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# Real-world outcomes in patients with advanced endometrial cancer: A retrospective cohort study of US electronic health records

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## HIGHLIGHTS

- This retrospective cohort study characterized real-world outcomes of women with advanced endometrial cancer in the USA.
- Most women received platinum-based combination chemotherapy as first systemic treatment for advanced/recurrent disease.
- Survival outcomes were poor overall, particularly in women with advanced uterine serous carcinoma.
- Black/African American women had worse outcomes than white women despite similar demographics and treatment pathways.

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## ABSTRACT

*Objectives.* To characterize clinical outcomes of women with advanced/recurrent endometrial cancer (AEC) in routine practice using electronic health records from a real-world database.

*Methods.* Adult women diagnosed with AEC (stage III/IV, or early stage with locoregional/distant recurrence) between January 1, 2013 and September 30, 2020, inclusive, were eligible provided they received platinum-based chemotherapy at any time following diagnosis and had ≥2 clinical visits. Follow-up was from initiation of systemic treatment after advanced diagnosis (index) until March 30, 2021, last available follow-up, or death, whichever occurred first. Outcomes, by histological subtype, included Kaplan–Meier estimates of overall survival (OS) and time to first subsequent therapy or death (TFST).

*Results.* Of the 2202 women with AEC, most were treated in a community setting (82.7%) and presented with stage III/IV disease at initial diagnosis (74.0%). The proportion with endometrioid carcinoma, uterine serous carcinoma (USC), and other AEC subtypes was 59.8%, 25.0%, and 15.2%, respectively. The most common first systemic treatment following advanced/recurrent diagnosis was platinum-based combination chemotherapy (82.0%). Median OS (95% CI) from initiation of first systemic treatment was shorter with USC (31.3 [27.7–34.3] months) and other AECs (29.4 [21.4–43.9] months) versus endometrioid carcinoma (70.8 [60.5–83.2] months). Similar results were observed for TFST. Black/African American women had worse OS and TFST than white women.

*Conclusions.* Women with AEC had poor survival outcomes, demonstrating the requirement for more effective therapies. To our knowledge, this is the most comprehensive evaluation of contemporary treatment of AEC delivered in a community setting to date.



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## 1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the USA [1]. Incidence and mortality are increasing, with the American Cancer Society projecting that there will be approximately 66,570 new cases and 12,940 deaths from EC in the USA in 2021 [1]. Although early-stage EC is associated with favorable 5-year relative survival of 95% [1], outcomes are poor in patients with advanced or recurrent/persistent disease. Five-year survival for stage III and IV EC is 20–60% [2], while in the 10–15% of patients with EC who experience recurrence, 5-year survival is 13–65% [3].

Historically, EC has been categorized into two distinct subtypes according to clinical and endocrine features: type I (endometrioid) and type II (non-endometrioid) tumors, comprising 80–90% and 10–20% of ECs, respectively [4]. Type I ECs are characterized by low-grade, excess estrogen exposure, positive hormone receptor status, and a generally favorable prognosis [4,5]. Type II tumors have a hormone-independent pathogenesis, are more common in non-white, older, and non-obese patients, and are associated with higher mortality and rates of recurrence [5,6].

Uterine serous carcinoma (USC) is an aggressive type II non-endometrioid EC representing less than 10% of all EC cases but accounting for approximately 50% of relapses and 40% of all EC-associated deaths [7,8]. Other non-endometrioid ECs include carcinosarcoma, undifferentiated EC, clear-cell carcinoma (CCC), and squamous-cell carcinoma, which account for 2–5%, 5%, 2–4%, and 0.1–0.5% of cases, respectively [4], and, in the case of carcinosarcomas and CCCs, also contribute to a disproportionate percentage of overall EC deaths (>16%) [9,10].

Significant progress has been made in understanding the molecular mechanisms that drive EC, with a range of alterations identified in tumors important for determining prognosis [5,11]. Recent advances in molecular subtyping have led to the development of several risk stratification strategies to help guide treatment, according to the presence of (listed from best to worst prognosis): *POLE* (tumors with *POLE* exonuclease domain mutations); mismatch repair deficiency (dMMR)/microsatellite instability (MSI; EC with MSI); no specific molecular profile/unclassifiable; low copy number (*TP53* wild type); and high copy number (*TP53* mutated/abnormal) [12–15].

Standard management of EC at diagnosis involves surgical treatment followed by chemotherapy and/or radiation therapy [16]. Hormonal therapy is the preferred systemic therapy for EC patients with low-grade carcinomas in the absence of rapidly progressive disease [16,17]. Carboplatin/paclitaxel combination treatment is the standard chemotherapy regimen for patients with advanced, recurrent, or metastatic EC, based on data collected between 2003 and 2009 in the GOG-0209 trial [16,18]. In patients who do not respond to platinum-based therapy in this setting, treatment options include non-platinum regimens such as doxorubicin and paclitaxel [16] and the anti-programmed cell death protein 1 (anti-PD-1) agents pembrolizumab (USA) and dostarlimab (USA and Europe) in patients with high-MSI (MSI-H)/dMMR solid tumors [16,19,20]. Pembrolizumab plus lenvatinib, an oral inhibitor of both vascular endothelial growth factor (VEGF) and fibroblast growth factor driven angiogenesis, is also approved in the USA for microsatellite-stable EC [21,22]. The addition of trastuzumab to carboplatin/paclitaxel for women with advanced or recurrent human epidermal growth factor receptor 2 (HER2)-positive USC has been shown to prolong progression-free survival and overall survival (OS) in clinical trials [5,23].

While treatment patterns and outcomes in patients with early-stage EC have been relatively well characterized, real-world contemporary information on outcomes in high-risk patients with specific histological subtypes of advanced EC is needed to inform treatment decisions and set clinical expectations. Additionally, defining areas of high unmet need can fuel development and provide guidance for clinical trials. This observational study characterized the real-world patient characteristics, current treatment patterns, and clinical outcomes in women with advanced EC by histological subtype.

## 2. Methods

### 2.1. Study design

This retrospective, longitudinal cohort study utilized the nationwide electronic health record (EHR)-derived Flatiron Health database, comprising de-identified patient-level structured and unstructured data from US community and academic cancer clinics. Comprehensive methodological details of the Flatiron Health database have been published previously [24,25] and are described in further detail in the Supplementary Material.

The study was performed in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and the applicable legislation on non-interventional and/or observational studies. Institutional review board approval of the study protocol was obtained prior to study conduct and included a waiver of informed consent.

### 2.2. Eligibility criteria

Eligibility criteria were applied to the Flatiron Health database to capture a probabilistic sample of patients diagnosed with advanced EC. Eligible patients were adult (aged ≥18 years) women diagnosed with advanced EC, defined as stage III–IV disease, as classified by the International Federation of Gynecology and Obstetrics (FIGO) and/or the American Joint Committee on Cancer (AJCC) at initial diagnosis, or earlier-stage disease at initial diagnosis with subsequent locoregional or distant recurrence. Diagnosis was based on International Classification of Diseases (ICD)-10 code C54.1 or ICD-9 code 182.0. Subtypes of EC were defined according to histological classification: endometrioid carcinoma, USC, CCC, carcinosarcoma/mixed Müllerian tumors (referred to throughout as carcinosarcoma), and EC not otherwise specified (NOS). Patients with known brain metastases or other central nervous system diseases or invasive malignancies (except for treated limited-stage basal- or squamous-cell carcinoma of the skin and carcinoma in situ of the breast or cervix) were ineligible because of potential confounding from poor prognosis.

The index date for entry into the cohort was the date of diagnosis of advanced disease, which, to ensure a comparable cohort of patients with up to 6 months' follow-up, had to fall between January 1, 2013 and September 30, 2020 (inclusive). Eligible patients were followed up from initiation of systemic treatment for advanced/recurrent disease (for which documented receipt of therapy was required) after advanced diagnosis until the date of data cut-off (March 30, 2021), last available date of follow-up, or death (whichever occurred first). To ensure that patients had active medical records in the observational period being studied, at least two documented clinical visits from January 1, 2013 to March 30, 2021 and at least one visit during platinum-based chemotherapy were required. Patients had to have been treated with ≥1 platinum-based regimen at any time following initial diagnosis of EC [17]. The full study schema is provided in Supplementary Fig. 1.

### 2.3. Study outcomes

The primary outcomes of the study were OS and time to first subsequent therapy or death (TFST). Index date was from initiation of systemic treatment after diagnosis of advanced disease or recurrence. Secondary objectives were to describe demographic, clinical, and molecular characteristics of patients at baseline and/or during follow-up, including stage and grade of disease, time from initial diagnosis to advanced diagnosis, select comorbidities (defined according to the Charlson Comorbidity Index), Eastern Cooperative Oncology Group

(ECOG) performance status, and biomarker test results for HER2, estrogen receptor (ER), progesterone receptor (PR), and dMMR/MSI.

Treatment patterns, characterized by histological subtype, were described according to frequency, duration, and type (platinum chemotherapy, non-platinum chemotherapy, endocrine-based therapy, pegylated liposomal doxorubicin [PLD], VEGF inhibitor, HER2-targeted therapy, PD-1/programmed death ligand 1 [PD-L1] therapy, mechanistic target of rapamycin [mTOR] inhibitor, and any combination thereof) of systemic first- and second-line regimen in the advanced setting. Lines of therapy were categorized according to oncologist-defined and rule-based algorithms.

### 2.4. Statistical analyses

Categorical data were analyzed using descriptive statistics and summarized using frequency counts and percentages. Continuous data were also analyzed descriptively and summarized using mean, standard deviation (SD), median, minimum and maximum, and interquartile range (IQR). For discrete or ordinal data, percentages were suppressed when the count was zero. Missing data were not imputed. All results were analyzed overall and by subgroup based on histological classification. The primary analysis considered endometrioid, USC, and other ECs, which included combined data from patients with CCC, carcinosarcoma, and EC NOS because of the smaller sample sizes for these subtypes.

Time-to-event analyses were undertaken to estimate OS and TFST from initiation of first-line treatment after diagnosis of advanced/recurrent disease (index date) using Kaplan–Meier (KM) methodology. For all KM analyses, KM curves, median time to event, and median follow-up time were calculated (in months with 95% confidence intervals [CIs; log-log method]). In the analysis of OS, the event was death from any cause, and patients who did not experience the event (i.e. who were alive at the end of available follow-up) were censored at the point of last contact, with clinical care recorded in the dataset before or at the end of the study period. In the analysis of TFST, the event was either initiation of subsequent line of therapy or death from any cause; patients who did not initiate a new therapy were censored as described above. Crude and weighted KM analyses were used to investigate OS and TFST between selected histological subtypes. Weighted models employed inverse probability weighting for age and cancer stage at advanced diagnosis. No direct statistical comparisons across histological subgroups were undertaken.

The following further subgroup analyses were conducted to understand whether differences in demographic/clinical characteristics or outcomes existed between: patients with stage I/II or unknown-stage disease compared with those who had stage III/IV disease at initial diagnosis; patients exposed to platinum therapy at/before first-line treatment in the advanced setting versus patients who were first exposed to platinum-based therapies at second-line treatment in the advanced setting; and patients with black/African American ethnicity versus patients with white ethnicity. The subgroup of patients who did not proceed to treatment following advanced diagnosis was also characterized and OS from advanced diagnosis estimated.

## 3. Results

### 3.1. Study cohort

In total, 2202 women with advanced EC were included in the analysis (Supplementary Fig. 2). The majority of patients had endometrioid carcinoma (59.8%, $n = 1317$), 25.0% ($n = 551$) had USC, and 15.2% ($n = 334$) had other ECs, which included 9.6% ($n = 212$) with EC NOS, 4.2% ($n = 92$) with CCC, and 1.4% ($n = 30$) with uterine carcinosarcoma (Fig 1). Most patients were treated in a community setting (82.7%; $n = 1822$) and presented with stage III/IV disease (74.0%; stage III $n = 1073$, stage IV $n = 557$) at initial diagnosis (Table 1).

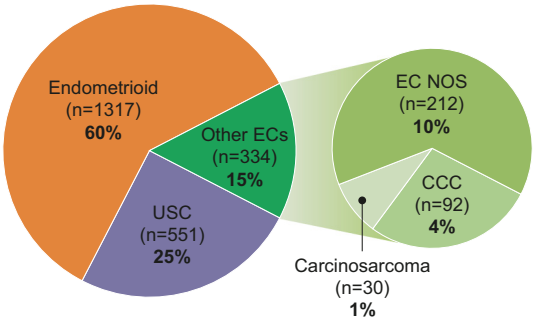


**Fig. 1.** Distribution of women across histological subtypes of advanced endometrial cancer. CCC, clear-cell carcinoma; EC, endometrial cancer; NOS, not otherwise specified; USC, uterine serous carcinoma.

Patients with endometrioid carcinoma were marginally younger at advanced diagnosis than those with USC or other ECs (Table 1; median [IQR] age 64.0 (56.0–70.0) vs 69.0 [64.0–74.0] and 66.5 [60.0–73.0] years, respectively). Compared with other subtypes, a higher proportion (26.3%) of women with USC were black/African American (Table 1). The overall median (IQR) body mass index (BMI) indicated that patients were mostly overweight or obese (32.1 [26.7–38.3] kg/m$^2$; Table 1); this observation was consistent among all subtypes.

Additional patient characteristics, including those in the subgroups of patients with CCC, carcinosarcoma, and EC NOS, are provided in Supplementary Tables 1 and 2.

### 3.2. Treatment in the advanced setting

Thirty-three patients did not undergo systemic therapy following diagnosis of advanced/recurrent EC; 21 died during follow-up, with a median survival from advanced diagnosis of 2.6 months (range 0.9–36.4), and 12 were censored at the end of follow-up, with a median follow-up of 7.4 months (range 0.0–67.4). In comparison with patients progressing to treatment, a higher proportion of untreated patients were black/African American (30.3% vs 14.2%) or had stage I/II disease (72.7% vs 20.7%) (Supplementary Table 3).

The most common first-line systemic treatments following diagnosis of advanced/recurrent disease were platinum-based combination chemotherapy (82.0%, $n = 1779/2169$), platinum-based single-agent chemotherapy (7.9%, $n = 172/2169$), and platinum-based chemotherapy plus HER2 therapy (2.9%, $n = 62/2169$); similar patterns were observed across histological subtypes (Fig. 2 and Supplementary Table 4). Of the 1179 patients treated with platinum-based combination therapy, 68.0% ($n = 1210$) had a taxane in their regimen. Overall median (IQR) duration of first-line treatment was 9.2 (4.1–23.2) months.

A total of 1001 patients received second-line systemic treatments; the most common therapy was platinum-based combination chemotherapy (27.8%, $n = 278$; a majority of whom received platinum and taxane: $n = 169/278$), endocrine-based therapy (17.0%, $n = 170$), and PLD single-agent therapy (11.0%, $n = 110$; data not shown). PD-1/PD-L1 monotherapy was used as second-line treatment in 5.0% ($n = 50$) of patients and in combination with VEGF inhibitors in 3.7% ($n = 37$) of patients. Overall median (IQR) duration of second-line treatment was 5.9 (2.8–12.4) months. When this subset of patients was further restricted to those who were platinum naïve at initiation of second-line therapy ($n = 61$), the most common therapy remained platinum-based combination chemotherapy (39.3%, $n = 24$), and more than half (59.0%, $n = 36$) of patients initiated platinum-based regimens.

### 3.3. Overall survival

In total, 2169 patients received systemic therapy following diagnosis of advanced/recurrent EC. Median OS (95% CI) from initiation of first

**Table 1**
Characteristics of women with advanced endometrial cancer, overall and by histological subtype.

| | | All patients ($N = 2202$) | Uterine serous carcinoma ($n = 551$) | Endometrioid carcinoma ($n = 1317$) | Other EC* ($n = 334$) |
|---|---|---|---|---|---|
| Median age at advanced diagnosis, years (IQR) | | 66.0 (59.0–72.0) | 69.0 (64.0–74.0) | 64.0 (56.0–70.0) | 66.5 (60.0–73.0) |
| BMI | Data available, n (%) | 654 (29.7) | 185 (33.6) | 371 (28.2) | 98 (29.3) |
| | Median BMI, kg/m$^2$ (IQR) | 32.1 (26.7–38.3) | 29.5 (25.0–36.6) | 33.6 (27.6–40.5) | 31.1 (26.5–35.4) |
| Race/ethnicity, n (%) | White | 1401 (63.6) | 309 (56.1) | 886 (67.3) | 206 (61.7) |
| | Black/African American | 318 (14.4) | 145 (26.3) | 124 (9.4) | 49 (14.7) |
| | Other | 284 (12.9) | 59 (10.7) | 176 (13.4) | 49 (14.7) |
| | Missing | 199 (9.0) | 38 (6.9) | 131 (10.0) | 30 (9.0) |
| ECOG performance status at advanced diagnosis, n (%) | 0 | 1125 (51.1) | 275 (49.9) | 681 (51.7) | 169 (50.6) |
| | 1 | 539 (24.5) | 136 (24.7) | 333 (25.3) | 70 (21.0) |
| | 2 | 126 (5.7) | 27 (4.9) | 77 (5.8) | 22 (6.6) |
| | Missing | 412 (18.7) | 113 (20.5) | 226 (17.2) | 73 (21.9) |
| Stage† at initial diagnosis, n (%) | I | 407 (18.5) | 82 (14.9) | 290 (22.0) | 35 (10.5) |
| | II | 66 (3.0) | 18 (3.3) | 39 (3.0) | 9 (2.7) |
| | III | 1073 (48.7) | 253 (45.9) | 700 (53.2) | 120 (35.9) |
| | IV | 557 (25.3) | 185 (33.6) | 239 (18.1) | 133 (39.8) |
| | Unknown | 99 (4.5) | 13 (2.4) | 49 (3.7) | 37 (11.1) |
| Health practice setting, n (%) | Academic | 380 (17.3) | 113 (20.5) | 212 (16.1) | 55 (16.5) |
| | Community | 1822 (82.7) | 438 (79.5) | 1105 (83.9) | 279 (83.5) |
| Comorbidity, n (%)‡ | Myocardial infarction | 4 (0.2) | 0 | 3 (0.2) | 1 (0.3) |
| | Congestive heart failure | 6 (0.3) | 1 (0.2) | 5 (0.4) | 0 |
| | Cerebrovascular disease | 7 (0.3) | 1 (0.2) | 4 (0.3) | 2 (0.6) |
| | Chronic pulmonary disease | 24 (1.1) | 4 (0.7) | 16 (1.2) | 4 (1.2) |
| | Rheumatic disease | 8 (0.4) | 1 (0.2) | 6 (0.5) | 1 (0.3) |
| | Peptic ulcer disease | 1 (0.1) | 0 | 0 | 1 (0.3) |
| | Mild liver disease | 1 (0.1) | 0 | 1 (0.1) | 0 |
| | Renal disease | 13 (0.6) | 5 (0.9) | 7 (0.5) | 1 (0.3) |
| Positive for ≥ 1 biomarker§ at any time | Positive | 1203 (54.6) | 257 (46.6) | 797 (60.5) | 149 (44.6) |
| | Negative/unknown result | 521 (23.7) | 185 (33.6) | 245 (18.6) | 91 (27.2) |
| | Not tested¶ | 478 (21.7) | 109 (19.8) | 275 (20.9) | 94 (28.1) |
| Year of advanced diagnosis, n (%) | 2013 | 205 (9.3) | 50 (9.1) | 114 (8.7) | 41 (12.3) |
| | 2014 | 233 (10.6) | 53 (9.6) | 143 (10.9) | 37 (11.1) |
| | 2015 | 289 (13.1) | 67 (12.2) | 182 (13.8) | 40 (12.0) |
| | 2016 | 316 (14.4) | 65 (11.8) | 212 (16.1) | 39 (11.7) |
| | 2017 | 350 (15.9) | 102 (18.5) | 207 (15.7) | 41 (12.3) |
| | 2018 | 314 (14.3) | 73 (13.2) | 182 (13.8) | 59 (17.7) |
| | 2019 | 309 (14.0) | 85 (15.4) | 172 (13.1) | 52 (15.6) |
| | 2020 | 186 (8.4) | 56 (10.2) | 105 (8.0) | 25 (7.5) |

*Includes patients with clear-cell carcinoma (n = 92), carcinosarcoma (n = 30), and EC not otherwise specified (n = 212); †As classified by FIGO and/or AJCC; ‡No patients had the following comorbidities: peripheral vascular disease, dementia, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, moderate or severe liver disease, AIDS/HIV; §Positive result for at least one of ER, PR, HER2, and dMMR/MSI; ¶Testing for specific biomarkers may not have been available for the full time period of the cohort.
AJCC, American Joint Committee on Cancer; BMI, body mass index; dMMR, mismatch repair deficiency; EC, endometrial cancer; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; MSI, microsatellite instability; PR, progesterone receptor.

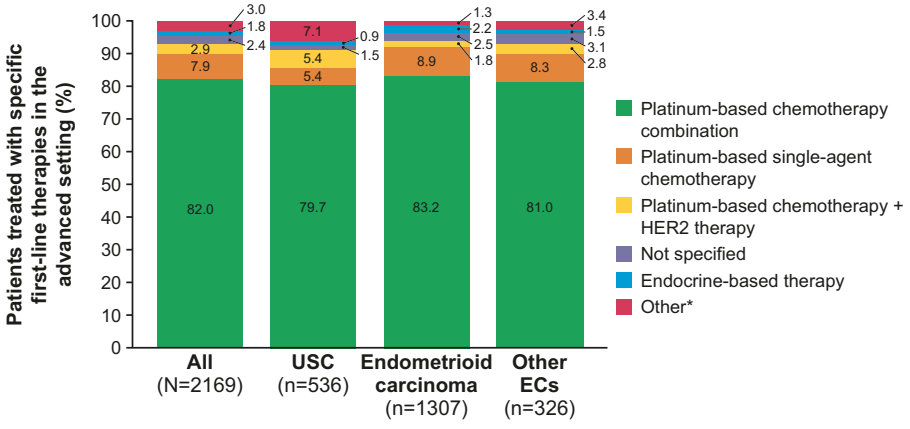


**Fig. 2.** Bar chart depicting frequency distribution of first-line treatment regimens in the advanced setting, overall and by histological subgroup. Thirty-three patients did not have recorded therapy following advanced EC diagnosis: 15 with USC, 10 with endometrioid carcinoma, five with CCC, one with carcinosarcoma, and two with EC NOS. Other EC includes patients with CCC ($n = 87$), carcinosarcoma ($n = 29$), and EC NOS ($n = 210$). *Other first-line therapy in the advanced setting includes: clinical study-drug-based therapies; non-platinum-based single-agent chemotherapy; platinum-based chemotherapy + PLD; VEGF inhibitor; PLD single-agent chemotherapy; platinum-based chemotherapy + endocrine-based therapy; non-platinum-based chemotherapy combination; PD-1/PDL-1 therapy; PLD + VEGF inhibitor; and non-platinum-based chemotherapy + VEGF inhibitor. CCC, clear-cell carcinoma; EC, endometrial cancer; NOS, not otherwise specified; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PLD, pegylated liposomal doxorubicin; USC, uterine serous carcinoma; VEGF, vascular endothelial growth factor.

systemic treatment following advanced/recurrent diagnosis (index date) was shorter in patients with USC (31.3 [27.7–34.3] months) and other ECs (29.4 [21.4–43.9] months) than in patients with endometrioid carcinoma (70.8 [60.5–83.2] months; crude analysis; Table 2). OS from initiation of first systemic treatment in patients with EC NOS, CCC, and uterine carcinosarcoma is provided in Supplementary Table 5.

In adjusted analysis, median OS (95% CI) from initiation of first systemic treatment following advanced/recurrent diagnosis remained shorter in patients with USC and other ECs versus patients with endometrioid carcinoma (34.0 [29.6–37.1] and 46.5 [30.9–not estimable] vs 61.0 [53.3–72.9] months, respectively; Fig. 3a and Table 2).

### 3.4. Time to first subsequent therapy or death

Median TFST (95% CI) from initiation of first systemic treatment was also shorter for patients with USC (10.6 [9.6–12.3] months) and other ECs (9.0 [7.7–11.0] months) than in the endometrioid subgroup (18.9 [15.8–21.7] months; crude analysis; Table 2). TFST from initiation of first systemic treatment in patients with EC NOS, CCC, and uterine carcinosarcoma is provided in Supplementary Table 5.

In adjusted analysis, median TFST (95% CI) from initiation of first systemic treatment following advanced/recurrent diagnosis remained shorter in patients with USC and other ECs versus patients with endometrioid carcinoma (10.8 [9.7–12.8] and 11.3 [8.4–16.4] vs 16.3 [13.7–19.7] months, respectively; Fig. 3b and Table 2).

### 3.5. Biomarker profile

Across all histological subgroups, the numbers of patients positive for each biomarker assessed (HER2, ER, PR, and dMMR/MSI) increased between 2011–2015 and 2016–2020 (Supplementary Table 6). Overall, 321 patients (14.6% of the cohort) were positive for dMMR/MSI. Regardless of time period or biomarker, the most common first-line treatment was platinum-based combination therapy (Supplementary Table 6).

### 3.6. Subgroup analysis

Median OS and TFST from initiation of first systemic treatment following advanced/recurrent diagnosis in patients exposed to platinum at first line or before were comparable with those seen for the full cohort (Supplementary Table 7).

Both median OS and TFST were shorter in patients with stage I/II or unknown-stage disease at initial diagnosis than in those who had stage III/IV disease at initial diagnosis (Supplementary Table 8).

Outcomes were consistently worse for black/African American women compared with white women with respect to both median OS and TFST from initiation of first systemic treatment following advanced/recurrent diagnosis (Supplementary Table 9).

## 4. Discussion

This large, retrospective, real-world study utilized EHR-derived data from a real-world database to examine the clinical outcomes of women with different subtypes of advanced/recurrent EC in clinical practice.

The results highlight the poor survival outcomes in women with advanced/recurrent EC, particularly women with non-endometrioid (type II) ECs in whom median OS from initiation of first systemic treatment was less than 3 years and TFST was less than 1 year. There is currently a lack of contemporary evidence focusing on outcomes in patients with different histological subtypes of advanced EC; nevertheless, the shorter OS and TFST observed here in women with advanced/recurrent USC and other ECs (including CCC and carcinosarcoma) than in patients with endometrioid carcinoma is consistent with the pattern shown across these histological subtypes in the limited number of previous real-world studies [26,27] and a pooled analysis of clinical trials [28]. Approximately one-quarter of the patients in our study had USC, which is similar to the proportion with serous histology participating in advanced EC clinical trials across a similar period of time (17.3–35.8%) [21,29–33]. Patients with USC have an increased risk of a higher stage at diagnosis versus those with endometrioid carcinoma [34], as well as a worse prognosis, when compared stage for stage [35]. In our analysis, after using inverse probability weighting for age and cancer stage at initial diagnosis, differences in OS and TFST between patients with endometrioid carcinoma and those with USC were still apparent.

Overall, more than three-quarters of patients presented with stage III/IV disease at initial diagnosis; the remainder presented as unknown stage or stage I/II before the disease advanced. Median OS was shorter in patients with stage I/II or unknown-stage disease at initial diagnosis versus those with stage III/IV disease (36.9 vs 56.8 months). A greater proportion of stage III/IV patients had USC (26.9% vs 19.8%) and were treated with first-line platinum-based therapy in the advanced/recurrent setting (95.8% vs 86.8%) compared with patients with stage I/II/unknown-stage disease, which may suggest differences in disease pathogenesis between early-stage and later-stage patients, or that more aggressive treatment was administered to patients first diagnosed at stage III/IV. However, as patients were selected based on platinum exposure, there was a potential bias toward selection of early-stage patients with poor prognosis.

**Table 2**
Median OS and TFST from initiation of first systemic treatment for advanced/recurrent endometrial cancer after advanced diagnosis, overall and by histological subtype.

| | | Crude | | | | Weighted‡ | | |
|---|---|---|---|---|---|---|---|---|
| | | All patients (*N* = 2169*) | USC (*N* = 536*) | Endometrioid (*N* = 1307*) | Other EC† (*N* = 326*) | USC (N = 536*) | Endometrioid (N = 1307*) | Other EC† (N = 326*) |
| OS | Median OS, months (95% CI) | 49.6 (43.9–56.3) | 31.3 (27.7–34.3) | 70.8 (60.5–83.2) | 29.4 (21.4–43.9) | 34.0 (29.6–37.1) | 61.0 (53.3–72.9) | 46.5 (30.9–NE) |
| | IQR for median OS, months | 18.1–89.5 | 15.4–61.8 | 24.8–NE | 9.5–NE | 15.9–65.3 | 21.3–NE | 12.9–NE |
| | Patients with event, n (%) | 798 (36.8) | 254 (47.4) | 394 (30.1) | 150 (46.0) | 254 (47.4) | 394 (30.1) | 150 (46.0) |
| | Censored patients, n (%) | 1371 (63.2) | 282 (52.6) | 913 (69.9) | 176 (54.0) | 282 (52.6) | 913 (69.9) | 176 (54.0) |
| | Median follow-up,§ months (95% CI) | 33.0 (30.6–35.0) | 32.2 (26.1–36.3) | 33.7 (31.0–35.6) | 31.7 (28.0–36.6) | 32.1 (25.7–36.9) | 33.3 (30.3–35.3) | 30.4 (26.4–35.6) |
| | IQR for median follow-up,§ months | 14.9–52.0 | 14.5–51.6 | 15.2–52.2 | 14.4–51.4 | 14.2–48.4 | 14.9–52.2 | 15.2–49.9 |
| TFST | Median TFST, months (95% CI) | 13.6 (12.1–15.1) | 10.6 (9.6–12.3) | 18.9 (15.8–21.7) | 9.0 (7.7–11.0) | 10.8 (9.7–12.8) | 16.3 (13.7–19.7) | 11.3 (8.4–16.4) |
| | IQR for median TFST, months | 4.9–70.8 | 5.3–25.3 | 5.1–87.9 | 3.9–37.9 | 5.4–28.1 | 4.9–87.9 | 4.4–NE |
| | Patients with event, n (%) | 1297 (59.8) | 381 (71.1) | 697 (53.3) | 219 (67.2) | 381 (71.1) | 697 (53.3) | 219 (67.2) |
| | Censored patients, n (%) | 872 (40.2) | 155 (28.9) | 610 (46.7) | 107 (32.8) | 155 (28.9) | 610 (46.7) | 107 (32.8) |
| | Median follow-up,¶ months (95% CI) | 34.0 (31.2–36.7) | 37.8 (34.4–40.6) | 31.7 (29.5–35.0) | 35.6 (29.9–43.6) | 37.4 (34.4–40.6) | 31.7 (29.4–35.0) | 35.6 (29.2–43.6) |
| | IQR for median follow-up,¶ months | 15.4–52.4 | 16.5–57.2 | 14.5–51.8 | 18.8–58.3 | 16.5–53.3 | 14.4–51.8 | 17.3–51.6 |

*Thirty-three patients did not have recorded therapy following diagnosis of advanced EC: USC (*n* = 15), endometrioid carcinoma (n = 10), CCC (n = 5), carcinosarcoma (n = 1), and EC NOS (n = 2); †Includes patients with CCC (n = 87), carcinosarcoma (n = 29), and EC NOS (n = 210); ‡Kaplan–Meier analyses weighted for age at advanced diagnosis and stage (I/II/unknown vs III/IV) at initial diagnosis; §Median follow-up for OS censored patients (death); ¶Median follow-up for TFST censored patients (death or new therapy). CCC, clear-cell carcinoma; CI, confidence interval; EC, endometrial cancer; IQR, interquartile range; NE, not estimable; NOS, not otherwise specified; TFST, time to first subsequent therapy or death; USC, uterine serous carcinoma.

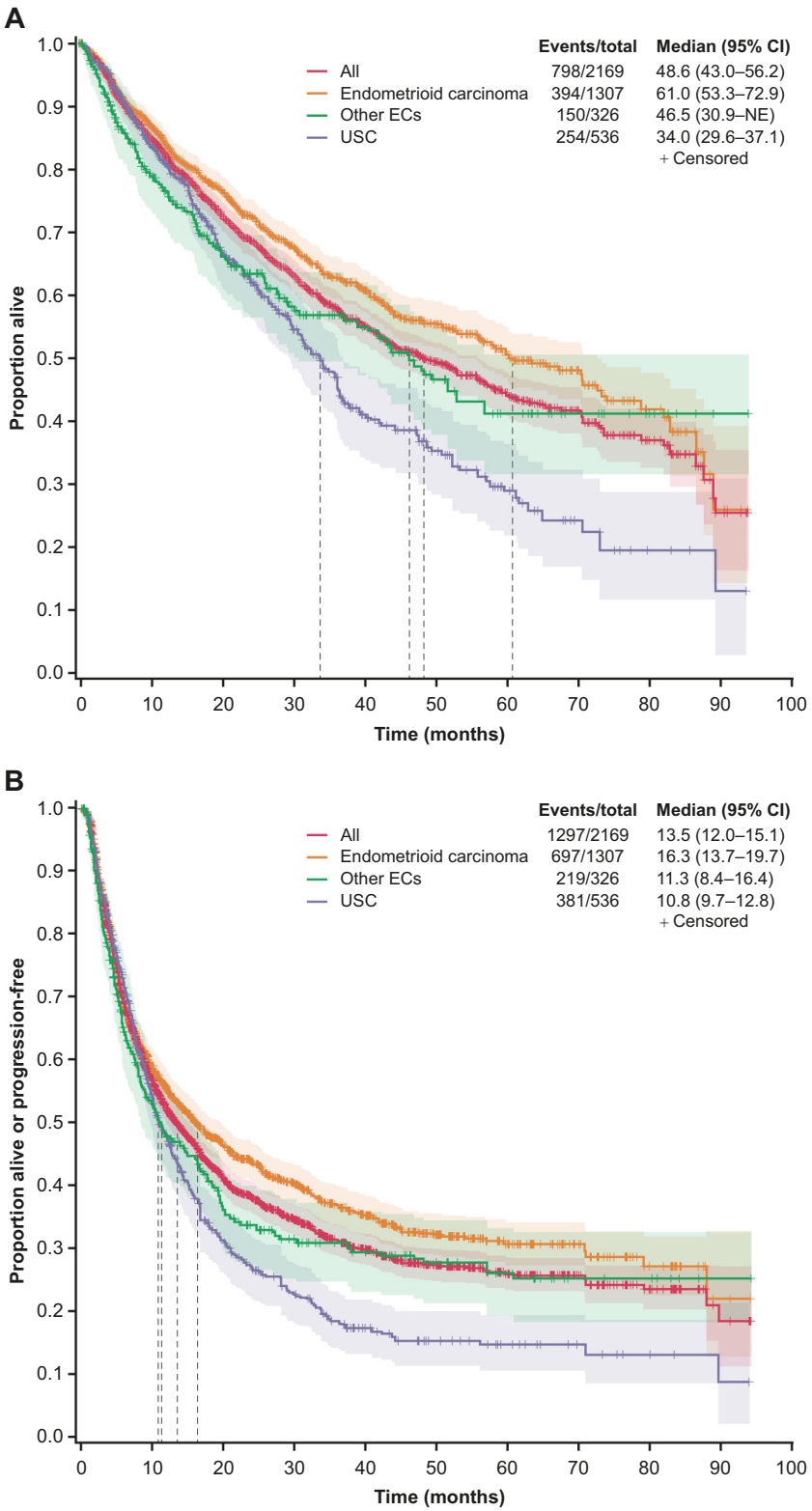


**Fig. 3.** Kaplan–Meier plots of (A) overall survival and (B) time to first subsequent therapy or death from initiation of first systemic treatment for endometrial cancer in the advanced setting (inverse probability weighting for age and cancer stage at advanced diagnosis). CI, confidence interval; EC, endometrial cancer; USC, uterine serous carcinoma.

Previous studies suggest that black women are more likely to present with non-endometrioid tumors and later-stage tumors than age-matched white women [36]. Over the last decade, increased mortality in black women with EC, especially those with non-endometrioid cancers, have become particularly apparent, and black women are approximately twice as likely to die from uterine cancer than other ethnicities [37]. We therefore undertook an exploratory subgroup analysis according to black/African American or white ethnicity. No obvious differences were observed in the patient characteristics or the frequency distribution of specific first-line therapies; however, outcomes were

markedly worse in black/African American women across all histological subgroups, highlighting the significant unmet need in this population. Further research is required to explore drivers of these differences.

Platinum-based combination chemotherapy was the most common treatment as both first- and second-line systemic therapy in the advanced/recurrent setting across all EC histological subtypes and regardless of positive biomarker testing; in most patients, this regimen included a taxane (first line: 68.0%; second line: 60.4%). This is consistent with current treatment recommendations for combination carboplatin and paclitaxel as the standard systemic therapy for EC in the advanced setting [16,17]. In the current study, the majority of patients were exposed to platinum therapy either at or prior to first-line therapy in the advanced/recurrent setting. To investigate the possible bias of including patients who had not been first exposed to platinum therapy until second-line therapy or later in the advanced/recurrent setting, we performed a subgroup analysis comparing these patients with those who were platinum exposed at, or prior to, initiation of first-line therapy. Except for OS in the USC and other EC subgroups, OS and TFST from initiation of first-line therapy in patients who were first platinum exposed at second line were shorter than in those exposed earlier. This may reflect poorer prognosis in non-endometrioid tumors regardless of treatment but must be interpreted with caution given the small numbers of patients across histological subtypes who were platinum naïve until second line.

Depending on country/region, options following platinum-based therapies in the advanced/recurrent setting include hormonal therapy, doxorubicin, paclitaxel, pembrolizumab, or dostarlimab in patients with MSI-H/dMMR EC, and pembrolizumab plus lenvatinib in microsatellite-stable EC [16,19–22]. Here, endocrine-based therapy and PLD single-agent chemotherapy were used in 18% and 11% of patients, respectively, while only 5% of patients received PD-1/PD-L1 monotherapy, and 3.7% received PD-1/PD-L1 in combination with VEGF inhibitors. This likely reflects the fact that pembrolizumab and dostarlimab are relatively recent additions to the treatment armamentarium; our study only considered patients diagnosed between January 1, 2013 and September 30, 2020, followed up to a data cut-off of March 30, 2021. There was evidence of increased biomarker testing over time in our study, especially for the dMMR/MSI phenotype, which may reflect a shift in strategy toward biomarker-driven treatment.

The poor outcomes in patients with advanced/recurrent EC observed here highlight the unmet need for new treatment options. It is noteworthy that the majority of studies with investigational agents conducted to date have focused on advanced EC overall with limited data adressing benefit specifically in subtypes with particularly poor prognosis, such as USC. Several ongoing trials with Wee1 inhibitors, anti-PD-1 agents, PARP inhbitors, and HER2 inhibitors are investigating the safety and efficacy of novel treatments in USC specifically, as summarized in Bogani et al. [4].

Thirty-three of 2202 patients (1.5%) did not receive systemic therapy following advanced/recurrent EC diagnosis, 21 of whom died during follow-up, with a median survival of 2.6 months (range 0.9–36.4). This subpopulation therefore likely represents patients receiving palliative care whose cancer was assessed to be so advanced that it would not respond to treatment. These patients were not included in the analysis of OS, TFST, or treatment patterns in the advanced setting, minimizing this potential source of bias on our effect estimates.

We deliberately selected a population exposed to platinum-based therapy following initial diagnosis of advanced/recurrent disease to provide a real-world reflection of the burden of EC in high-risk patients by histological subgroup. Our data reflect real-world treatment patterns and outcomes in a mainly community, as opposed to an academic, setting and fill an important unmet need in the literature for data on outcomes of high-risk patients in this setting. The limited real-world data published specifically in advanced EC to date [38,39] do not provide comparable populations with which to compare our results. Nevertheless, the scale and scope of the real-world dataset analyzed, and its rich source of both structured and unstructured data, may be nationally representative of the US population, so results from our analyses may be generalizable to other patients outside the dataset. Compared with national cancer registries, patients in the real-world database analyzed here have been shown to have similar sex and geographic distributions but are generally diagnosed with later stages of disease and have differing age distribution [25], which should be considered when interpreting the results.

There were several limitations in this study. Data were derived from the patients' medical records from predominantly community-based clinical sites, which may not offer an empirical record of the treatment journey. Missing data is an inherent limitation of EHR-derived studies, and no attempt was made to impute missing data in our study. Patients were required to have structured activity in their medical record within 90 days of diagnosis of advanced EC. Requiring at least two documented clinical visits could have introduced some selection bias by potentially excluding patients diagnosed as advanced/recurrent at their first documented visit who then died before their second visit. However, mandating a minimum number of clinical visits is a common approach in analyzing EHR-derived data to minimize bias caused by inclusion of patients with incomplete or missing clinical information. TFST and OS could potentially be overestimated through exclusion of patients who did not receive systemic treatment following advanced/recurrent diagnosis. Inverse probability weighting for age and cancer stage at advanced/recurrent diagnosis was employed for estimates of OS and TFST; weighting by ECOG status and cancer grade was not possible because of missing data. Furthermore, the demarcation of lines of therapy with algorithms may have led to misclassification, but this is unlikely to be differential with respect to histology. This study deliberately took a high-level approach to defining lines of therapy to make the results more generalizable. Although alternative definitions based on factors such as stage, grading, residual disease, and biomarker profile have been used previously, our definition may be more applicable to the real-world setting, given that biomarker testing is not routinely performed.

In summary, this retrospective study is the most comprehensive evaluation of contemporary treatment of advanced/recurrent EC generally delivered in a community setting conducted to date. It offers an insight into real-world treatment patterns and outcomes, helping to inform treatment decisions and set future clinical expectations. Consistent with current literature [16,17], the results highlight the poor prognosis in patients with advanced/recurrent EC, particularly patients with USC and other type II ECs. Given the tumor biology of these EC subtypes and the limited number of available treatments, there is an urgent need for more effective therapies that help to prolong survival in women with advanced/recurrent disease.

## Disclosures

Dr. Monk reports honoraria for speaking/consulting engagements from AstraZeneca, Clovis, Easai, Merck, and Tesaro/GSK, and honoraria for consulting engagements from Elevar, Genmab/Seattle Genetics, Karyopharm, McKesson, and Sorrento.

Dr. Smith and Dr. Lima have nothing to disclose.

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## Data statement

The data that support the findings of this study were originated by Flatiron Health, Inc. These de-identified data may be made available upon request and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.12.008.

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