Endometrial cancer (EC) is the most common gynecologic cancer in high-income countries, with the highest incidence in North America. Worldwide, the overall incidence has increased by >130% in the last 30 years, and disease-associated mortality in the United States is increasing 2.5% annually on average. The worsening mortality rate is pronounced among Black women, for reasons including decreased healthcare access, treatment disparities, and molecular tumor differences.

Obesity, a strong risk factor for EC, accounts for approximately 50% of cases in Europe and the United States. Obesity may contribute to EC pathogenesis through insulin resistance and abnormalities of insulin growth factor 1 signaling, resulting in increased cell proliferation, chronic low-grade inflammation, alterations in adipokine physiology, and cellular and vascular perturbations that promote oncogenesis. Excess endogenous or exogenous estrogen exposure from early menarche, late menopause, or tamoxifen exposure also increase EC risk. Individuals with Lynch syndrome and Cowden syndrome have genetic increased risk of EC, and emerging data indicate a potential role for BRCA1/2 germline pathogenic variants in the development of high-grade EC.

Recent studies have highlighted the molecular underpinnings of EC and associated outcomes. The Cancer Genome Atlas (TCGA) Research Network has identified the following 4 widely accepted molecular EC subtypes: POLE ultra-mutated, mismatch repair (MMR)–deficient (MMRd), copy number low, and copy number high (CN-H). Each molecular subtype has its own prognostic significance, with the POLE subtype associated with the best survival outcomes and the CN-H subtype associated with the poorest survival outcomes. Although histology and stage are currently used to stratify patients for treatment and to predict outcomes, recent studies have found considerable histologic diversity within EC subtypes, underscoring the importance of the molecular classification of all EC tumors. Molecular subtyping has informed significant therapeutic advancements in advanced/recurrent EC, as outlined in this review, and has been increasingly exploited for risk stratification for optimal personalized therapy.
treatment. The largest cohort of patients with EC who have undergone complete molecular characterization was recently presented by investigators at Memorial Sloan Kettering Cancer Center (Figure 1). Although these patients were treated at a specialized referral center and are disproportionately at higher risk than the general endometrial cancer population, Figure 1 depicts the heterogeneity of patients with EC.

Although most patients with EC present with early-stage disease and have favorable prognoses, those with stage III and IV disease have 5-year survival rates of 48% and 15%, respectively. At diagnosis, approximately 20% to 30% of ECs are considered high-risk based on traditional prognostic factors, including stage, histology, myometrial invasion, and lymphovascular invasion, and are associated with recurrence rates of up to 30%. Systemic therapy for advanced/recurrent EC is the cornerstone of treatment. This review discusses evidence-based therapeutic options for advanced/recurrent EC and reviews ongoing investigational therapies that may impact the future treatment landscape. Systemic treatment in advanced/recurrent EC remains palliative; therefore, patient quality of life must be prioritized within the shared decision-making process.

First-Line Therapy of Newly Diagnosed Advanced EC

The standard first-line (1L) therapy for newly diagnosed advanced/recurrent EC regardless of molecular subtype consists of carboplatin/paclitaxel (TC) chemotherapy with

![Figure 1. Endometrial cancer molecular subtypes and histologies. Molecular subtyping of 1,906 endometrial cancers at Memorial Sloan Kettering Cancer Center. All 4 molecular subtypes consist of varying proportions of endometrial cancer histologies. Results presented at the 2022 SGO Annual Meeting on Women’s Cancer; March 18–21, 2022; Phoenix, AZ. These results are preliminary and will be published in finalized form.](image-url)
or without primary surgical cytoreduction. Key clinical trials assessing systemic therapy for advanced/recurrent EC are summarized in Table 1. TC was established as the standard 1L regimen based on findings from the phase III, randomized noninferiority GOG 209 trial. TC demonstrated noninferiority over adriamycin, cisplatin, and paclitaxel (TAP) in patients with stage III/IV or recurrent chemotherapy-naïve EC, with an overall survival (OS) of 37 months versus 41 months, respectively (90% CI, 0.9–1.12). TC was also associated with significantly fewer adverse events (AEs) (P < .05).

In patients with newly diagnosed advanced EC, primary surgical cytoreduction is considered when optimal cytoreduction (to <1 cm residual disease), or preferably, complete gross resection (no visible residual disease) is feasible. However, this approach is largely based on retrospective data, and there is limited high-quality evidence for cytoreduction in advanced EC; recommendations are often extrapolated from ovarian cancer literature. Trends in the up-front treatment of advanced EC are changing, and neoadjuvant chemotherapy is now more commonly used than primary surgical cytoreduction for stage IVB endometrial cancer according to a recent analysis of SEER data. A neoadjuvant chemotherapy approach for advanced EC has been associated with less surgical morbidity and no difference in OS compared with primary surgical cytoreduction.

For locally advanced EC, radiation is routinely used with chemotherapy to reduce the risk of pelvic relapse based on the results of 2 landmark clinical trials—GOG 258 and PORTEC-3—the latter of which demonstrated a survival benefit with chemoradiation over radiation alone for stage III EC (OS, 78.7% vs 69.8%, respectively; P = .114).

**Recurrent EC**

**Chemotherapy**

Retrospective data suggest platinum rechallenge has diminished efficacy. Platinum sensitivity, defined as a platinum-free interval of >6 months in ovarian cancer, is terminology that has not been prospectively evaluated or validated in EC. A retrospective analysis of patients re-treated with TC whose disease recurred >6 months after completion of adjuvant TC showed an overall response rate (ORR) of 50%, median progression-free survival (PFS) of 10 months, and median OS of 27 months. Retrospective studies have found time to recurrence after prior chemotherapy is predictive of survival in EC. The largest of these studies, a pooled analysis of phase III GOG studies (GOG 107, 122, 163, and 177), which assessed second-line (2L) chemotherapy following primary platinum chemotherapy, showed time to progression after primary platinum chemotherapy was the most predictive factor for survival following 2L chemotherapy.

Patients with a platinum-free-interval >6 months compared with <6 months had a 30% lower risk for death (hazard ratio [HR], 0.70; 95% CI, 0.59–0.84; P < .01). There is limited evidence for platinum-based combinations versus single-agent chemotherapy in the 2L or beyond. Following frontline TC, the benefit of subsequent chemotherapy is modest, with a median PFS of 3 to 4 months and OS of 6 to 12 months.

The anti-VEGF antibody bevacizumab is also active in advanced EC as monotherapy and has been explored in combination with TC. The randomized, phase II NRG/GOG 86P trial compared 1L TC + bevacizumab; TC + temsirolimus; and ixabepilone and carboplatin + bevacizumab, and found improved median OS with the addition of bevacizumab to TC compared with historic data from GOG 209 (34 vs 23 months, respectively). Improvements in OS with bevacizumab were most robust among patients with a TP53 mutation on next-generation sequencing or p53 overexpression on immunohistochemistry (IHC), with a median OS for TC + bevacizumab of 30.0 months compared with 14.4 months for TC + temsirolimus in this TP53-altered subgroup. The MITO Group End-2 trial looked at TC ± bevacizumab in patients whose disease had progressed >6 months after completion of 1L therapy. Patients in the bevacizumab arm had a higher ORR, median PFS, and OS, although these differences were not statistically significant. At this time, definitive evidence for the addition of bevacizumab to standard chemotherapy is limited.

Options for single-agent chemotherapy are limited and include agents such as liposomal doxorubicin, doxorubicin, cisplatin, topotecan, docetaxel, and paclitaxel, with ORRs ranging from 9.5% to 15%. The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Uterine Neoplasms also include single-agent topotecan, as well as combinations that contain cisplatin, docetaxel, and ifosfamide, all with poor or undocumented efficacy.

**HER2**

HER2 is emerging as a promising target for the treatment of EC. HER2 is overexpressed in approximately 25% to 30% of CN-H, serous/serous-like ECs and 13% of carcinosarcomas. When HER2 is overexpressed, tyrosine kinase becomes constitutively activated, leading to dysregulation of DNA transcription through activation of PIK3CA/akt/mTOR and RAS/RAF/MAPK pathways. Findings from a randomized, phase II trial of TC versus TC plus the monoclonal HER2-targeting antibody trastuzumab in patients with HER2+ stage III/IV or recurrent serous EC demonstrated improved median PFS (12.9 vs 8.0 months, respectively) and OS (29.6 vs 24.4 months, respectively) with TC + trastuzumab. This benefit was most notable in stage III/IV disease with trastuzumab as part of primary
### Table 1. Key Clinical Trials Assessing Systemic Therapy for Advanced/Recurrent Endometrial Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Key Inclusion Criteria</th>
<th>Treatment Arms</th>
<th>Endpoint(s)</th>
<th>Key Findings/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
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</table>
- No prior chemotherapy or radiotherapy  
- Complete surgical staging  
- No single site of residual tumor > 2 cm | Arm 1: Whole-abdominal irradiation 10 Gy in 20 fractions, with 15-Gy boost; n=202  
Arm 2: Doxorubicin + cisplatin; n=199 | Primary - FFS  
Secondary - OS | - Arm 2 had improved PFS (HR, 0.71; 95% CI, 0.55-0.91)  
- Arm 2 had improved OS (HR, 0.68; 95% CI, 0.52-0.89)  
- Arm 2 had more grade 3/4 adverse events |
| GOG 163 (PMID: 15277255) Enrollment: 8/12/1996-11/30/1998 | - Stage III/IV or recurrent EC  
- No prior cytotoxic chemotherapy | Arm 1: Doxorubicin (60 mg/m²) + cisplatin (50 mg/m²); n=157  
Arm 2: Doxorubicin (50 mg/m²) + paclitaxel (150 mg/m²) + filgrastim; n=160 | Primary - ORR  
Secondary - PFS  
Secondary - OS | - No difference in ORR (OR, 1.12; 95% CI, 0.69-1.79)  
- No difference in PFS (HR, 0.90; 95% CI, 0.79-1.42)  
- No difference in OS (HR, 0.90; 95% CI, 0.57-0.988) |
| GOG 177 (PMID: 15169803) Enrollment: 12/28/1998-8/14/2000 | - Stage III/IV or recurrent EC  
- No prior cytotoxic chemotherapy | Arm 1: Doxorubicin (60 mg/m²) + cisplatin (50 mg/m²); n=129  
Arm 2: Doxorubicin (45 mg/m²) + cisplatin (50 mg/m²) + paclitaxel (160 mg/m²) + filgrastim; n=134 | Primary - ORR  
Secondary - PFS  
Secondary - OS | - Arm 2 had improved PFS (HR, 0.60; 95% CI, 0.46-0.78)  
- Arm 2 had improved OS (HR, 0.75; 95% CI, 0.57-0.98) |
| GOG 209 (PMID: 32078978) Enrollment: 8/25/2003-4/20/2009 | - Stage III/IV or recurrent EC with poor potential for cure by surgery and/or radiation therapy  
- No prior cytotoxic chemotherapy | Arm 1: Paclitaxel (160 mg/m²) + doxorubicin (45 mg/m²) + cisplatin (50 mg/m²); n=640  
Arm 2: Carboplatin (AUC 6) + paclitaxel (160 mg/m²); n=664 | Primary - ORR  
Secondary - PFS  
Secondary - Toxicity  
Secondary - HRQoL | - Arm 2 was not inferior: OS (HR, 1.00; 95% CI, 0.71-1.42),  
PFS (HR, 1.03; 90% CI, 0.93-1.15)  
Arm 2 had a more favorable toxicity profile and HRQoL difference |
| PORTEC 3 (PMID: 29449189) Enrollment: 11/26/2006-12/20/2013 | - Stage IIA or IB grade 3 endometrioid carcinoma, stage III endometrioid carcinoma, or stage IB-III serous or clear cell EC  
- No prior chemotherapy or radiotherapy | Arm 1: Carboplatin (50 mg/m², 2 cycles) with EBRT followed by carboplatin (AUC 5, 4 cycles); n=330  
Arm 2: EBRT; n=330 | Primary - OS  
Secondary - PFS  
Secondary - Recurrence rate  
Secondary - Toxicity  
Secondary - HRQoL | - No difference in 5-year OS (HR, 0.76; 95% CI, 0.54-1.06)  
Arm 1 had significantly more grade 3 complications vs Arm 2 (60% vs 12%, P<0.01) |
| GOG 258 (PMID: 31189035) Enrollment: 6/20/2009-7/28/2014 | - Stage III/IV EC or stage I/II clear cell/serous EC with positive washings  
- Complete surgical staging, pelvic/paraortic LN biopsy or dissection was optional  
- No single site of residual tumor > 2 cm | Arm 1: Carboplatin (50 mg/m², 2 cycles) with EBRT followed by carboplatin (AUC 5-6) + paclitaxel (175 mg/m²); n=370  
Arm 2: Carboplatin (AUC 6) + paclitaxel (175 mg/m²); n=360 | Primary - ORR  
Secondary - PFS  
Secondary - Toxicity  
Secondary - HRQoL | - No difference in OS (HR, 0.90; 95% CI, 0.74-1.10)  
Arm 1 had decreased vaginal recurrences (HR, 0.36; 95% CI, 0.16-0.82)  
Arm 1 had decreased pelvic/paraortic LN recurrences (HR, 0.43; 95% CI, 0.28-0.66)  
Arm 1 had increased distant recurrences (HR, 1.36; 95% CI, 1.01-1.86)  
- Similar incidence of grade 3 or higher toxicity |
| GOG 261 (PMID: 35007153) Enrollment: 8/17/2009-3/24/2014 | - Any stage or recurrent uterine or ovarian carcinomas  
- Prior radiation therapy allowed but must have been discontinued | Arm 1: Paclitaxel (175 mg/m²) + carboplatin (AUC 6); n=224 (uterine)  
Arm 2: Ifosfamide (7.6 g/m²); mesna + paclitaxel (135 mg/m²) + filgrastim; n=204 (uterine) | Primary - OS  
Secondary - PFS  
Secondary - AEIs  
Secondary - QoL | - Arm 1 was not inferior to Arm 2  
Arm 1 had improved OS (HR, 0.87; 95% CI, 0.70-1.08)  
Arm 1 had improved PFS (HR, 0.74; 95% CI, 0.58-0.93)  
Arm 1 had more hematologic toxicities  
Arm 2 had more confusion and genitourinary hemorrhage |
- No prior chemotherapy or radiotherapy  
- No single site of residual tumor > 2 cm | Arm 1: Carboplatin (50 mg/m²) + doxorubicin (45 mg/m²) + tumor directed radiotherapy; n=288  
Arm 2: Carboplatin (50 mg/m²) + doxorubicin (45 mg/m²) + paclitaxel (160 mg/m²) + tumor directed radiotherapy; n=298 | Primary - OS  
Secondary - PFS  
Secondary - RT  
Secondary - AEs  
Secondary - Safety | - Arm 2 did not have improved PFS (P=.91, one-tail)  
Arm 2 was associated with increased toxicity |
| GOG 66P (PMID: 29804638) Enrollment: 9/14/2009-1/9/2012 | - Stage III/IV or recurrent EC  
- No prior cytotoxic chemotherapy | Arm 1: Paclitaxel (175 mg/m²) + carboplatin (AUC 6); n=215  
Arm 2: Paclitaxel (175 mg/m²); n=111  
Arm 3: Paclitaxel (175 mg/m²) + bevacizumab (15 mg/kg); n=116  
Arm 4: Paclitaxel (175 mg/m²) + carboplatin (AUC 5); temsirolimus (25 mg); n=115  
Arm 5: Paclitaxel (175 mg/m²); n=130  
Arm 6: Paclitaxel (175 mg/m²) + bevacizumab (15 mg/kg); n=118 | Primary - OS  
Secondary - PFS  
Secondary - ORR  
Secondary - AEs  
Secondary - Safety | - PFS was not significantly increased in any arm compared with historical controls  
- An unplanned analysis of PFS stratified by stage/disease status suggested a benefit for Arm 1 compared with historical controls (HR, 0.75; 95% CI, 0.58-0.95)  
- ORR was not significantly increased in any arm compared with historical controls |
**Table 1. Key Clinical Trials Assessing Systemic Therapy for Advanced/Recurrent Endometrial Cancer (cont.)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Key Inclusion Criteria</th>
<th>Treatment Arms</th>
<th>Endpoint(s)</th>
<th>Key Findings/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITO Group End-2 trial (PMID: 31678780)</td>
<td>- Stage III/IV or recurrent EC with measurable disease (RECIST 1.1)</td>
<td>Arm 1: Carboplatin (AUC 5) + bevacizumab (15 mg/kg); n=54</td>
<td>Primary - PFS</td>
<td>- No difference in PFS (HR, 0.84; 95% CI, 0.5–1.3)</td>
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<td>- Excluded carcinosarcoma</td>
<td>Arm 2: Carboplatin (AUC 5) + pembrolizumab (200 mg); n=54</td>
<td>Secondary - OS</td>
<td>- No difference in OS (HR, 0.71; 95% CI, 0.31–1.36)</td>
</tr>
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<td></td>
<td>- One prior platinum allowed if last treatment &gt;6 months from study initiation</td>
<td>Arm 2: Physician’s choice of doxorubicin (60 mg/m²) or paclitaxel (80 mg/m²); n=416</td>
<td>Secondary - ORR</td>
<td>- ORR 53% in Arm 1 and 74% in Arm 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Arm 2 had increased cardiovascular toxicity and treatment discontinuation</td>
</tr>
<tr>
<td>KEYNOTE 775 (PMID: 35045221)</td>
<td>- Advanced, recurrent, or metastatic EC with measurable disease (RECIST 1.1)</td>
<td>Arm 1: Lenvatinib (20 mg) + pembrolizumab (200 mg); n=411</td>
<td>Primary - PFS</td>
<td>- Arm 1 had improved PFS (HR, 0.56; 95% CI, 0.47–0.66)</td>
</tr>
<tr>
<td></td>
<td>- Excluded carcinosarcoma and sarcoma</td>
<td>Arm 2: Carboplatin (AUC 5) + paclitaxel (175 mg/m²); n=54</td>
<td>Secondary - OS</td>
<td>- Arm 1 had improved OS (HR, 0.62; 95% CI, 0.51–0.75)</td>
</tr>
<tr>
<td></td>
<td>- At least one prior platinum therapy</td>
<td></td>
<td>Secondary - ORR</td>
<td>- Arm 1 had more grade 3 adverse events vs Arm 2 (88.9% vs 72.7%)</td>
</tr>
<tr>
<td></td>
<td>- Two lines prior platinum allowed if one line was given in neoadjuvant setting</td>
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</tr>
<tr>
<td></td>
<td>- No prior PD-1 or VEGF therapies</td>
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</tbody>
</table>

Abbreviations: AE, adverse event; AUC, area under the curve; EBRT, external-beam pelvic radiotherapy; EC, endometrial carcinoma; FFS, failure-free survival; HR, hazard ratio; HRQoL, health-related quality of life; LN, lymph node; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PMID, PubMed ID number; QoL, quality of life.

*Comparative patients on the TC arm of trial GOG 209 were used as historical controls.

**treatment.**

As a result, TC + trastuzumab is now a recommended regimen for HER2-overexpressed EC. In a phase II clinical trial assessing the efficacy and safety of the antibody–drug conjugate (ADC) trastuzumab deruxtecan in HER2-expressing, unresectable, chemotherapy-refractory uterine carcinosarcoma demonstrated a median PFS in IHC HER2 2+ /3+ disease of 6.2 months (95% CI, 4.0–8.8). Trastuzumab deruxtecan is also being investigated in an ongoing phase II study in HER2-expressing endometrial cancer (NCT04482309). Other ADCs currently being investigated in phase I/II studies include HER2-targetting DB-1303 (NCT05150691), folate receptor alpha (FRα)-targeting farletuzumab ecteribulin (NCT04300556), and mirvetuximab soravtansine (IMGN853) monotherapy (NCT03832361) and in combination with pembrolizumab (NCT03835819) (Table 2).

**MMRd/Microsatellite Instability–High/Tumor Mutational Burden–High**

Approximately 17% to 33% of advanced and recurrent ECs are mismatch repair–deficient/microsatellite instability–high (MMRd/MSI-H). In MMRd, MSI-H, and tumor mutational burden–high (TMB-H; >10 mutations/megabase) recurrent EC, the recommended 2L systemic therapy is the anti–PD-1 monoclonal antibody pembrolizumab. Other recommended PD-1/PD-L1 agents for the treatment of MMRd/MSI-H EC include dostarlimab, nivolumab, and avelumab.

FDA approval of pembrolizumab for treatment of MMRd/MSI-H EC was largely based on the findings of the phase II KEYNOTE-158 study in patients with advanced MMRd/MSI-H EC, which demonstrated an ORR of 48% and median PFS of 13 months. In 2021, dostarlimab was granted accelerated FDA approval for MMRd/MSI-H EC based on the results of the phase I/II GARNET study, which demonstrated an ORR of 42% and median PFS of 8.1 months in this setting. The PD-1 inhibitor nivolumab has not yet been granted FDA approval but can be used in MMRd/MSI-H EC based on the results of the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial, which showed a 12-month PFS rate of 46.2% in patients with MMRd EC of endometrioid and carcinosarcoma histologies.

MSI is a clear biomarker for response to immune checkpoint inhibitors (ICIs) in EC. However, the underlying mechanisms leading to MSI vary and include germ-line (Lynch syndrome) and somatic (Lynch-like) MMR gene alterations and sporadic alterations associated with MLH1 methylation. The effect of the underlying mechanism for MSI on immune checkpoint response is unclear. In a phase II study, pembrolizumab was evaluated in recurrent Lynch, Lynch-like, and sporadic MLH1-methylated EC, demonstrating 3-year PFS and OS rates of 100% in Lynch/Lynch-like patients versus 30% and 43%, respectively, in sporadic MLH1-methylated EC.

In the sporadic MLH1-methylated group, mechanism of resistance to PD-L1 agents was associated with acquired loss of beta-2 microglobulin and JAK3, suggesting a lack of surface HLA-class I expression and defective response to induction with type I and II interferons. Higher TMB and greater infiltration of CD68+ macrophages in EC have been proposed as potential mechanisms of...
Table 2. Active/Ongoing Trials for Advanced/Recurrent Endometrial Cancer

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov Identifier)</th>
<th>Study Start Date</th>
<th>Recruitment Status</th>
<th>Treatment Arms</th>
<th>Experimental Maintenance Therapy</th>
<th>Molecular Assessment</th>
<th>Estimated Enrollment</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-3475-C93/KEYNOTE-C93/GOG-3064/ENGOT-en15 (NCT015173987)</td>
<td>2/3/2022</td>
<td>Recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=350 (MMRd only)</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>MK-3475-B21/KEYNOTE-B21/ENGOT-en11/GOG-3053 (NCT04634877)</td>
<td>1/10/2021</td>
<td>Recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=990</td>
<td>DFS, OS</td>
</tr>
<tr>
<td>DUO-E (NCT04269200)</td>
<td>5/21/2020</td>
<td>Recruiting</td>
<td>Comparator: Arm A: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=699</td>
<td>PFS</td>
</tr>
<tr>
<td>NRG-GY018 (NCT03914612)</td>
<td>7/16/2019</td>
<td>Recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=590 (MMRd)</td>
<td>N=220 (MMRd)</td>
</tr>
<tr>
<td>RUBY (NCT03981796)</td>
<td>7/18/2019</td>
<td>Active, not recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=785</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>ENGOT-EN9/LEAP-001 (NCT03884101)</td>
<td>4/11/2019</td>
<td>Active, not recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=875</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>AtTEnd (NCT0363184)</td>
<td>10/2/2018</td>
<td>Active, not recruiting</td>
<td>Comparator: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab + olaparib</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=550</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>NRG-GY026 (NCT05256225)</td>
<td>8/12/2022</td>
<td>Recruiting</td>
<td>Comparator: Arm I: Carboptin + paclitaxel + placebo; Experimental: Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=525 (HER2+ serous carcinoma or carcinosarcoma only)</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>XPORT-EC (NCT05611931)</td>
<td>11/1/2022</td>
<td>Recruiting</td>
<td>Completed a single line of platinum-based therapy</td>
<td>Pembrolizumab</td>
<td>MMRd/MSI</td>
<td>N=220</td>
<td>PFS</td>
</tr>
<tr>
<td>DESTINY-PanTumor02 (NCT04482309)</td>
<td>6/16/2023</td>
<td>Active, not recruiting</td>
<td>Trastuzumab deruxtecan</td>
<td>HER2</td>
<td>N=268</td>
<td>ORR</td>
<td></td>
</tr>
<tr>
<td>IMGN853 (NCT03832361)</td>
<td>7/15/2020</td>
<td>Recruiting</td>
<td>Mirvetuximab soravtansine</td>
<td>FRα</td>
<td>N=50</td>
<td>ORR</td>
<td></td>
</tr>
<tr>
<td>18-602 (NCT03635819)</td>
<td>1/2/2020</td>
<td>Recruiting</td>
<td>Mirvetuximab soravtansine + pembrolizumab</td>
<td>FRα and MMRp</td>
<td>N=35</td>
<td>ORR, PFS</td>
<td></td>
</tr>
<tr>
<td>18-322 (NCT032912572)</td>
<td>11/14/2016</td>
<td>Recruiting</td>
<td>Avelumab</td>
<td>MSI and/or POLE</td>
<td>N=105</td>
<td>ORR, PFS</td>
<td></td>
</tr>
<tr>
<td>18-301 (NCT03075893)</td>
<td>12/24/2018</td>
<td>Recruiting</td>
<td>Letrozole + abemaciclib</td>
<td>ER-positive</td>
<td>N=40</td>
<td>ORR, PFS</td>
<td></td>
</tr>
<tr>
<td>INCAGN02385 (NCT04463771)</td>
<td>1/26/2021</td>
<td>Recruiting</td>
<td>Avelumab</td>
<td>MSI, POLE, PD-L1, FGFR1/2/3</td>
<td>N=300</td>
<td>ORR</td>
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</table>

(continued on next page)
response to immunotherapy.36,37 Although predictive of immune checkpoint response in other cancers, PD-L1 expression is not predictive of response in EC.38 The anti–PD-L1 agents avelumab and durvalumab have also shown promise as monotherapy in phase II studies in advanced MMRd/MSI-H EC, with ORRs of 27% and 47%, shown promise as monotherapy in phase II studies in advanced MMRd/MSI-H EC, with ORRs of 27% and 47%, respectively.39,40

The benefit of incorporating immunotherapy earlier in the therapeutic course, as 1L treatment, is under investigation. There are several ongoing phase III trials of cytotoxic chemotherapy alone or in combination with PARP inhibitors, ICIs, and/or VEGF tyrosine kinase inhibitors (TKIs) in 1L therapy of EC, with pending results (Table 2). Whether combination immune checkpoint blockade is more effective than ICI monotherapy in MMRd/MSI-H EC is of great interest. The phase II NRG-GY025 (NCT05112601) trial of nivolumab versus nivolumab/ipilimumab in recurrent MMRd EC aims to address this question.

Table 2. Active/Ongoing Trials for Advanced/Recurrent Endometrial Cancer (cont.)

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov Identifier)</th>
<th>Study Start Date</th>
<th>Recruitment Status</th>
<th>Treatment Arms</th>
<th>Experimental Maintenance Therapy</th>
<th>Molecular Assessment</th>
<th>Estimated Enrollment</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II (cont.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-447 (NCT05156248)</td>
<td>1/27/2022</td>
<td>Recruiting</td>
<td>Pembrolizumab + olaparib</td>
<td>p53</td>
<td>N=25</td>
<td>ORR</td>
<td></td>
</tr>
<tr>
<td>NRG-GY025 (NCT05112601)</td>
<td>2/7/2022</td>
<td>Recruiting</td>
<td>- Experimental Arm I: ipilimumab + nivolumab - Active Comparator Arm II: nivolumab</td>
<td>MMRd/MSI</td>
<td>N=12</td>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>NU 18G07 (NCT04049227)</td>
<td>8/12/2019</td>
<td>Recruiting</td>
<td>Abemaciclib + letrozole</td>
<td>MMR, PTEN, cyclin D1, p16, pRB</td>
<td>N=27</td>
<td>Ki-67 expression</td>
<td></td>
</tr>
<tr>
<td>ZN-c3-004 (NCT04841108)</td>
<td>6/1/2021</td>
<td>Recruiting</td>
<td>ZN-c3</td>
<td>N=110</td>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I/II</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MORAb-202 (NCT04300556)</td>
<td>8/6/2020</td>
<td>Recruiting</td>
<td>Farletuzumab ecterubin</td>
<td>FRα</td>
<td>N=55</td>
<td>Dose escalation/confirmation</td>
<td></td>
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<tr>
<td>DB-1303 (NCT05150691)</td>
<td>1/31/2022</td>
<td>Recruiting</td>
<td>DB-1303</td>
<td>HER2</td>
<td>N=360</td>
<td>Dose escalation/confirmation</td>
<td></td>
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<tr>
<td>ZN-c3-001 (NCT04158336)</td>
<td>11/1/2019</td>
<td>Recruiting</td>
<td>ZN-c3</td>
<td>N=110</td>
<td>Safety/Tolerability, ORR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; EBRT, external-beam radiation therapy; ER, estrogen receptor; FRα, folate receptor alpha; MMR, mismatch repair; MMRd, mismatch repair–deficient; MMRp, mismatch repair–proficient; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VBT, vaginal brachytherapy; wt, wild-type.

The standard of care radiotherapy regimen may include, at the discretion of the investigator, EBRT at 4,500 cGy with variable dose frequency, with or without cisplatin, 50 mg/m² intravenously on days 1 and 29 of EBRT, and/or VBT.

MMR-Proficient
Most patients with EC have MMR-proficient (MMRp) tumors, which have limited response to single-agent ICIs (ORR, 3%–14%).33,38–40 However, recent studies have established the combination of the multikinase inhibitor lenvatinib + pembrolizumab as an effective 2L treatment option. Findings from the phase Ib/II Study 111/KEYNOTE-146 trial in patients with advanced EC demonstrated an ORR at week 24 (ORRwk24) of 38.0%. The ORRwk24 was 63.6% for MSI-H tumors (n=11) and 36.2% for microsatellite-stable tumors (n=94). Regardless of MSI status, the median duration of response was 21.2 months, median PFS was 7.4 months, and median OS was 16.7 months in previously treated patients. Responses were seen regardless of PD-L1 expression or histology.41 These results led to the FDA accelerated approval of lenvatinib + pembrolizumab for advanced EC that is not MSI-H/MMRd and has progressed following prior systemic therapy.

In the confirmatory phase III Study 309/KEYNOTE-775 trial, patients with recurrent EC with measurable disease and one prior platinum-based chemotherapy were enrolled regardless of MMR status. Patients were stratified based on MMR status and randomized 1:1 to lenvatinib + pembrolizumab or investigator’s choice of doxorubicin or paclitaxel. The median PFS was longer with lenvatinib + pembrolizumab compared with chemotherapy (MMRp population: 6.6 vs 3.8 months; P<.001; overall: 7.2 vs 3.8 months; P<.001). The median OS was also longer (MMRp population: 17.4 vs 12.0 months; P<.001; overall: 18.3 vs 11.4 months; P<.001).
PFS and OS analyses in all subtypes, including MMR status, histology, and prior lines of therapy, favored lenvatinib + pembrolizumab; no substantial differences in health-related quality of life scores were appreciated.21

Endocrine Therapy
In hormone (estrogen or progesterone) receptor–positive EC, endocrine therapy is a viable treatment option for advanced or recurrent EC. In a translational study of advanced EC tissues from study GOG 119, 40% and 45% of the 45 evaluable tumors were estrogen receptor (ER)–positive and progesterone receptor–positive, respectively.42 Estrogen and progesterone receptors are typically evaluated with IHC, although timing of when this should be performed is not well established. Current NCCN Guidelines recommend hormone receptor testing for stage III, stage IV, or recurrent endometrioid carcinoma.22

Endocrine therapy is generally well tolerated and can be considered in patients with minimal symptoms and low-grade or more indolent disease. A systematic review from 2007 reported that up to 30% of advanced or recurrent ECs respond to endocrine therapy, with the highest response rates in low-grade EC (up to 56% in grade 1/2 endometrioid carcinoma).43 In the phase II GOG 119 study in advanced EC, alternating tamoxifen and megestrol acetate demonstrated an ORR of 27%, median PFS of 2.7 months, and OS of 14.0 months.44 Other endocrine therapies include progestational agents alone (medroxyprogesterone acetate or megestrol acetate), aromatase inhibitors, tamoxifen alone, or fulvestrant, a selective ER degrader.22,45

Anti-VEGF Therapy
Beyond the combination of bevacizumab with cytotoxic chemotherapy, anti-VEGF therapies have been studied as monotherapy and in combination with other agents in advanced EC. In GOG 229E, bevacizumab monotherapy in previously treated EC was associated with an ORR of 13.5%, and 40.4% of patients were progression-free at 6 months.46 Lenvatinib monotherapy in a phase II trial in the 2L setting was associated with an ORR of 13.3% and median PFS of 5.6 months.47

The NRG-GY012 protocol compared the efficacy of olaparib (PARP inhibitor) monotherapy, cediranib (VEGF receptor TKI) monotherapy, and combination olaparib/cediranib in patients with advanced EC who had received at least 1 prior line of platinum-based chemotherapy and no more than 2 prior lines of chemotherapy; median PFS was 2.0, 3.8, and 5.5 months, respectively.48 Findings from a randomized phase II trial in recurrent EC demonstrated median PFS for combination nivolumab/cabozantinib (a TKI) and single-agent nivolumab of 5.3 and 1.9 months, respectively; ORRs were 25% and 16.7%, respectively.49

Cell Signaling–Targeted Therapy
Cyclin-dependent kinase inhibitors (CDKis) such as palbociclib and abemaciclib function by selectively inhibiting CDK4 and CDK6, which are crucial for the cell cycle G1/S phase transition.50 The randomized, phase II PALEO trial of letrozole with/without palbociclib demonstrated improved PFS with the combination (8.3 vs 3.0 months; HR, 0.56; P=.04).51 Data from a phase II trial in patients with ER-positive recurrent EC demonstrated an ORR of 30% and median PFS of 9.1 months with abemaciclib + letrozole at a median follow-up of 12.5 months.52 These studies suggest a role for CDK4/6 inhibitors in subsets of advanced ECs, warranting further investigation, which is the subject of ongoing trials (Table 2).

Wee1 Kinase Inhibitors
Wee1 kinase regulates cell cycle checkpoints of G2/M and S phase. TP53-mutant cancers such as serous EC are often deregulated at the G1/S phase checkpoint, allowing for early S phase entry, rendering them more vulnerable to Wee1 inhibition. Adavosertib is a highly selective inhibitor of Wee1 kinase that, in a phase II study in recurrent EC, resulted in an ORR of 30%, median PFS of 6.1 months, and median duration of response of 9 months.53 Additional Wee1 inhibitors are being evaluated in ongoing studies.

XPO1 Inhibition
Selinexor is an orally available potent inhibitor of XPO1 resulting in retention of tumor suppressor proteins in the nucleus. A phase I open-label study of selinexor with TC in advanced ovarian cancer or EC demonstrated good safety and tolerability.54 A subsequent phase II study of selinexor monotherapy in advanced EC showed a 35% disease control rate.55 Results of the randomized phase III SIENDO trial of maintenance selinexor versus placebo following response to TC chemotherapy in EC showed the greatest therapeutic benefit in p53 wild-type EC, with a 10-month PFS improvement over placebo.56 The recently opened phase III XPORT-EC trial (NCT05611931) will evaluate selinexor as maintenance therapy after systemic therapy for p53 wild-type advanced or recurrent EC (Table 2).

Unanswered Questions and Future Directions
Current NCCN Guidelines recommend universal testing for MMR proteins in EC to assess for genetic predisposition to Lynch syndrome and encourage molecular subtyping when available to inform future treatment decisions.22 Although molecular analysis for all ECs is resource-intensive, molecular subtyping is considered more predictive of outcomes than other risk stratification criteria in patients with early-stage disease and is anticipated to
play an increasing role in adjuvant therapeutic decision-making.57–99

In advanced and recurrent disease, molecular analysis is essential in informing optimal treatment options, delineating predictive biomarkers, and identifying patients eligible for clinical trials investigating emerging therapeutic options based on molecular drivers of EC subtypes. The refinement of MSI-H/MMRd predictive subgroups (eg, assessment of mutational thresholds and signatures) may identify patients whose disease will not respond or will rapidly progress after an initial response to single-agent ICIs and who could benefit from novel combination strategies. Clinical studies among larger cohorts of patients with Lynch/Lynch-like versus those with sporadic MSI-H disease treated with ICIs are warranted. The potential for response to immunotherapy after prior immunotherapy also warrants investigation, as does delineation of mechanisms of response to ICIs in the minority of responding MMRp ECs.

Conclusions
Understanding of EC biology has been greatly expanded by modern molecular characterization, which has defined molecularly and clinically distinct EC subtypes. Given the heterogeneity of this malignancy, patients with advanced disease should undergo molecular profiling to optimize treatment strategies and inform clinical trial eligibility.

The therapeutic ceiling with traditional chemotherapy has been reached, and we must look to relevant biologic targets to individualize treatment. Although surgical resection or radiation therapy may be appropriate for localized disease, advanced EC requires systemic therapy. Ongoing phase III studies evaluating immunotherapeutic approaches will likely change the standard of care for 1L management of EC, which will necessitate refinement of 2L and beyond management. Although the incidence and number of deaths from EC has increased worldwide, we must advocate for research to improve the quality of life and outcomes for patients with EC.

References