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Real-life efficacy and safety of cemiplimab in advanced cervical cancer from a nominal use program in Italy: The MITO 44 study

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ABSTRACT

Background: cemiplimab is an immunoglobulin G4 monoclonal antibody targeting the programmed cell death-1 receptor. A nominal use program is available in Italy in advanced cervical cancer (CC) patients treated with platinum based chemotherapy based on the results of EMPOWER-Cervical 1/GOG-3016/ENGOTcx9 trial. This real-world, retrospective cohort, multicenter study aimed at describing clinical outcomes of patients with advanced CC treated with cemiplimab in Italy.

Methods: The primary objective of the study was to assess the feasibility and the replicability of the initial results in a real world setting of cemiplimab nominal use. The primary endpoint of our analysis was progression free survival (PFS). Secondary endpoints included overall response rate (ORR), overall survival (OS) and safety data.

Results: From March 2022 to December 2023, 135 patients were treated in 12 Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) Centers. Forty-two percent of patients had one or more comorbidities, hypertension being the most common (23.4%). Median PFS was 4.0 months (range 3.0–6.0) and median OS was 12.0 months (12.0- NR) with no differences according to PD-L1 status. Complete response (CR) or no evidence of disease (NED) were observed in 8.6%; partial response (PR) in 21.1%, stable disease (SD) in 14.8% and progression was recorded in 44.5% of patients. Most common drug related adverse events (AEs) were anemia (39.1%) and fatigue (27.8%). Immune related AEs occurred in 18.0%.

Conclusions: This study confirms the feasibility and the replicability of the cemiplimab nominal use in advanced CC, in a real-world practice in Italy.

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1. Introduction

Cervical cancer (CC) is a leading cause of women cancer-related mortality worldwide that continues to pose a significant health burden despite advancements in prevention, early detection, and therapeutic interventions, counting around 54,517 new cases diagnosed yearly in Europe [1].

Squamous cell carcinoma (SCC), adenocarcinoma (ADK), and adenosquamous carcinoma (ADSC) are the three prevalent histological subtypes, accounting for up 70%, 25%, and 5% of cases, respectively [2]. The overall survival (OS) at 5 years is approximately 92%, 65%, and 17% for early-stage, locally advanced, and metastatic disease, respectively [3].

The backbone of treatment for persistent, recurrent, or metastatic CC is platinum-based chemotherapy. This treatment regimen usually includes cisplatin or carboplatin, paclitaxel, and bevacizumab, as it strikes a balance between effectiveness and safety [4].

Despite the improvement in OS conferred by bevacizumab, most patients progress after first line therapy and have limited treatment option.

The first immune-checkpoint inhibitors (ICI) approved in the United States was pembrolizumab as second line therapy for patients with recurrent CC [5].

Based on KEYNOTE-826 trial [4] results, pembrolizumab was also approved for patients with a PD-L1 combined positive score (CPS) of at least 1, in combination with platinum-based chemotherapy with or without bevacizumab, as a first-line treatment [6–8]. Recently, the BEATcc trial (ENGOT-Cx10–GEICO 68-C–JGOG1084–GOG-3030) showed that adding atezolizumab to a standard bevacizumab plus platinum regimen for metastatic, persistent, or recurrent cervical cancer significantly improves progression-free survival (PFS) and OS [9].

However, there is currently no established conventional treatment approach for recurrent, persistent or metastatic CC following the failure of first line treatment, resulting in enduring challenges such as reduced quality of life (QoL), impaired functioning, and persistent symptoms. Cemiplimab, an immunoglobulin G4 monoclonal antibody targeting the programmed cell death-1 receptor, significantly improved PFS and OS compared to the investigator's chosen chemotherapy in a multicenter phase III randomized study. The EMPOWER-Cervical 1/GOG-3016/ENGOTcx9 enrolled patients with recurrent, persistent or metastatic CC, who had progressed after first line platinum-based chemotherapy regardless PD-L1 status and not previously exposed to ICI [10,11]. Based on these results a nominal use program of cemiplimab in this setting is ongoing in Italy.

Cemiplimab is approved for patients with cutaneous squamous cell carcinoma (CSCC)[12–14], basal cell carcinoma (BCC)[15–17], and non-small cell lung cancer (NSCLC)[18–21].

We conducted the MITO 44, retrospective multicenter, real-life study on the efficacy and safety of cemiplimab in Italian patients with advanced CC treated within the nominal use program.

2. Materials and methods

2.1. Patients

This retrospective cohort study included data from patients treated within the nominal use program in 12 Italian MITO centers. Data were collected from the patients' medical records using REDCap (research electronic data capture) v14.1.2. Inclusion/exclusion criteria were those of the EMPOWER-CERVICAL-1 trial. Inclusion criteria were age $>$ 18 years and histologically confirmed diagnosis of recurrent, persistent or metastatic CC previous treated with platinum-based chemotherapy, not eligible or able to participate in a clinical trial in this indication. Serum creatinine $\leq$ 1.5x ULN or estimated creatinine clearance $>$ 45 mL/min, adequate bone marrow and liver function were even required. Exclusion criteria were patients with a history of solid organ transplant, ongoing or within 5 years autoimmune disease that requires immunosuppressive treatments, prior treatment with an anti-PD (L)− 1 mAb (monoclonal antibody), prior treatment with other immune modulating agents that was within fewer than 28 days prior to the first dose of cemiplimab, presence of untreated brain metastasis that may be considered active, treatment with corticosteroid $>$ 10 mg/day or equivalent) $<$ 4 weeks prior to the first dose of cemiplimab, active infection (bacterial, viral, fungal or mycobacterial) requiring therapy, including infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), receipt of live vaccine (including attenuated) within 30 days of first dose of cemiplimab, history of non-infectious pneumonitis within the last 5 years, history of documented allergic reactions or acute hypersensitivity reaction attributed to mAb treatment, breast feeding, positive, serum pregnancy test and prior treatment with idelalisib. Common toxicity criteria (CTCAE), version 5.0, were applied to grade the side-effects. All patients signed a written informed consent and the study was approved by local ethics committees.

2.2. Treatment

Cemiplimab was administered at the dose of 350 mg flat dose in a three weeks schedule. No dose reduction was allowed. Cemiplimab was continued as long as it was clinically appropriate, based on tumour assessment (until disease progression or inadequate therapeutic effect and in presence of unacceptable side-effects) and judgement of the treating physician. Disease evaluation was done as per clinical practice every 12 to 14 weeks with thorax and abdomen computed tomography (CT) scans. Efficacy assessments where defined using RECIST 1.1 criteria.

2.3. Statistical analysis

The primary objective of the study was to assess the feasibility and the replicability of the initial results in a real world setting of cemiplimab nominal use. The primary endpoint of our analysis was PFS. Secondary endpoints included overall response rate (ORR), OS, duration of response (DOR) and safety data. Results are presented as median and inter-quantile range [IQR] for continuous variables and number and percentage for categorical ones.

PFS and OS were estimated using the Kaplan–Meier method and compared with the log-rank test. PFS and survival time were reported as median survival times with their respective 95% confidence interval (95%CI). ORR was estimated as a percentage.Statistical significance was set at 0.05 probability level for all the tests. All the statistical analyses were performed using the statistical software R version 4.3.0.

3. Results

3.1. Patients characteristics and response to therapy

From March 2022 to December 2023, 135 patients were enrolled in the nominal use program at 12 MITO Centers and 128 started treatment with cemiplimab. Figure 1.

*at the data cut-off (December 2023).

Demographic and clinical baseline characteristics are summarized in Table 1.

The total period for data collection was 21 months, and this time frame spans from the 'day of the first patient treated' to the 'day of the last patient collection data'.

The majority of patients had squamous cell carcinoma (SSC) (77.3%, 90/128), HPV-related in 39.8% (51/128) of cases. The median age at the start of therapy with cemiplimab was 53.1 years (range 44.8–59.7), ECOG PS was 0 in 48.4% (62/128) of patients and 56.2% (75/128) patients were treated with previous bevacizumab. Best response to platinum before cemiplimab was as follow: CR 21.1% (27/128), PR

37.5% (48/128), SD 18.0% (23/128), PD 23.4% (30/128).

Best response was CR or no evidence of disease (NED, for patient who undergone complete surgery before cemiplimab) in 11 patients (8.6%), PR in 27 patients (21.1%), SD in 19 patients (14.8%) and PD in 57 patients (44.5%); response was not evaluable in 14 patients (10.9%).

Only one patient had surgery at metastatic, recurrent, or persistent setting and was NED as the best response to cemiplimab. Median DOR was 11.6 months (range 7.8–15.4).

Median PFS was 4.0 months (range 3.0–6.0). Median OS was 12.0 months (12.0- NR months). For the patients were PDL1 expression was known (25,8%), no difference according to PDL1 expression (<1% vs > 1% vs unknown) were identified for PFS neither for OS ($p = 0.23$ and $p = 0.79$, respectively). Figure 2.

A: progression free survival (PFS), B: PFS according to PD-L1 status (PD-L1 < 1: green line, PD-L1 ≥ 1: red line, unknown PD-L1 status: blue line), C: overall survival (OS), D: OS according to PD-L1 status (PD-L1 < 1: green line, PD-L1 ≥ 1: red line, unknown PD-L1 status: blue line).

In patients with ECOG PS 2 at the start of cemiplimab, PFS was 4 months (range 3–6) and OS was 12 months (range 11-NR). Figure 1S

More than half patients (56.2%) were treated with previous bevacizumab, but no difference in OS and PFS were detected in our real-life series between patients treated previous with bevacizumab or not ($p = 0.64$ and $p = 0.9$). (Figure 3).

A: progression free survival (PFS) according to previous exposure to bevacizumab (red line) and not (red line), B: overall survival (OS) according to previous exposure to bevacizumab (red line) and not (red line).

Also no differences in terms of PFS and OS were detected between histotypes (squamous vs adenocarcinoma, $p = 0.41$ and $p = 0.14$ respectively).

At the univariate and multivariate analyses, PDL1 status, previous use of bevacizumab, presence of comorbidities and previous surgery at diagnosiswere not statistically significant for OS, but previous radiotherapy is statistically significant both for PFS ($p = 0.035$) and OS ($p = 0.028$). (Table 1S).

Patients with clinical characteristics that could have been eligible for the enrollment in the EMPOWER-CERVICAL 1 trial were 128 (100%). In our real word setting, CR or NED (for patient who underwent complete surgery before starting cemiplimab) was 8.6%, PR was 21.1%, SD was 14.8% and PD was 44.5% (Table 2).

3.2. Toxicities

All patients were evaluable for toxicity and presented at least one adverse event (AE). The most frequent adverse events (AEs) of any grade were: anemia (39.1%), asthenia (26.6%) and fatigue (25.8%). Considering grade 3–4 (G3-G4) AEs the most frequent were: fatigue (17.2%), asthenia (10.9%) and decreased appetite (10.2%). No grade 5 toxicity has been reported.

A total of 18.0% of immune related adverse events (irAEs) were accounted. The most frequent was dysthyroidism: hypothyroidism 3.1% and hyperthyroidism 2.3%. No hepatitis occurred. (Table 3).

At the univariate and multivariate analyses the irAEs are statistically significant for PFS ($p = 0.027$ and $p = 0.035$) and OS ($p = 0.04$ and $p = 0.03$). (Table 1S).

4. Discussion

Nominal use of cemiplimab in the setting of advanced CC in patient treated with platinum based chemotherapy was opened in Italy following the positive results of the EMPOWER-CERVICAL-1 trial showing OS and PFS advantage for patients treated with the drug compared to investigator's choice of single-agent chemotherapy (HR 0.69 95% CI 0.56–0.84 for OS and HR 0.75 95% CI 0.63–0.89 for PFS) regardless to PD-L1 status [10].

All patients in our study were treated in centers with high expertise

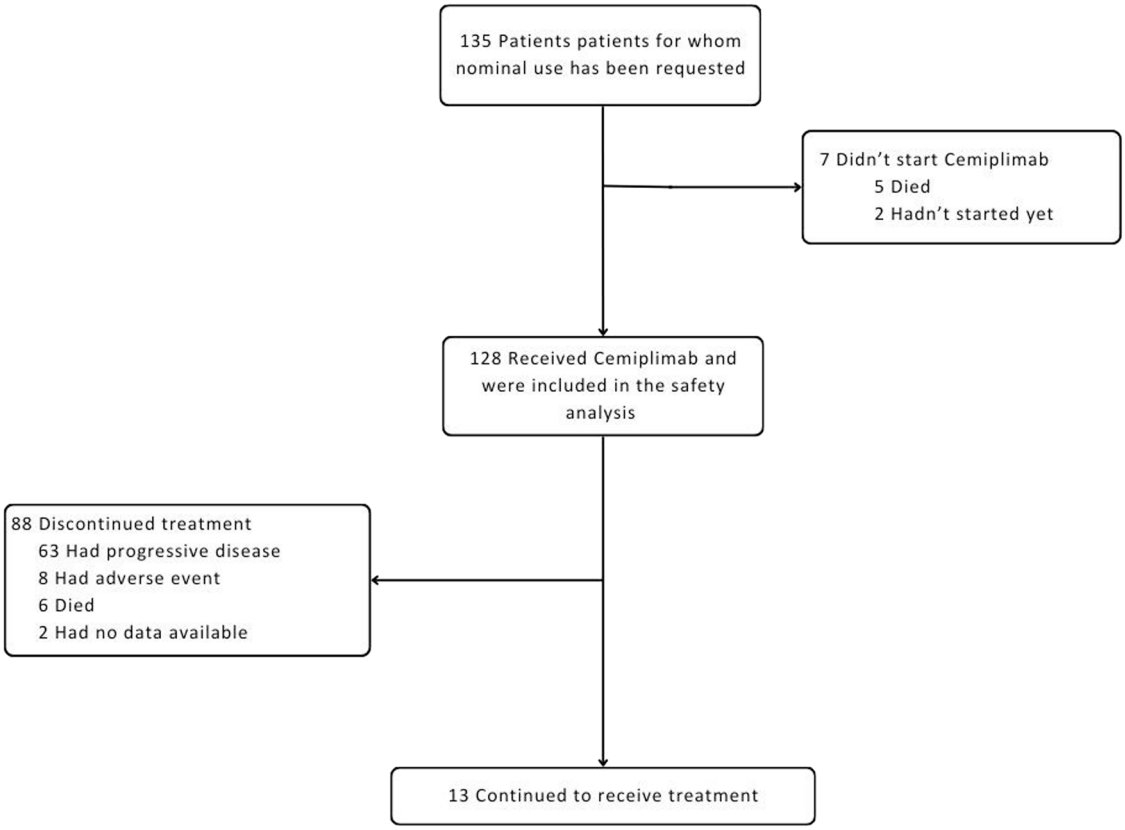

Fig. 1. Flow chart of the study.

Table 1
Demographic and Disease Characteristics of the Patients at the Baseline.

CharacteristicN= 128	Number of patients (percent)
Age at the diagnosis	
Median [range] – yr	49.6 [42.3, 57.3]
Age at the beginning of treatment	
Median [range] – yr	53.1 [44.8, 59.7]
Histologic type	
Squamous cell carcinoma	90 (77.3%)
Adenocarcinoma	24 (18.8%)
Adeno-squamous carcinoma	7 (5.5%)
Other	7 (5.5%)
HPV	
Yes	51 (39.8%)
No	19 (14.8%)
Not reported	58 (45.3%)
ECOG performance-status score before start of cemiplimab	
0	62 (48.4%)
1	42 (32.8%)
2	24 (18.8%)
FIGO stage at diagnosis	
IA1	2 (1.6%)
IA2	4 (3.1%)
IB1	5 (3.9%)
IB2	3 (2.3%)
IB3	1 (0.8%)
IIA1	7 (5.5%)
IIA2	2 (1.6%)
IIB	16 (12.5%)
IIIA	2 (1.6%)
IIIB	15 (11.7%)
IIIC1	24 (18.8%)
IIIC2	6 (4.7%)
IVA	13 (10.2%)
IVB	27 (21.1%)
Not reported	1 (0.8%)
PDL1 value	
$>1\%$	26 (20.3%)
$<1\%$	7 (5.5%)
Not reported	95 (74.2%)
Surgery at the diagnosis	
Yes	53 (41.4%)
No	75 (58.6%)
Chemotherapy at the diagnosis	
Yes	96 (75.0%)
No	32 (25.0%)
Radiotherapy at the diagnosis	
Yes	84 (65.6%)
Concomitant with chemotherapy	59 (70.2%)
Adjuvant radiotherapy	18 (21.4%)
Palliative radiotherapy	6 (7.1%)
Not specified	1 (1.2%)
No	43 (33.6%)
Not reported	1 (0.8%)
Previous number of surgeries	
0	64 (50.0%)
1	45 (35.2%)
2	12 (9.4%)
3	6 (4.7%)
>3	1 (0.8%)
Previous lines of therapies	
1	72 (56.2%)
2	37 (28.9%)
3	13 (10.2%)
>3	6 (4.8%)
Other cases of cervical tumor in the family	
Yes	7 (5.5%)
No	121 (94.5%)
Comorbidity	
Yes	54 (42.2%)
No	74 (57.8%)
Diabetes	10 (7.8%)
Hypertension	30 (23.4%)
Heart disease	8 (6.2%)
Immunologic disease	7 (5.5%)
Others	29 (22.7%)
Previous Bevacizumab use	
Yes	75 (56.2%)
No	56 (43.8%)
Presence of measurable disease	
Yes	124 (96.9%)
No	2 (1.6%)
Not reported	2 (1.6%)
Best response to platinum before Cemiplimab	
CR	27 (21.1%)
PR	48 (37.5%)
SD	23 (18.0%)
PD	30 (23.4%)

yr= year; HPV= human papilloma virus; FIGO= International Federation of Gynecology and Obstetrics;; PDL1 = Programmed Death Ligand 1, CR= complete response, PR= partial response; SD= stable disease, PD= progressive disease.

in the management of immunotherapy in gynecologic malignancies. It was already known for different rare tumors, how the experience of the treating sites could improve patients' outcome.

This retrospective cohort, multicenter study confirms the feasibility and the replicability of the initial results of cemiplimab nominal use in advanced CC, in a real-world setting in Italy.

PFS and OS in our real-life study are consistent with those in the phase III trial, even if our population was more compromised for clinical characteristics from patients enrolled in the EMPOWER-CERVICAL-1 trial, in particular 18.8% of patients had ECOG PS 2 in comparison to 0% (ECOG PS 2 was an exclusion criteria in the EMPOWER-CERVICAL-1 trial); 43.9% of patients have already received $\geq$ two systemic treatment versus 40.8% in the EMPOWER-CERVICAL-1 trial and 14.9% of patients underwent two or more surgeries before starting cemiplimab. Moreover, although our patients were treated within a cooperative group with similar clinical internal guidelines, we cannot rule out that PFS and d OS might be at least partially influenced by frequency of local restaging (mostly done however every 12–14 weeks). Of note, the EMPOWER-CERVICAL-1 trial required measurable disease and excluded patients who had prior surgeries like pelvic exenteration. Also data of PFS and OS according to PD-L1 status were similar to those of EMPOWER-CERVICAL-1 trial, with no differences between patients with tumour expressing PD-L1 or not.

PFS and OS in patients with ECOG PS 2 at the start of cemiplimab were similar to those patients with ECOG 0 or 1, confirming the efficacy of cemiplimab also in frail patients.

Consistently with the EMPOWER-CERVICAL-1 trial, in our real life study, prior exposure to bevacizumab does not influence activity.

Side-effects involved all evaluable patients. Although cross comparisons between studies are not methodologically correct, as expected, in our series, the rate of AEs of grade ≥ 3 seems higher compared to that reported in EMPOWER-CERVICAL-1 trial.

Anemia (any grade) was the most commonly reported AE both in our real life study and in the EMPOWER-CERVICAL-1 trial.

Interestingly, anemia was the most common grade ≥ 3 AE (12%) in the EMPOWER-CERVICAL-1 trial phase III trial while in our real-life study, fatigue was the most common AE (17.2%). From experience in the EMPOWER-CERVICAL-1 trial fatigue is one of the most distressing AEs to control and cannot be managed with effective treatments, except for psychoeducational approaches. Thyroid disfunctions may contribute to fatigue in this specific population.

At the univariate and multivariate analyses the irAEs are statistically significant for PFS and OS. This is a controversial question in literature. Some analyses, in the setting of metastatic melanoma, suggest that development of irAEs is associated with increased response to checkpoint inhibitors and improved outcomes [22]. Other studies have not

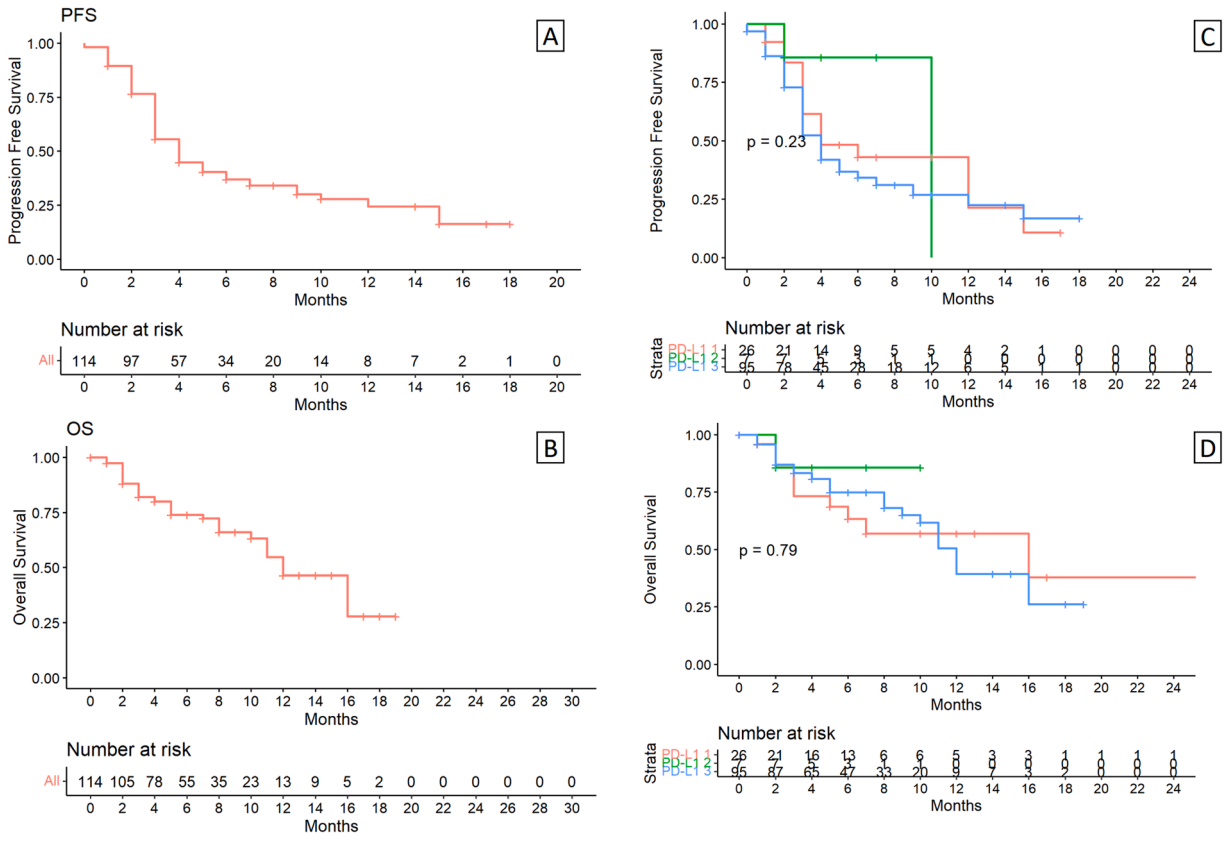

Fig. 2. Progression free survival and overall survival.

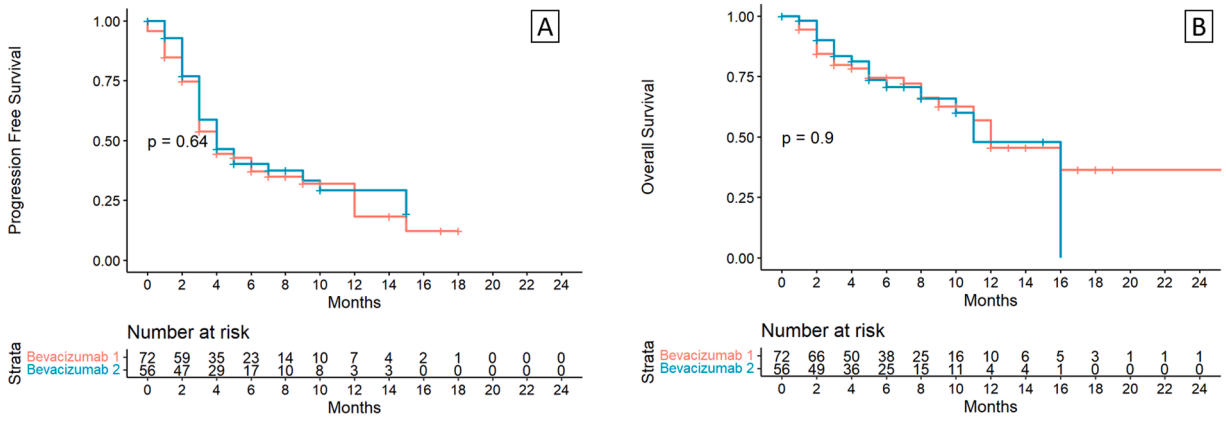

Fig. 3. Progression free survival and overall survival according to previous bevacizumab or not.

observed this effect [23]. We do not know whether some patients in our series were treated with steroids or not, but their role in tumor response is at least controversial. In some studies, the use of corticosteroids to treat irAEs seemed to improve the efficacy of the immune checkpoint inhibitors. For example, in a cohort study of metastatic melanoma advanced melanoma treated with first-line ipilimumab and nivolumab, second-line immunosuppression for irAEs was associated with impaired PFS, OS, and melanoma-specific survival (MSS)[24]. There is growing evidence that the occurrence of irAEs may predict the efficacy of immune checkpoint inhibitors. The question of whether this association applies to all irAEs or just those in specific organs or systems remains open. Thyroid irAE is one of the most frequently reported irAEs is linked to anti-tumor effects of immune checkpoint inhibitors and thus can serve as a surrogate marker for clinical response [25].

Rates of irAEs in gynecologic cancers are consistent with rates in other tumor types [26]. Clinical trials of checkpoint inhibitors in gynecologic cancers have shown a similar incidence (5–17%) and pattern of irAEs compared with other tumor types [5,26]. At the univariate and multivariate analyses previous RT at the diagnosis improves PFS ($p = 0.035$) and OS ($p = 0.028$). In literature, previous use of RT seem to be a resistance factor for chemotherapy [27,28]. Cervical cancer recurrence is typically associated with the tumor's innate radiation resistance, which includes cell proliferation, apoptosis, DNA repair, the tumor microenvironment, tumor metabolism, and stem cells. The mechanism of RT resistance for chemotherapy in CC has been widely explored over the last few decades, however due to its complexity, is still not entirely understood [27]. Conversely, RT can have a synergistic effect with immunotherapy by inducing the immunogenic death of tumor

Table 2
Indirect comparison of cemiplimab nominal use in Italy (MITO 44) with the EMPOWER-CERVICAL 1 trial.

	MITO 44 Italy (n = 128)	EMPOWER-CERVICAL 1 trial (n = 304)
CR or NED (n, %)	11 (8.6%)	10 (3.3%)
PR (n, %)	27 (21.1%)	40 (13.2%)
SD (n, %)	19 (14.8%)	125 (41.1%)
PD (n, %)	57 (44.5%)	105 (34.5%)
Not evaluable (n, %)	14 (10.9%)	24 (7.9%)
PFS	4.0 (range 3.0-6.0) months	2.8 (2.6-3.9) months
OS	12.0 (range 12.0, NR) months	12.0 (10.3-13.5) months

CR= complete response, NED= no evidence of disease, PR= partial response, SD=stable disease, PD= progressive disease, PFS= progression-free survival, OS= overall survival, CI, confidence interval

Table 3
Adverse events.

	Real-life Italy		EMPOWER-CERVICAL 1 trial	
Adverse event	Any gradeN (%)	Grade 3 or 4 N (%)	Any gradeN (%)	Grade 3,4,5 N (%)
Anemia	50 (39.1%)	11 (8.6%)	75 (25%)	36 (12%)
Nausea	18 (14.1%)	7 (5.5%)	55 (18%)	1 (0.3%)
Vomiting	12 (9.4%)	5 (3.9%)	48 (16%)	2 (0.7%)
Fever	16 (12.5%)	6 (4.7%)	35 (11.7%)	1 (0.3%)
Constipation	19 (14.8%)	5 (3.9%)	45 (15.0%)	0
Decreased appetite	24 (18.8%)	13 (10.2%)	45 (15.0%)	1 (0.3%)
Fatigue	33 (25.8%)	22 (17.2%)	50 (16.7%)	4(1.3%)
Neutropenia	14 (10.9%)	3 (2.3%)	6 (2.0%)	3 (1.0%)
Asthenia	34 (26.6%)	14 (10.9%)	33 (11%)	7 (2.3%)
Diarrhea	7 (5.5%)	3 (2.3%)	32 (10.7%)	3 (1.0%)
Urinary tract infections	14 (10.9%)	6 (4.7%)	35 (11.7%)	15 (5.0%)
Abdominal pain	24 (18.8%)	12 (9.4%)	29 (9.7%)	3 (1.0%)
Arthralgia	20 (15.9%)	8 (6.2%)	31 (10.3%)	1 (0.3%
Back pain	20 (15.6%)	4 (3.1%)	33 (11.0%)	4 (1.3%)
Immune related	23 (18.0%)		47 (15.7%)	
Hypothyroidism	4 (3.1%)		16 (6.0%)	
Hyperthyroidism	3 (2.3%)		9 (3.0%)	
Hepatitis	0		7 (2.3%)	
Pneumonitis	1 (0.8%)		4 (1.3%)	
Rash	1 (0.8%)		3 (1.0%)	
Other	15 (11.7%)			

N = number

cells, normalizing tumor vessels, regulating tumor cell phenotype and promoting immune cell infiltration [29].

In conclusion, our real life had some limitations due to the retrospective nature and a limited sample size of patients. Even if efficacy assessments where defined using RECIST 1.1 criteria, the different timing of performing evaluations (per clinical practice every 12 to 14 weeks in our real life versus at day 42 in cycles 1 to 4, 6, 8, 10, 12, 14, and 16 in the phase III trial) impacted comparisons with EMPOWER-CERVICAL-1.

5. Conclusions

This retrospective cohort, multicenter study confirms the feasibility and the replicability of cemiplimab in advanced CC, in a real-world setting in Italy. Efficacy and safety favorably compared to experimental data from EMPOWER-CERVICAL-1 trial.

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CRediT authorship contribution statement

Eleonora Geninatti: Data curation, Writing – review & editing. **Monica Rizzetto:** Data curation, Writing – review & editing. **Sandro Pignata:** Data curation, Supervision, Writing – review & editing. **Serafina Mammoliti:** Data curation, Writing – review & editing. **Valentina Tuninetti:** Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Carmen Azzolina:** Writing – review & editing, Data curation. **Gabriella Ferrandina:** Data curation, Writing – review & editing. **Giuseppa Scandurra:** Data curation, Writing – review & editing. **Mara Mantiero:** Data curation, Writing – review & editing. **Maria Cristina Petrella:** Data curation, Writing – review & editing. **Chiara Rognone:** Data curation, Writing – review & editing. **Monika Ducceschi:** Data curation, Writing – review & editing. **Vittoria Carbone:** Data curation, Writing – review & editing. **Giacinto Turitto:** Data curation, Writing – review & editing. **Lucia Borsotti:** Data curation, Writing – review & editing. **Andrea Ricotti:** Formal analysis. **Marco Bellero:** Data curation, Writing – review & editing. **Carmela Pisano:** Data curation, Writing – review & editing. **Giorgio Valabrega:** Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Grazia Artioli:** Data curation, Writing – review & editing. **Elisa Virano:** Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Raffaella Cioffi:** Data curation, Writing – review & editing. **Vanda Salutari:** Data curation, Writing – review & editing. **Valeria Forestieri:** Data curation, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Valentina Tuninetti**: honoraria from MSD Oncology, GSK and EISAI, **Elisa Virano**: None declared, **Vanda Salutari**: Honoraria: AstraZeneca, MSD Oncology, GSK, PhamaMar, Novocure, Consulting: AstraZeneca, Novocure, Travel, Accomodations, Expenses: GSK, PharmaMar, **Andrea Ricotti**: None declared, **Carmela Pisano**: Advisory board: AstraZeneca, MSD Oncology, GSK, **Monica Ducceschi**: None declared, **Giacinto Turitto**: None declared, **Giuseppa Scandurra**: None declared, **Maria Cristina Petrella**: Honoraria from Astrazeneca, MSD, GSK, **Valeria Forestieri**: None declared, **Monica Rizzetto**: None declared, **Serafina Mammoliti**: None declared, **Grazia Artioli**: honoraria from AstraZeneca, MSD Oncology, GSK, **Raffaella Cioffi**: None declared, **Lucia Borsotti**: None declared, **Marco Bellero**: None declared, **Chiara Rognone**: None declared, **Vittoria Carbone**: None declared, **Gabriella Ferrandina**: None declared, **Mara Mantiero**: None declared, **Carmen Azzolina**: None declared, **Eleonora Geninatti**: None declared, **Sandro Pignata**: Research Funding: AstraZeneca, MSD Oncology, Roche, GSK, Pfizer, Honoraria: AstraZeneca, MSD Oncology, Roche, GSK, Novartis, EISAI, PharmaMar, **Giorgio Valabrega**: Consulting fees from GSK; honoraria from AstraZeneca, GSK, and MSD; travel support from AstraZeneca and PharmaMar; participation in advisory boards for AstraZeneca, EISAI, GSK, and MSD.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114039.

References

[1] Liontos M, Kyriazoglou A, Dimitriadis I, Dimopoulos MA, Bamias A. Systemic therapy in cervical cancer: 30 years in review. Crit Rev Oncol Hematol 2019;137:9–17.

[2] Mori S, Gotoh O, Kiyotani K, Low SK. Genomic alterations in gynecological malignancies: histotype-associated driver mutations, molecular subtyping schemes, and tumorigenic mechanisms. J Hum Genet 2021;66(9):853–68.
[3] Gennigens C, Jerusalem G, Lapaille L, De Cuypere M, Streel S, Kridelka F, et al. Recurrent or primary metastatic cervical cancer: current and future treatments. ESMO Open 2022;7(5):100579.
[4] Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385(20):1856–67.
[5] Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2019;37(17):1470–8.
[6] Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, et al. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. J Clin Oncol 2023;41(36):5505–11.
[7] Monk BJ, Tewari KS, Dubot C, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2023;24(4):392–402.
[8] Tewari KS, Colombo N, Monk BJ, Dubot C, Cáceres MV, Hasegawa K, et al. Pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer: subgroup analyses from the KEYNOTE-826 randomized clinical trial. JAMA Oncol 2023.
[9] Oaknin A, Gladieff L, Martínez-García J, Villacampa G, Takekuma M, De Giorgi U, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet 2024;403(10421):31–43.
[10] Oaknin A, Monk BJ, Vergote I, Cristina de Melo A, Kim YM, Lisyanskaya AS, et al. EMPOWER CERVICAL-1: effects of cemiplimab versus chemotherapy on patient-reported quality of life, functioning and symptoms among women with recurrent cervical cancer. Eur J Cancer 2022;174:299–309.
[11] Tewari KS, Monk BJ, Vergote I, Miller A, de Melo AC, Kim HS, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386(6):544–55.
[12] Ferrarotto R, Nagarajan P, Maronge JM, Johnson JM, Rosenthal DI, Myers JN, et al. Outcomes of treatment with neoadjuvant cemiplimab for patients with advanced, resectable cutaneous squamous cell carcinoma of the head and neck: secondary analysis of a phase 2 clinical trial. JAMA Otolaryngol Head Neck Surg 2023;149(9):847–9.
[13] Gross ND, Miller DM, Khushalani NI, Divi V, Ruiz ES, Lipson EJ, et al. Neoadjuvant cemiplimab and surgery for stage II-IV cutaneous squamous-cell carcinoma: follow-up and survival outcomes of a single-arm, multicentre, phase 2 study. Lancet Oncol 2023;24(11):1196–205.
[14] Gross ND, Miller DM, Khushalani NI, Divi V, Ruiz ES, Lipson EJ, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. N Engl J Med 2022;387(17):1557–68.
[15] Stratigos AJ, Sekulic A, Peris K, Bechter O, Prey S, Lewis KD, et al. Phase 2 open-label, multicenter, single-arm study of cemiplimab in patients with locally advanced basal cell carcinoma after hedgehog inhibitor therapy: extended follow-up. J Am Acad Dermatol 2024;90(2):414–8.
[16] Lewis KD, Peris K, Sekulic A, Stratigos AJ, Dunn L, Eroglu Z, et al. Final analysis of phase II results with cemiplimab in metastatic basal cell carcinoma after hedgehog pathway inhibitors. Ann Oncol 2023.
[17] Stratigos AJ, Sekulic A, Peris K, Bechter O, Prey S, Kaatz M, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol 2021;22(6):848–57.
[18] Dehghani T, Shahrjerdi A, Kahrizi MS, Soleimani E, Ravandeh S, Merza MS, et al. Targeting programmed cell death protein 1 (PD-1) for treatment of non-small-cell lung carcinoma (NSCLC); the recent advances. Pathol Res Pr 2023;246:154470.
[19] Gümüş M, Chen CI, Ivanescu C, Kilickap S, Bondarenko I, Özgüroğlu M, et al. Patient-reported outcomes with cemiplimab monotherapy for first-line treatment of advanced non-small cell lung cancer with PD-L1 of ≥50%: the EMPOWER-Lung 1 study. Cancer 2023;129(1):118–29.
[20] Özgüroğlu M, Kilickap S, Sezer A, Gümüş M, Bondarenko I, Gogishvili M, et al. First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2023;24(9):989–1001.
[21] Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 2021;397(10274):592–604.
[22] Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35(7):785–92.
[23] Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 2015;33(28):3193–8.
[24] van Not OJ, Verheijden RJ, van den Eertwegh AJM, Haanen JBG, Aarts MJB, van den Berkmortel FWJ, et al. Association of immune-related adverse event management with survival in patients with advanced melanoma. JAMA Oncol 2022;8(12):1794–801.
[25] Cheung YM, Wang W, McGregor B, Hamnvik OR. Associations between immune-related thyroid dysfunction and efficacy of immune checkpoint inhibitors: a systematic review and meta-analysis. Cancer Immunol Immunother 2022;71(8):1795–812.
[26] Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. J Clin Oncol 2017;35(36):4035–41.
[27] Zhang H, Wang X, Ma Y, Zhang Q, Liu R, Luo H, et al. Review of possible mechanisms of radiotherapy resistance in cervical cancer. Front Oncol 2023;13:1164985.
[28] Moreno-Acosta P, Vallard A, Carrillo S, Gamboa O, Romero-Rojas A, Molano M, et al. Biomarkers of resistance to radiation therapy: a prospective study in cervical carcinoma. Radiat Oncol 2017;12(1):120.
[29] Yang X, Ren H, Fu J. Combinations of radiotherapy with immunotherapy in cervical cancer. J Cancer 2022;13(5):1480–9.