tested population, cemiplimab increased OS versus chemotherapy in patients with PD-L1 < 1 %, with a 35 % lower risk of death [28].

The safety profile of cemiplimab is consistent with published data, with no new safety signals identified in this longer-term follow-up study (NCT03257267) [29–31]. Although patients had a longer median

duration of exposure to cemiplimab (15.2 weeks) compared with chemotherapy (10.1 weeks), cemiplimab-treated patients experienced similar rates of AEs of any grade to those who received chemotherapy. The safety profile is also consistent with those of other PD-1 or PD-L1 inhibitors used to treat cervical cancer: 47 % of patients in the cemiplimab arm experienced at least one grade $\geq$ 3 AE. In a randomized, placebo-controlled study of pembrolizumab, 82 % of patients treated with pembrolizumab experienced at least one grade $\geq$ 3 AE [23]; in a phase II study of nivolumab, 48 % of patients experienced a grade 3 AE [32]. Although these studies were in slightly different treatment settings, the overall findings are largely comparable.

Immune checkpoint inhibitors have shown compelling efficacy outcomes that have led to a paradigm shift in the treatment of cervical cancer. The anti-PD1 agent, pembrolizumab is approved in the US for treatment of locally advanced cervical cancer in combination with concurrent chemo-radiotherapy followed as maintenance for patients with FIGO 2014 Stage III/IVA disease. It is also approved in combination with platinum-based chemotherapy plus or minus bevacizumab as first-line therapy in patients with recurrent, persistent and metastatic cervical cancer patients whose tumors are combined positive score $\geq$ 1 %. Finally, pembrolizumab is also approved as monotherapy for patients with recurrent or metastatic disease and PD-L1 expression $\geq$ 1 % following disease progression on or after platinum-based chemotherapy [33].

Unlike the license for pembrolizumab in the setting of first-line and after platinum failure, which is limited to patients with PD-L1 expression $\geq$ 1 % using combined positive score (calculated using PD-L1 expression on the tumor and immune cells) [34,35], our results indicate that cemiplimab has benefit for all comers irrespective of PD-L1 expression status.

Other immune checkpoint inhibitors such as nivolumab and atezolizumab have also shown clinically beneficial results as treatment of recurrent cervical cancer after platinum failure in the context of single arm studies [7,15,16,25].

In the future, therefore, it may be likely that many patients with cervical cancer will have been exposed to prior immunotherapy before progressing to second-line treatment. As cemiplimab is an approved second-line therapy, it would be valuable to discern potential cemiplimab efficacy for patients who progress after first-line pembrolizumab-based therapy [21]. The degree to which switching between different PD-1 inhibitors offers additional benefit will need to be addressed, as will concerns about resistance [17]. Due to the recent approval of pembrolizumab in locally advanced cervical cancer, questions remain regarding the timing of immunotherapy treatment for cervical cancer; it should be determined whether to incorporate pembrolizumab as part of concurrent chemo-radiation or as part of first-line therapy [36].

The treatment landscape for those patients who had progressed on platinum therapy is rapidly evolving since many of these patients had already been treated with immunotherapy. To date there are a plethora of antibody drug conjugates (ADCs) under investigation and a few of them already approved. Tisotumab vedotin, an ADC targeting tissue factor, has shown a statically significant improvement in overall survival in the second line therapy compared with single-agent chemotherapy (HR 0.70; $p = 0.0038$) [37], moreover, the trial included 25 % of patients who had received previous immunotherapy. In light of these outcomes, tisotumab vedotin is already approved by the US Food and Drug Administration for those patients who have progressed to platinum therapy [37]. Moreover, trastuzumab deruxtecan targeting human epidermal growth factor receptor 2 has been approved by the US Food and Drug Administration as agnostic indication for those patients whose tumors overexpressed human epidermal growth factor receptor 2 3+ including cervical cancer. In the phase II Destiny Pantumor-02 trial, 40 patients with cervical cancer received trastuzumab deruxtecan, with a median PFS of 7.0 months and a median OS of 13.6 months [38]. In the phase II EVER-132–003 trial, 18 patients with advanced cervical cancer received sacituzumab govitecan, a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate, with a median PFS 8.1 months [39]. Furthermore, there are planned phase III studies investigating MK-2870, an anti-TROP2 ADC, as a second line treatment for cervical cancer.

5. Conclusion

The final analysis of OS from the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 phase III study confirms that cemiplimab maintains a survival benefit for adults with recurrent cervical cancer after progression on platinum-containing chemotherapy. Improved OS was observed in patients receiving cemiplimab versus chemotherapy, regardless of PD-L1 level. Cemiplimab should therefore be considered a standard second-line systemic option for platinum pre-treated, immunotherapy-naïve recurrent cervical cancer.

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The funder participated in the study design, data analysis and interpretation, manuscript writing, and maintains the study database. All authors had full access to the data and were responsible for all content and editorial decisions.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115146.

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