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Lenvatinib plus pembrolizumab compared to carboplatin plus paclitaxel for carboplatin and paclitaxel pretreated, recurrent, or advanced endometrial cancer

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Abstract

Background Lenvatinib plus pembrolizumab has demonstrated improved survival compared with doxorubicin or paclitaxel monotherapy in patients with advanced or recurrent endometrial cancers (ECs). However, response rates to monotherapy are poor in recurrent settings. Herein, we performed a retrospective analysis using real-world data to compare the outcomes of lenvatinib plus pembrolizumab, carboplatin plus paclitaxel (PT), and doxorubicin for patients with PT-pretreated, advanced, or recurrent ECs.

Methods We performed a multi-institutional retrospective analysis using de-identified electronic health record database (TriNetX) to compare lenvatinib plus pembrolizumab, carboplatin plus paclitaxel (PT), and doxorubicin outcomes in patients with PT-pretreated, advanced, or recurrent ECs. A 1:1 propensity score matching (PSM) was conducted. The primary outcome was the overall survival (OS) among treatment groups. The secondary outcome was the adverse event profile.

Results Between January 2012 and September 2023, we identified 397 patients with PT-treated, advanced, or recurrent ECs who received lenvatinib plus pembrolizumab, and 469 patients receiving PT at a platinum-free interval of over 6 months. Following PSM, no significant difference in median OS was observed between the lenvatinib plus pembrolizumab and re-challenge PT groups (19.1 vs. 18.5 months, $p=0.60$; hazard ratio: 1.08, 95% confidence interval 0.81–1.46). However, lenvatinib plus pembrolizumab provided better survival benefits than doxorubicin. Adverse event analysis showed more hypothyroidism, hypertension, and proteinuria with lenvatinib plus pembrolizumab, and more hematologic toxicities in both chemotherapy groups.

Conclusions Lenvatinib plus pembrolizumab was not associated with improved survival when compared with re-challenge PT in patients with a platinum-free interval of over 6 months. Re-challenge PT remains a valid option for PT-treated, recurrent, or advanced ECs, especially in patients with a substantially long platinum-free interval.

Keywords Endometrial cancer, Lenvatinib, Pembrolizumab, Carboplatin, Paclitaxel, Doxorubicin

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Background

Endometrial cancer (EC) is the most common gynecological malignancy, and its incidence is continuously increasing. Although most ECs are diagnosed early, approximately 21% of patients are diagnosed at advanced stages. The prognosis for advanced or recurrent EC is generally poor, with a reported median survival of 12–15 months among patients with measurable disease [1, 2]. Despite numerous studies on different chemotherapeutic agents and target therapies in recent years, progress in survival outcomes has been limited.

Tri-weekly carboplatin plus paclitaxel (PT) has become the first-line therapy for recurrent or advanced ECs since the publication of the Gynecologic Oncology Group (GOG) study 0209 in 2012, which reported a 45–78% response rate in chemo-naïve patients [3–5]. However, the outcomes of second-line therapies are generally poor. Single-agent doxorubicin or paclitaxel are both associated with poor efficacy as second-line treatment, with the overall survival (OS) being 8.2 and 10.3 months, respectively [6, 7]. Despite the introduction of bevacizumab, a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, the OS and progression-free survival (PFS) were still not significantly improved [8]. Different combinations of chemotherapeutic agents and target therapy have shown some improvements in the response rates; however, the incidence of severe adverse events has also escalated [9–12].

Lenvatinib is an oral multi-kinase inhibitor that targets VEGF receptors 1–3, fibroblast growth factors receptors 1–4, platelet-derived growth factors α receptor, RET, and KIT [13]. When used alone as second-line treatment for recurrent or metastatic ECs, lenvatinib's objective response rate was 14%, similar to bevacizumab [13]. Pembrolizumab, a programmed cell death inhibitor, has demonstrated promising efficacy among patients with a deficient mismatch repair (dMMR) or high micro-satellite instability (MSI-H) advanced EC [14]. In the KEYNOTE-146/Study-111, the combination of lenvatinib and pembrolizumab showed a 63.6% objective response rate among 11 patients with MSI-H metastatic ECs [15]. Subsequently, the KEYNOTE-775 study compared lenvatinib plus pembrolizumab to single-agent doxorubicin or weekly paclitaxel in a cohort with platinum-treated, 84% pMMR, advanced ECs, which revealed a longer OS [18.3 vs. 11.4 months, 95% confidence interval (CI) 0.51–0.75] over the chemotherapy arm [2]. Although the adverse events were generally manageable, dose reductions and interruptions were common with lenvatinib plus pembrolizumab [2]. Moreover, as second-line monotherapy with either doxorubicin or paclitaxel is associated with poor response rates, the superiority of lenvatinib plus pembrolizumab should be re-examined with a more potent control arm [6, 7]. Additionally, the concept of "platinum sensitivity" regarding recurrent ECs has been described in the literature [16]. Although PT re-challenge has not been universally accepted as second-line treatment, the reported response rates were generally higher when compared with that of other therapeutic options [16–18]. Herein, we performed a retrospective analysis based on real-world data in patients with PT-pretreated, advanced, or recurrent ECs treated with either pembrolizumab plus lenvatinib or re-challenge PT.

Methods

Data sources and participants

We conducted a retrospective, multi-institutional study using de-identified data from electronic health records provided by TriNetX Research Network (Cambridge, MA, USA). The TriNetX Research Network provides access to the electronic medical records of approximately 111 million patients across 80 healthcare organizations (HCOs), with the majority of the HCOs located in the United States and Europe. The TriNetX platform complies with the Health Insurance Portability and Accountability Act and has received a waiver from the Western Institutional Review Board, as all data are displayed in aggregate form and the information is de-identified [19, 20].

The data used in this study were collected on September 29, 2023, from the TriNetX Research Network. The study participants were identified using the International Classification of Disease (ICD) codes from January 2012 to September 2023. Only patients aged 18–90 years were included in this study. Advanced EC was defined as EC along with the ICD codes for metastasis to the lymphatic systems and distant metastasis, while histological findings including carcinosarcoma and sarcoma were excluded. Chemotherapy, immunotherapy, and target therapy regimens were identified using the RxNorm and Healthcare Common Procedure Coding System (HCPCS) codes. Surgical procedures and history of irradiation were identified using Current Procedural Terminology (CPT) codes. All codes used in this study were listed in Additional file 1: Table S1.

All patients must have completed first-line chemotherapy, which consists of at least 6 cycles of PT, prior to the start of second-line therapies. The index event for the lenvatinib plus pembrolizumab group was identified as the initiation date of lenvatinib plus pembrolizumab, and for the re-challenge PT group, it was defined as the resumption date of PT or carboplatin plus docetaxel. Patients who received lenvatinib plus pembrolizumab or re-challenge PT within the 6 months following the completion of their first-line PT were excluded (Additional file 1: Figure S1). As for the doxorubicin group, the

index event was defined as the date when doxorubicin was prescribed following the completion of first-line PT. When compared with doxorubicin, the lenvatinib plus pembrolizumab group was not subjected to the exclusion criteria of a 6-month treatment-free interval. Subgroup analyses were further conducted among those who received lenvatinib plus pembrolizumab or re-challenge PT with platinum-free intervals of 6 to 12 months and over 12 months after completing first-line PT. All designated treatments were labeled with the TriNetX-curated term "chemotherapy line 2" or "line 3", while those labeled with "chemotherapy line 1" were excluded to avoid misclassification as extended first-line treatments. Patients who received pembrolizumab or lenvatinib before and after the initiation of second-line treatment were excluded from both chemotherapy groups. Those with an Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2 points before second-line treatment were precluded from analysis. Patients who underwent a major operation within the 3 weeks before the initiation of lenvatinib plus pembrolizumab, re-challenge PT, or doxorubicin were also excluded.

Outcomes

The primary outcome of this study was the median OS for the lenvatinib plus pembrolizumab and re-challenge PT groups. Additional survival analysis included a comparison between lenvatinib plus pembrolizumab and doxorubicin, and subgroup analyses comparing lenvatinib plus pembrolizumab to re-challenge PT among patients with platinum-free intervals between 6 to 12 months and ≥ 12 months from their last adjuvant PT. The primary end-point was estimated from the date of the index event in each treatment group to the date of death. Patients were censored after the last observation in their records. We also performed a secondary analysis assessing adverse events among the three study groups. Hematological, hepatic, thyroid profiles and systemic adverse events were assessed from the date of the index event. Any adverse events that occurred within 6 months before the designated treatment were excluded from analyses. Treatment toxicities were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [21].

Statistical analysis

All statistical analyses were performed using the SAS version 9.4 (SAS Institute). The baseline comorbidities and disease burden were assessed using the Charlson Comorbidity Index score (CCI score), which included a list of 19 conditions with each assigned a weight from 1 to 6 [22, 23]. To reduce potential confounders between treatment groups, we conducted 1:1 propensity score matching (PSM) with matched covariates including age, previous chemotherapy lines, history of irradiation, and CCI score [24]. Baseline characteristics between the treatment groups were compared using the Pearson chi-square test and independent sample t-test before PSM, and the McNemar test and paired t-test were used after matching. A greedy nearest-neighbor matching algorithm with a 0.1 pooled standard deviation caliper was used. Therefore, patients with distinct propensity scores were not matched in this study. Survival outcomes were compared using the stratified log-rank test to determine the difference in OS among the treatment groups. The adjusted hazard ratios (aHRs) were generated using conditional Cox regression after PSM [25, 26]. Statistical significance was defined as a two-sided p-value of < 0.05.

Results

We identified 27,303 patients aged 18–90 years who were diagnosed with advanced or recurrent EC across 80 HCOs between January 2012 and September 2023. After applying the inclusion and exclusion criteria, we identified 397 patients who received pembrolizumab plus lenvatinib and 469 patients who received PT, all with a platinum-free interval of 6 months or more. As for the doxorubicin group, a total of 378 patients were identified. The baseline characteristics of the lenvatinib plus pembrolizumab and re-challenge PT groups were displayed in Table 1, and the details of CCI score in Additional file 1: Table S2. In the lenvatinib plus pembrolizumab group, a higher percentage of patients were African-American, received radiotherapy and two prior lines of therapy, and had pelvic lymph node metastasis before the index date; in contrast, the re-challenge PT group had higher rates of peritoneal carcinomatosis and colorectal metastasis. A comparison of baseline characteristics between the lenvatinib plus pembrolizumab and doxorubicin groups was shown in Additional file 1: Table S3 and Table S4.

After 1:1 PSM, the lenvatinib plus pembrolizumab and re-challenge PT cohorts were well-balanced and contained 334 patients each (Table 1) (Additional file 1: Figure S2). A total of 149 patients died in the pembrolizumab plus lenvatinib group, and 168 patients died in the re-challenge PT group. The median OS did not differ significantly between lenvatinib plus pembrolizumab and re-challenge PT (19.1 vs. 18.5 months, $p = 0.60$) (Fig. 1), and the aHR was 1.08 (95% CI 0.81–1.46). Subgroup analysis among patients with platinum-free intervals of 6 to 12 months resulted in 154 patients in the lenvatinib plus pembrolizumab group and 122 patients in the re-challenge PT group. Following PSM, there was no statistically significant difference in survival between both treatment groups (median OS: 19.5 vs. 17.1 months, $p = 0.53$; aHR: 0.88, 95% CI 0.62–1.24) (Fig. 2A). The

Table 1 Baseline characteristics of the lenvatinib plus pembrolizumab and re-challenge PT cohorts, before and after PSM

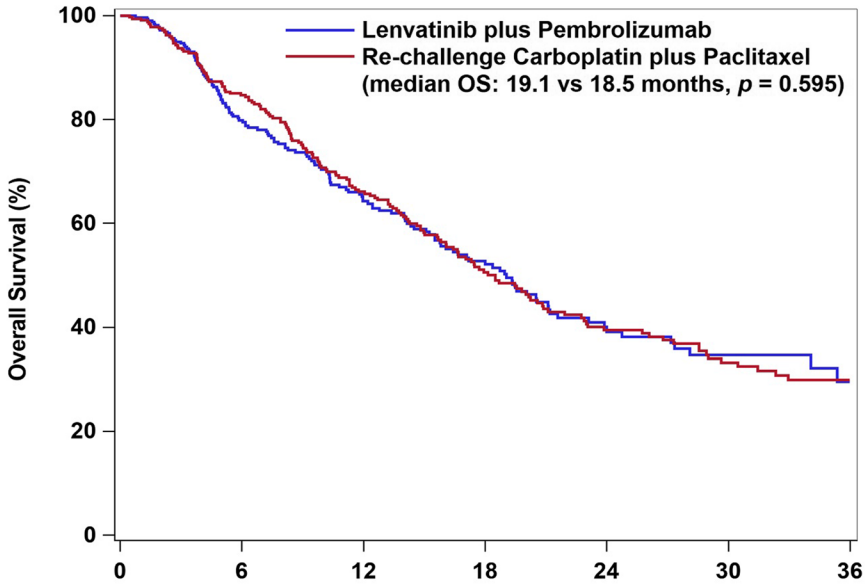
	Before match			After Matched		
	Lenvatinib + Pembrolizumab *N* = 397	**Re-challenge PT *N* = 469**	***p*-value**	**Lenvatinib + Pembrolizumab *N* = 334**	**Re-challenge PT *N* = 334**	***p*-value**
Age at index*	66.8	65.5	0.04	66.8	66.8	0.99
< 65 years	145 (37)	185 (39)	0.38	125 (37)	116 (35)	0.42
≧65 years	252 (64)	284 (61)	0.38	209 (63)	218 (65)	0.42
Race						
White	250 (63)	311 (66)	0.31	206 (62)	224 (67)	0.14
African-American	76 (19)	65 (14)	0.04	62 (19)	49 (15)	0.19
Asian	21 (5)	19 (4)	0.39	19 (6)	13 (4)	0.29
Unknown	49 (12)	64 (14)	0.57	46 (14)	45 (14)	0.90
Charlson Comorbidity Index score*	8.4	8.8	0.06	8.6	8.7	0.82
History of irradiation*	183 (46)	118 (25)	< 0.001	123 (37)	114 (34)	0.29
Prior lines of therapy received before designated treatment*						
One line	397 (100)	469 (100)	NA	334 (100)	334 (100)	NA
Two lines	206 (52)	160 (34)	< 0.001	147 (44)	147 (44)	1
Therapies received before designated treatment						
Carboplatin	397 (100)	469 (100)	NA	334 (100)	334 (100)	NA
Paclitaxel	397 (100)	469 (100)	NA	334 (100)	334 (100)	NA
Docetaxel	18 (5)	19 (4)	0.73	17 (5)	17 (5)	1
Doxorubicin	58 (15)	58 (12)	0.33	38 (11)	53 (16)	0.08
Liposomal- doxorubicin	35 (9)	38 (8)	0.71	25 (8)	35 (11)	0.17
Bevacizumab	86 (22)	84 (18)	0.17	65 (20)	69 (21)	0.69
Sites of metastasis						
Lymph node	185 (47)	182 (39)	0.02	152 (46)	139 (42)	0.30
Para-aortic LN	88 (22)	93 (20)	0.40	69 (21)	67 (20)	0.85
Pelvic LN	100 (25)	86 (18)	0.01	80 (24)	66 (20)	0.17
Lung	81 (20)	95 (20)	0.96	67 (20)	75 (23)	0.45
Liver	67 (17)	89 (19)	0.42	53 (16)	55 (17)	0.83
Peritoneum	169 (43)	280 (60)	< 0.001	154 (46)	188 (56)	0.01
Colorectal	47 (12)	81 (17)	0.03	42 (13)	54 (16)	0.20

Data are presented as No. (%). Demographic data were obtained from the TriNetX Research network. The baseline characteristics were documented one day before the index date. Variables marked with * were selected for PSM

PT Carboplatin plus paclitaxel, *PSM* Propensity score matching, *LN* Lymph nodes, *NA* Not available

survival outcome of the subgroup of platinum-free intervals over 12 months remained comparable between both groups (median OS: 19.0 vs. 19.5 months, $p = 0.50$; aHR: 1.08, 95% CI 0.81–1.46) (Fig. 2B). With respect to the survival analysis between lenvatinib plus pembrolizumab and doxorubicin after PSM (Additional file 1: Figure S3), lenvatinib plus pembrolizumab showed survival benefits over doxorubicin monotherapy (median OS: 16.7 vs. 9.1 months, $p < 0.001$; aHR: 0.44, 95% CI 0.32–0.59) (Fig. 3). Subgroup analyses based on platinum-free intervals < 12 months included 185 patients in the lenvatinib plus pembrolizumab group and 213 patients in the doxorubicin group. The result showed a consistent survival benefit with lenvatinib plus pembrolizumab (median OS: 17.2 vs. 8.4 months, $p < 0.001$; aHR: 0.54, 95% CI 0.41–0.71).

In the adverse event analyses, patients who received lenvatinib plus pembrolizumab had a higher risk of developing hypothyroidism, hypertension, grade 3 hypertension, proteinuria, diarrhea, fatigue, and arthralgia when compared with those in the re-challenge PT group. The lenvatinib plus pembrolizumab group had a lower incidence of hematological adverse events including neutropenia, grade 3 neutropenia, and grade 3 thrombocytopenia (Fig. 4). Similarly, a comparison between lenvatinib plus pembrolizumab and doxorubicin showed



Number at risk (number censored)							
Lenvatinib plus Pembrolizumab	334 (0)	220 (50)	143 (39)	85 (36)	43 (23)	25 (14)	11 (12)
Re-challenge Carboplatin plus Paclitaxel	334 (0)	253 (32)	167 (35)	100 (32)	67 (13)	45 (13)	30 (11)

Fig. 1 Three-year OS between lenvatinib plus pembrolizumab and re-challenge PT after propensity score matching. OS, overall survival

significantly higher rates of liver toxicity, hypothyroidism, hypertension, proteinuria, diarrhea, and arthralgia in the lenvatinib plus pembrolizumab group, and more hematological toxicities were observed in the doxorubicin group. A comparison of the adverse events is shown in the Additional file 1: Figure S4.

Discussion

In this study, we performed analyses based on multi-institutional real-world data and compared the outcomes of lenvatinib plus pembrolizumab, re-challenge PT, and doxorubicin as second-line treatment in patients with PT-pretreated, recurrent, or advanced ECs. After balanced PSM, our study showed no significant difference in OS between the lenvatinib plus pembrolizumab and re-challenge PT groups (19.1 vs. 18.5 months, $p=0.60$; aHR: 1.08, 95% CI 0.81–1.46). Regarding subgroup analyses, the outcomes were also comparable between both treatment groups for platinum-free intervals of 6 to 12 months and over 12 months. Nevertheless, the survival benefit was significant when comparing lenvatinib plus pembrolizumab with doxorubicin monotherapy, which was consistent with the findings of the KEYNOTE-775 study (16.7 vs. 9.1 months, $p<0{\cdot}001$; aHR: 0.44, 95% CI 0.32–0.59). As for safety analyses, a higher incidence of hypothyroidism, hypertension, proteinuria, diarrhea, fatigue, and arthralgia was observed among patients receiving lenvatinib plus pembrolizumab; in contrast, patients receiving re-challenge PT or doxorubicin were at risk for more severe hematologic toxicity. Our data are also in line with previously reported values [2, 27–30].

Pembrolizumab demonstrated a 64% objective response rate and a sustained progression-free interval among patients with advanced, dMMR or MSI-H ECs [15]. However, dMMR or MSI-H tumors only account for 16–31% of all ECs [2, 31–33]. Thus, the KEYNOTE-775 study was conducted without biomarkers pre-selection and demonstrated a 31.9% objective response rate along with an OS of 18.3 months among a cohort with 84% of patients having pMMR tumors treated with lenvatinib plus pembrolizumab [2]. Although lenvatinib plus pembrolizumab provided a survival benefit when compared with single-agent doxorubicin or paclitaxel, as demonstrated in the KEYNOTE-775 trial, the efficacy of doxorubicin or paclitaxel monotherapy had been modest in the literature [6, 7].

Most trials regarding cytotoxic therapy for advanced or recurrent ECs were conducted before 2012, when study GOG-0209 led to the standardization of triweekly PT as first-line adjuvant treatment for advanced EC [34–36]. Hence, there is a paucity of prospective studies investigating the efficacy of second-line treatment in platinum-treated patients. Historically, doxorubicin was used as the first-line chemotherapy for advanced ECs, which had a 19–25% response rate

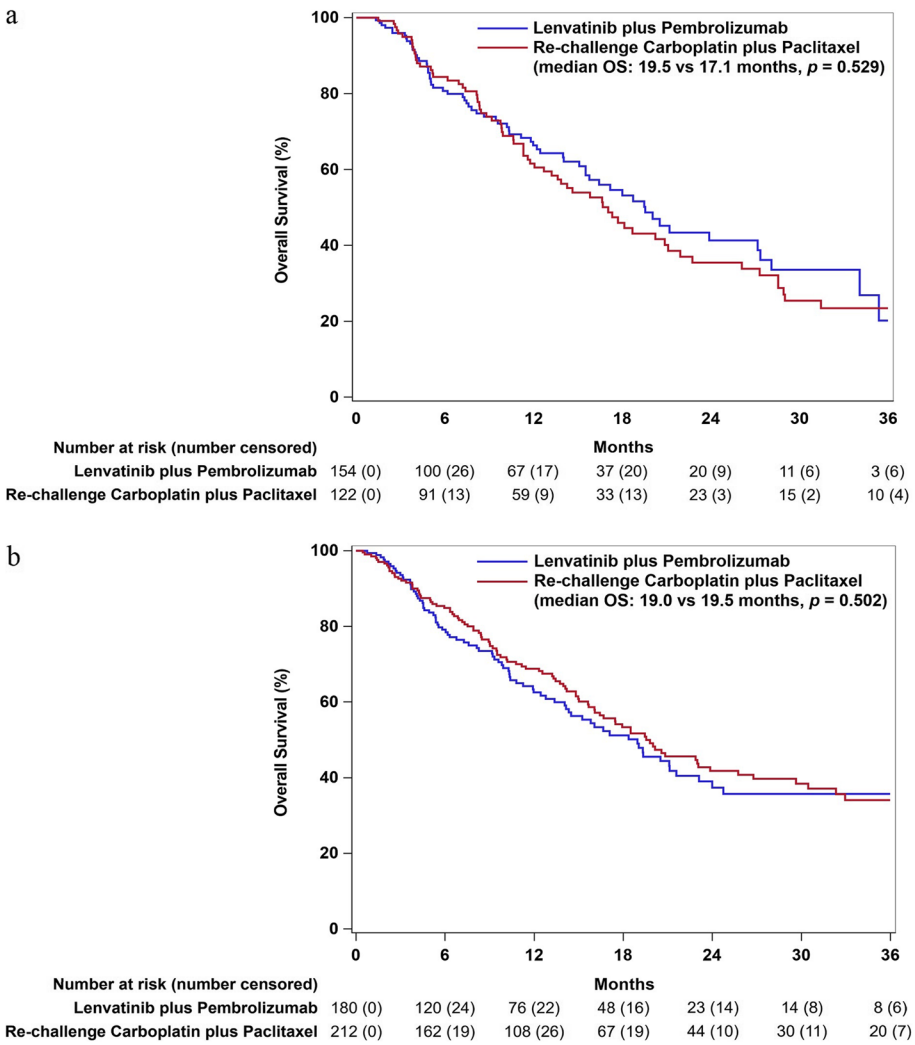
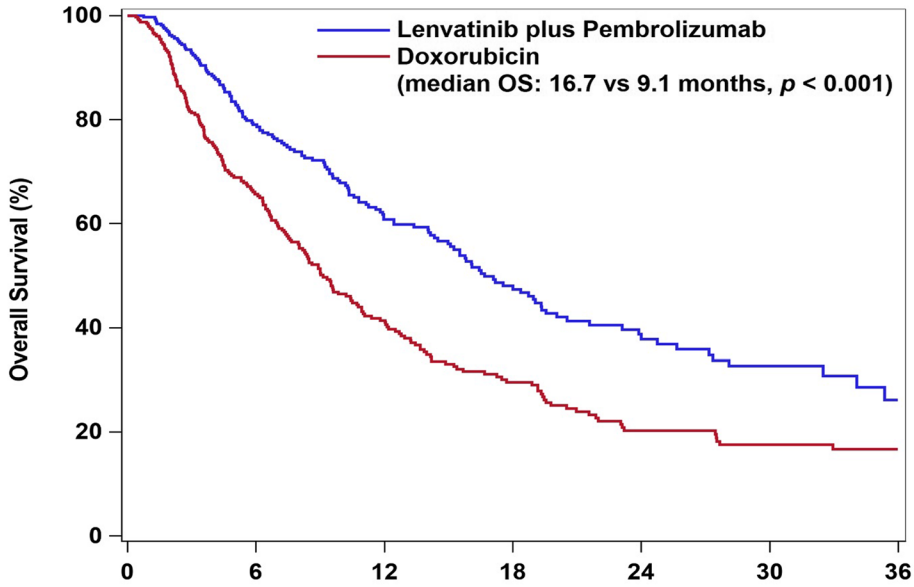


Fig. 2 Subgroup analysis of 3-year OS between lenvatinib plus pembrolizumab and re-challenge PT. **a** Lenvatinib plus pembrolizumab and re-challenge PT with a platinum-free interval of 6 to 12 months. **b** Lenvatinib plus pembrolizumab and re-challenge PT with a platinum-free interval over 12 months. PT, carboplatin plus paclitaxel. OS, overall survival

for chemo-naïve patients [17]. In practice, a preponderance of selecting doxorubicin over paclitaxel for patients with platinum-pretreated ECs was observed, also shown in the constitution of the chemotherapy arm, determined by physicians' preference in the KEYNOTE-775 study (289 patients received doxorubicin, and only 99 patients received paclitaxel) [2]. Nevertheless, doxorubicin had poor efficacy when used as second-line treatment, with a reported response rate of 9.5% and a median OS of 8.5 months [6]. One retrospective study showed no response to doxorubicin among 17 patients pretreated with PT [37]. In contrast, paclitaxel monotherapy, when used in the second-line setting, was associated with a 27.3% overall response rate and a median OS of 10.3 months [7]. However, the study was performed on paclitaxel-naïve patients. The National Comprehensive Cancer Network guidelines recommended PT as first-line chemotherapy for advanced EC, which may limit the number of paclitaxel-naïve patients who could have benefited from the 27.3% response rate in the setting of recurrent tumors [35]. Other single-agent therapies including oxaliplatin, docetaxel, ixabepilone, and bevacizumab were associated with poor response rates (approximately 5–15%) [8, 38–40]. A study utilizing data from the National Cancer Registration and Analysis Service (NCRAS) in England revealed that among 999 patients who experienced progression after first-line treatment, the most common second-line treatments received for patients with recurrent or advanced ECs were PT (28%), carboplatin



Number at risk (number censored)							
Lenvatinib plus Pembrolizumab	340 (0)	208 (67)	127 (39)	76 (28)	41 (21)	26 (10)	11 (12)
Doxorubicin	340 (0)	185 (46)	97 (26)	56 (15)	32 (8)	24 (4)	18 (5)

Fig. 3 Three-year OS between lenvatinib plus pembrolizumab and doxorubicin. OS, overall survival

	Lenvatinib plus Pembrolizumab	Re-challenge Carboplatin plus Paclitaxel		
	No. of Event / N		HR (95%CI)	*p* value
Anemia	54/84	60/79	0.69 (0.48–1.01)	0.053
Grade 3 anemia	74/276	96/264	0.81 (0.60–1.10)	0.186
Neutropenia	23/282	45/278	0.51 (0.31–0.85)	0.009
Grade 3 neutropenia	22/301	69/281	0.29 (0.18–0.46)	<0.001
Thrombocytopenia	35/312	57/305	0.67 (0.44–1.02)	0.062
Grade 3 thrombocytopenia	21/322	50/313	0.44 (0.27–0.74)	0.002
Liver toxicity	113/297	97/287	1.30 (0.99–1.70)	0.063
Hypothyroidism	125/302	32/298	5.72 (3.86–8.47)	<0.001
Hypertension	101/190	73/194	1.72 (1.27–2.33)	0.001
Grade 3 hypertension	88/246	63/242	1.60 (1.16–2.22)	0.005
Proteinuria	143/207	107/192	1.68 (1.31–2.17)	<0.001
Diarrhea	76/306	59/301	1.53 (1.09–2.15)	0.015
Fatigue	100/288	75/281	1.61 (1.19–2.18)	0.002
Nausea & vomiting	105/264	114/264	1.04 (0.80–1.35)	0.786
Arthralgia	72/302	51/306	1.70 (1.18–2.45)	0.004

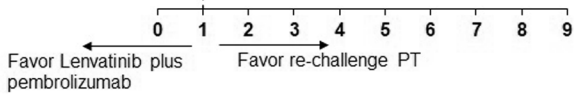


Fig. 4 Adverse events among patients receiving lenvatinib plus pembrolizumab and re-challenge PT. aHR, hazard ratio; CI, confidence interval

plus pegylated liposomal doxorubicin (14%), liposomal doxorubicin (13%), doxorubicin (4%), and paclitaxel monotherapy (12%). The median OS associated with those treatments were 14.2 months for PT, 13.9 months for carboplatin plus liposomal doxorubicin, 4.9 months for liposomal doxorubicin, and 6.6 months for paclitaxel, respectively [18].

In the current literature, the reported response rates for first-line PT were 40–62% and the OS was 13–29 months [5, 34]. Although there has been no

consensus on "platinum sensitivity" in the treatment of recurrent EC, practitioners often consider platinum re-challenge at recurrence due to the lack of available options. However, platinum re-challenge has not been investigated prospectively, and retrospective studies have reported diverse outcomes, mostly because of small sample sizes and different compositions of platinum-free intervals in each cohort. In a study of 262 patients with recurrent EC priorly treated with platinum-based regimens, the reported response rates were 25%, 38%, 61%, and 65% in patients with platinum-free intervals of < 6 months, 6–11 months, 12–23 months, and ≥ 24 months, respectively. The median OS was 13.8 months and 40.9 months among patients with platinum-free intervals of < 12 months and ≥ 12 months.[16] In another case series involving 20 patients with recurrent EC and a platinum-free interval of ≥ 6 months, a 50% response rate and a median OS of 27 months were reported [41]. These observations aligned with our subgroup analysis, suggesting that a longer platinum-free interval may be linked with a trend toward improved survival among patients receiving re-challenge PT. After a reasonably long platinum-free interval, re-challenge PT may offer decent response rates and survival compared with other cytotoxic alternatives.

Regarding safety analyses, the most common adverse events for lenvatinib plus pembrolizumab in previous studies were hypertension (59–65%), fatigue (34–65%), diarrhea (43–64%), hypothyroidism (47–59%), proteinuria (23–31%), and arthralgia (23–32%) [2, 26–29]. Although the adverse events of lenvatinib plus pembrolizumab were generally considered manageable, the reported rates for dose interruption and reduction were approximately 70%; 33% of the patients had to discontinue their treatment due to adverse events [2]. Furthermore, the average cost of lenvatinib plus pembrolizumab is high at approximately $58,318 per cycle, this promotes significant concern in terms of patient and healthcare system expenses [42]. Feng et al. performed a Markov analysis using clinical data derived from the KEYNOTE-775 study. They showed that compared with chemotherapy, lenvatinib plus pembrolizumab provided an additional 0.64 quality-adjusted life years (QALYs) at an incremental cost of $241,278 [43]. The incremental cost-effectiveness ratio (ICER) was $378,251 per QALY, and the number would increase to $413,256/QALY in the pMMR subgroup [42]. In brief, although the combination of lenvatinib plus pembrolizumab has shown promise to the limited options of second-line treatments in managing recurrent ECs, the absence of a prospective randomized trial with a better potent comparator may lead to increased adverse events and costs without substantial improvements in survival.

The limitations of this study include the lack of information regarding the MMR status, histology compositions, and dosage received for each treatment. Furthermore, the study relied on ICD, RxNorm, HCPCS, and CPT coding systems to identify patient diagnosis, adverse events, lines of chemotherapy, and regimens of each treatment cohort. Any misclassification or delay in reporting mortality data may have affected the outcomes of our analysis. Moreover, 15% of the patients received carboplatin plus anthracycline as second-line therapy before rechallenge PT, which may introduce potential selection bias and underestimation of benefits from platinum rechallenge. In addition, the survival outcome related to lenvatinib plus pembrolizumab may improve with excellent response rates and survival from dMMR or MSI-H tumors compared with re-challenge PT. However, data regarding MMR status are insufficient on the TriNetX platform; therefore, a direct comparison between lenvatinib plus pembrolizumab and re-challenge PT could not be conducted for pMMR tumors.

Conclusions

In this study, we found no significant survival benefit when comparing lenvatinib plus pembrolizumab with re-challenge PT in patients with PT-pretreated, advanced, or recurrent ECs. Our findings remain to be confirmed using prospective trials under more rigorous supervision and controlled conditions.

Abbreviations

CCI Score	Charlson comorbidity index score
CPT	Current procedural terminology
EC	Endometrial cancer
HCO	Healthcare organizations
HCPCS	Healthcare common procedure coding system
ICD	International classification of disease
MMR	Mismatch repair
MSI-H	High microsatellite instability
OS	Overall survival
PFS	Progression-free survival
PSM	Propensity score matching
PT	Carboplatin plus paclitaxel
QALY	Quality-adjusted life years
VEGF	Vascular endothelial growth factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03989-0.

Additional file1: Table S1-S4. 2. Figure S1-S4. Table S1. Details of query codes used in our analysis. Table S2. Assessment of baseline comorbidities between lenvatinib plus pembrolizumab and re-challenge PT using the Charlson Comorbidity Index. Table S3. Baseline characteristics of the lenvatinib plus pembrolizumab and doxorubicin groups, before and after propensity score matching. Table S4. Assessment of baseline comorbidities between lenvatinib plus pembrolizumab and doxorubicin using the Charlson Comorbidity Index. Figure S1-S4. Figure S1. Visual timeline illustrating the treatment course and starting point of overall survival estimation. Figure S2. Distribution of propensity score matching before and

after matching for the lenvatinib plus pembrolizumab and carboplatin plus paclitaxel groups. Figure S3. Distribution of propensity score matching before and after matching for the lenvatinib plus pembrolizumab and doxorubicin groups. Figure S4. Adverse events among patients receiving lenvatinib plus pembrolizumab and doxorubicin.

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Authors' contributions
The authors confirm their contribution to the paper as follows. CHL was responsible for the study conception and design. HHC helped acquire the data and design of the study. YFC, TFL, and YHS helped acquire the tables, figures, and literature review. HHC, STH, CKL, and SFH helped with data analysis and interpretation, and participated in the search for literature and manuscript editing. SJW wrote the original draft of the manuscript. CHL, SJW, HHC, JKC, and LS reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the TriNetX platform, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the TriNetX platform. A data-sharing agreement may be required, and data access fees may apply.

Declarations

Ethics approval and consent to participate
This work was conducted in compliance with the principles of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Taichung Veterans General Hospital (CE24073C). Consent to participate is waived in this study as TriNetX has recieved a waiver of informed consent from the Western Institutional Review Board. All data and statistical summaries were displayed in aggregated counts, and no identifiable information can be accessed.

Consent for publication
All data were anonymized to protect individuals' confidentiality, and no personally identifiable information is accessible or shareable. Only aggregate data derived from the analyses will be published. As a result, informed consent from individual participants was waived for this study.

Competing interests
The authors declare no competing interests.

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