Endometrial carcinosarcoma

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HIGHLIGHTS
⇒ Endometrial carcinosarcoma is a high-grade endometrial carcinoma with secondary sarcomatous de-differentiation.
⇒ Approximately 70% of cases of endometrial carcinosarcoma are classified as p53 abnormal, being characterized by an aggressive nature.
⇒ Endometrial carcinosarcoma with endometrioid component are more likely to exhibit ultra- and hypermutator (POLE and MSI-H) subtypes.
⇒ MSI-H/dMMR (accounting for 7% in endometrial carcinosarcoma) represents an emerging biomarker, suggesting the efficacy of immunotherapy, even in endometrial carcinosarcoma.
⇒ Novel molecular-targeted therapies are emerging that could potentially improve care.

ABSTRACT
Endometrial carcinosarcoma is a rare and aggressive high-grade endometrial carcinoma with secondary sarcomatous trans-differentiation (conversion theory). The clinical presentation and diagnostic work-up roughly align with those of the more common endometrioid counterpart, although endometrial carcinosarcoma is more frequently diagnosed at an advanced stage. Endometrial carcinosarcoma is not a single entity but encompasses different histological subtypes, depending on the type of carcinomatous and sarcomatous elements. The majority of endometrial carcinosarcomas are characterized by p53 abnormalities. The proportion of POLE and microsatellite instability-high (MSI-H) is directly related to the epithelial component, being approximately 25% and 3% in endometrioid and non-endometrioid components. The management of non-metastatic disease is based on a multimodal approach with optimal surgery followed by (concomitant or sequential) chemotherapy and radiotherapy, even for early stages. Palliative chemotherapy is recommended in the metastatic or recurrent setting, with carboplatin/paclitaxel doublet being the first-line regimen. Although the introduction of immunotherapy plus/minus a tyrosine kinase inhibitor shifted the paradigm of treatment of patients with recurrent endometrial cancer, patients with endometrial carcinosarcoma were excluded from most studies evaluating single-agent immunotherapy or the combination. However, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the use of pembrolizumab and lenvatinib in endometrial cancer (all histotypes) after progression on chemotherapy and single-agent immunotherapy in MSI-H cancers. In the era of precision medicine, emerging knowledge on molecular endometrial carcinosarcoma is opening new promising therapeutic options for more personalized treatment. The present review outlines state-of-the-art knowledge and future directions for patients with endometrial carcinosarcoma.

INTRODUCTION
Endometrial carcinosarcoma is a rare and aggressive high-grade endometrial carcinoma, accounting for about 5% of all uterine malignancies and nearly 20% of non-endometrioid endometrial cancer. 12 Although non-endometrioid histotypes account for 10–20% of all endometrial cancers, they are responsible for more than 40% of endometrial cancer-related deaths. In particular, endometrial carcinosarcoma is responsible for 15% of deaths from uterine malignancies. 12

Endometrial carcinosarcoma is an intriguing entity as it is a biphasic tumor characterized by coexisting carcinomatous (epithelial) and sarcomatous (mesenchymal) elements. 3 It is diagnosed at an advanced stage more often than other endometrial cancers. The stage at diagnosis follows a bimodal distribution: 40–50% of cases are early stage (International Federation of Gynecology and Obstetrics (FIGO) I–II) and 50–60% are advanced (FIGO III–IV). Up to 30–40% of patients present with lymph node metastases at diagnosis, and 10% have distant metastatic spread, especially in the lungs. 2–5 Over 60% of patients with apparently early-stage disease at the time of initial diagnosis are upstaged following comprehensive surgical evaluation due to occult metastatic spread. Despite the multimodal treatment strategy (surgery, platinum-based chemotherapy, radiotherapy),
Consensus statement

Pathological characteristics of endometrial carcinosarcoma. (1) Gross appearance of uterine carcinosarcoma as polypoid lesion filling the uterine cavity. (2) Carcinomatous and sarcomatous components (both high grade) are juxtaposed, like a broken puzzle (hematoxylin and eosin (H&E), 10x). (3) High-grade serous carcinoma and rhabdomyosarcoma admixed (H&E, 10x), best highlighted with an immunohistochemical stain for myogenin (inset). (4) Rhabdomyosarcoma is the most frequent heterologous component of carcinosarcoma (H&E, 10x) and sometimes predominates.

Figures 1 and 2

Prognosis remains poor. The median overall survival is less than 2 years, and the 5-year overall survival rate is less than 30% (about 50% and 20% in early and advanced stages, respectively). Even patients with early-stage disease have a 5-year recurrence rate of 45% and 5-year related mortality of 50%.2–5

The increasing incidence and poor outcomes of endometrial carcinosarcoma underscore an unmet need for novel therapeutic strategies to treat these challenging patients. Prior to the current millennium endometrial carcinosarcoma was considered a sarcoma, and it was not included in trials on endometrial cancer. Moreover, due to the rarity of endometrial carcinosarcoma, epidemiological studies and high-quality evidence are scarce and future international collaborative projects in this field are warranted. This comprehensive review summarizes the state-of-the-art knowledge on the clinical features of, and treatment options for endometrial carcinosarcoma, with a focus on the most recent molecular updates and promising therapeutic targets on the horizon.

Epidemiology and Clinical Characteristics

Endometrial carcinosarcoma is a rare gynecologic cancer, but its incidence has been gradually increasing over the past two decades, with an annual percentage growth rate of nearly 2%.5–7 Accordingly, the proportion of endometrial carcinosarcomas within all endometrial carcinomas has also grown significantly from 1.7% to 5.6%.5–7 Since endometrial carcinosarcoma occurs, almost exclusively, in post-menopausal women (usually over 60–65 years of age), the aging global population may in part explain this increase in incidence, together with a raised awareness of endometrial carcinosarcoma by pathologists. Endometrial carcinosarcoma typically affects the elderly with a peak incidence between 70 and 79 years of age.5–7 However, in recent years the age of affected patients has decreased, with patients aged 60–69 years demonstrating the largest change in incidence rate (annual increase: 2.7%).5–7 The average age of patients with endometrial carcinosarcoma at diagnosis is currently 67 years. Apart from age, other risk factors for endometrial carcinosarcoma include black race, prior pelvic radiotherapy (eg, previous radiotherapy for cervical or rectal cancer), and, for endometrioid endometrial cancers, those factors leading to hyperestrogenism, such as obesity, nulliparity, exposure to exogenous estrogen and tamoxifen.5–7

The clinical presentation and diagnosis of endometrial carcinosarcoma are non-specific and typically similar to those of most endometrial carcinomas.27 In clinical practice, it is difficult to distinguish endometrial carcinosarcoma from other uterine neoplasms merely based on clinical features. Typically, symptoms of endometrial carcinosarcomas include persistent or post-menopausal abnormal uterine bleeding, leukorrhea, and/or abdominal pain associated with a rapidly growing fleshy uterine mass (often bulging into the vagina). Other symptoms, such as dysuria, dyspareunia, and bone pain are rarer.4–6 Endometrial biopsy or biopsy of a protruding polypoid mass is a key element for the diagnosis of endometrial carcinosarcoma. It is important to highlight that in a few cases endometrial sampling might reveal only one of the two components (carcinomatous and sarcomatous), and the final diagnosis is obtained only after hysterectomy. Transvaginal ultrasound, pelvic MRI, (thoracic and abdominopelvic) CT, and/or positron emission tomography are beneficial as imaging techniques for diagnostic and staging purposes. The basal level of serum CA125 correlates with an advanced stage and poor prognosis, and it may be useful to guide not so much the diagnosis but the follow-up.4,8 The metastasis pattern of endometrial carcinosarcomas follows the lymphatic and intraperitoneal routes as in epithelial tumors more than the typical hematogenous dissemination of sarcomas, and metastases are usually of epithelial origin. Endometrial carcinosarcomas are characterized by aggressive behavior with a 5-year survival rate of 25–30% (stage I: ~55%; stage II: ~37%; stage III: ~25%; stage IV: ~10%), which has not changed much over the past three decades.4–6 The prognosis correlates strongly with the histologic subtype, tumor size (≥5 cm in ~60%), FIGO stage, lymphovascular space involvement (~60%), post-surgical residual disease, malignant peritoneal cytology, and the molecular signature as well as treatment. These survival statistics suggest the need for further research and approaches to the management of endometrial carcinosarcomas.2–5–7

Pathological Features: The Conversion Theory

The pathological classification of endometrial carcinosarcoma has changed over time. Historically, endometrial carcinosarcoma was regarded as a malignant mixed Müllerian tumor and the most common and aggressive type of uterine sarcomas.10 Presently, however, endometrial carcinosarcoma is widely recognized as an epithelial de-differentiated/metaplastic subset of endometrial cancers and it is staged and managed accordingly, as a high-grade endometrial carcinoma.10 Therefore, pathologists should accurately identify the presence of an epithelial component before making the
final diagnosis of endometrial carcinosarcoma. Endometrial carcinosarcoma is a biphasic malignant tumor consisting of endometrial adenocarcinomas admixed with a mesenchymal component.10

The epithelial part is the most dominant element and is typically a high-grade (serous, endometrioid, clear cell, mixed, or undifferentiated) histotype, whereas the sarcomatous element can be either homologous (leiomyosarcoma, fibrosarcoma, endometrial stromal sarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma, osteosarcoma), according to whether the mesenchymal component resembles or not the uterine tissues. Heterologous differentiation is seen in about 40% of endometrial carcinosarcoma and is associated with poorer survival compared with homologous alterations. Moreover, sarcomatous dominance (ie, >50%), is seen in 40% of cases of endometrial carcinosarcoma and is most probably associated with heterologous differentiation and decreased survival. The combination of high-grade carcinoma, and heterologous sarcomatous differentiation and dominance is associated with the worst prognosis.10

Figure 1 shows the pathological characteristics of endometrial carcinosarcoma. Interestingly, few studies reported a higher 5-year overall survival in patients with endometrioid endometrial carcinosarcoma than in those without endometrioid (serous, clear cell) subtypes (50–55% vs 30–35%, respectively).5–8 10 Moreover, it is important to point out that the epithelial component is more commonly observed at distant metastatic sites; the sarcomatous component is associated with local tumor extension.10

The epithelial and sarcomatous components were initially thought to develop as a combination of cellular masses secondary to an early divergence from a common precursor cancer stem cell (combination theory) or as a result of the collision between independent but adjacent epithelial and mesenchymal progenitors (collision theory).8 10 Recently, several molecular and clonality studies have suggested that the endometrial carcinosarcoma arises from a single malignant epithelial clone (carcinoma lineage) that subsequently undergoes sarcomatous trans-differentiation, through a process of epithelial-to-mesenchymal transition (conversion theory).10–12 The monoclonal origin of endometrial carcinosarcoma is supported on genetic, molecular, and clinical grounds.10–13

The epithelial and mesenchymal elements share common genetic mutational profiles, and stromal cells often show positive immunohistochemical staining for epithelial markers.10–13

MOLECULAR LANDSCAPE

The majority of endometrial carcinomas share molecular and genomic similarities with high-grade serous ovarian carcinoma and serous endometrial carcinoma, while only a minority resembles the endometrioid counterpart.3 4 10 12–15 In particular, TP53 (60–97%), FBXW (10–44%), PPP2R1A (11–30%), HER2 (9–18%) serous-like mutations are common, whereas endometrioid-like mutations such as ARID1A (10–25%), KRAS (8–15%), PTEG (10–50%), and PIK3CA (20–40%) are less frequent.3 4 10 12 The mutational rates vary across the studies depending on the different endometrial carcinosarcoma subtypes included (eg, low-grade vs high-grade carcinomas). Endometrial carcinosarcoma is not a single entity but encompasses different histological subtypes, depending on the type of carcinomatous and sarcomatous elements.10

Thanks to the analyses of The Cancer Genome Atlas (TCGA) Research Network and the Proactive Molecular risk classifier for Endometrial cancer (ProMisE) classification, four novel molecular endometrial cancer subgroups were identified.16 17 The new classification includes: POLE/ultramutated (POLE mutated), microsatellite-instable/hypermutated (MSI-H), copy-number-high/TP53-abnormal (P53-abn), and copy-number-low/TP53-wild-type or non-specific molecular profile endometrial cancers. This classification overcomes the limitation of the dualistic Bokhman model, representing an excellent tool for prognostication and treatment recommendation.10 14 15 However, we have to point out that no prospective randomized studies are validated the predictive value of adoption of the genomic/molecular profiling (with the except of MIS-H, being an agnostic marker supporting the adoption of immunotherapy).18 Validation studies are still ongoing.14 15 19

Interestingly, the TCGA study included only the endometrioid and serous histotypes while little is known regarding less common endometrial cancer histotypes, such as endometrial carcinosarcoma.16 Recently, a meta-analysis of four studies (231 patients) reported the pooled prevalence of the TCGA groups among endometrial carcinosarcomas: 5.3% POLE, 7.3% MSI-H, 73.9% p53-abnormal, and 13.5% non-specific molecular profile.20–23 The vast majority of endometrial carcinosarcoma (73.9%) are classified within the serous-like, p53-abn risk group (which accounts for 5–15% of endometrial cancers and resembles type II endometrial cancers). As aforementioned, those tumors are characterized by advanced stage at diagnosis, late-onset, mutant-like/abnormal p53 immunohistochemical staining, low mutational burden (<10 mutations per megabase), aggressive behavior, high risk of early relapse, and a dismal prognosis.

Another recent meta-analysis of five studies (263 patients) assessed the prognostic value of the TCGA molecular classification in endometrial carcinosarcoma. POLE mutated endometrial carcinosarcoma showed an excellent prognosis similar to that of POLE mutated endometrioid endometrial cancers, supporting their inclusion in the same low-risk category for treatment purposes in the current European Society of Gynecological Oncology (ESGO), the European SocietY for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines.3 On the other hand, the prognosis of p53-abn and non-specific molecular profile endometrial carcinosarcoma was even worse than that of their endometrioid/serous counterparts, while that of MSI-H/dMMR tumors was unclear and remains to be clarified.4 20–27 Table 1 shows the current evidence regarding the molecular/genomic profiling of endometrial carcinosarcomas.

STANDARD TREATMENT

Due to the rarity of endometrial carcinosarcoma, there is only limited evidence regarding current standard of care, largely from retrospective or non-randomized studies.7 No standard and definitive consensus on the optimal management of endometrial carcinosarcoma exists. Since endometrial carcinosarcoma is now considered a primary endometrial carcinoma, its treatment aligns with that of other non-endometrioid high-grade endometrial cancer, as suggested by the ESGO/ESTRO/ESP and the National Comprehensive Cancer Network (NCCN) guidelines.9 28 A multimodal approach,
Consensus statement

Combining surgery, chemotherapy, and/or radiotherapy is the current mainstay of treatment. Given the absence of solid data, adequate patient counseling should be always offered.

Surgery

Figure 2 outlines the surgical treatment algorithm for endometrial carcinosarcoma. Complete surgical staging is the standard treatment approach for non-metastatic endometrial carcinosarcoma. Standard surgical procedures include hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, peritoneal biopsies, peritoneal cytology, and only for early stages, retroperitoneal staging (eg, systematic (pelvic and para-aortic) lymphadenectomy or sentinel lymph node biopsy). Peritoneal cytology is not mandatory as it is not a cancer staging factor, but it can be useful as a risk factor for tailoring the adjuvant treatment.7 9

Minimally invasive surgery is the preferred surgical approach in apparently early-stage disease and should be undertaken cautiously, avoiding tumor fragmentation and peritoneal dissemination.9 If vaginal extraction risks uterine rupture, other measures should be taken (eg, mini-laparotomy, use of endobag).8 9 In advanced stages (FIGO III–IV), open abdominal cytoreductive surgery should be considered when complete macroscopic resection is feasible, with an acceptable morbidity and quality of life profile.8 9 Retrospective studies suggest that suboptimal debulking does not confer additional survival benefit over chemotherapy alone in endometrial carcinosarcomas, thus thorough patient selection is key, and surgery should be pursued only if complete macroscopic resection can be achieved.9 28 A few small studies have also investigated the potential role of neoadjuvant protocols, such as platinum-based chemotherapy or concurrent chemoradiotherapy, to increase complete resection rates, reporting interesting results warranting prospective large-scale validation.29 30 Ovarian preservation and fertility-sparing surgery are not recommended for endometrial carcinosarcoma.7 9

Infracolic omentectomy and random peritoneal biopsies are considered part of the surgical staging even for apparent stage I endometrial carcinosarcoma, such as in serous and undifferentiated histotypes.8 9 No specific data regarding the role of peritoneal staging in patients with endometrioid and non-endometroid component exists.

Nodal involvement is not uncommon in endometrial carcinosarcoma (pelvic: 20–25%, para-aortic: 15%), especially in cases of deep myometrial invasion (30–50% of cases) where pelvic and para-aortic nodal metastases are observed in 30–60% and 25–30% of cases, respectively.31–33 Only resection of enlarged lymph nodes, but no systematic lymphadenectomy, is recommended for

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**Table 1** Molecular/genomic profiling of endometrial carcinosarcoma

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of patients</th>
<th>POLE mut</th>
<th>MSI-H/dMMR</th>
<th>p53 abnormal</th>
<th>NSMP TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>McConehey et al, 2015</td>
<td>30</td>
<td>1 (3.3%)</td>
<td>1 (3.3%)</td>
<td>23 (76.7%)</td>
<td>5 (16.7%) Not reported</td>
</tr>
<tr>
<td>Cherniack et al, 2017</td>
<td>57</td>
<td>1 (1.8%)</td>
<td>2 (3.5%)</td>
<td>50 (87.7%)</td>
<td>4 (7%) Not reported</td>
</tr>
<tr>
<td>Jones et al, 2017</td>
<td>361</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>68.8%</td>
<td>Not assessed Not reported</td>
</tr>
<tr>
<td>Gotoh et al, 2019</td>
<td>92</td>
<td>10 (10.9%)</td>
<td>24 (26.1%)</td>
<td>49 (53.3%)</td>
<td>9 (9.8%) Not reported</td>
</tr>
<tr>
<td>Saijo et al, 2019</td>
<td>57</td>
<td>Not assessed</td>
<td>6 (10.5%)</td>
<td>34 (59.6%) Not assessable*</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jones et al, 2021</td>
<td>27</td>
<td>Not assessed</td>
<td>12 (44.4%)</td>
<td>11 (40.7%) Not assessable*</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kobayashi et al, 2021</td>
<td>4</td>
<td>0</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
<td>1 (25%) Not reported</td>
</tr>
<tr>
<td>Wilhite et al, 2022</td>
<td>26 black patients</td>
<td>Not assessed</td>
<td>2 (7.7%)</td>
<td>19 (73.1%) Not assessable*</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td></td>
<td>23 white patients</td>
<td>Not assessed</td>
<td>1 (4.5%)</td>
<td>20 (86.4%) Not assessable*</td>
<td>1 (4.5%)</td>
</tr>
</tbody>
</table>

*Not assessable since POLE was not tested.

MSI-H/dMMR, microsatellite instability high/mismatch repair deficient; NSMP, not specific mutational pattern; POLE, DNA polymerase epsilon, catalytic subunit gene; TMB, tumor mutational burden.
advanced stages. On the other hand, systematic lymphadenectomy (up to the level of the left renal vein) has been traditionally recommended in patients with early-stage endometrial carcinosarcoma as a staging procedure because of the high prevalence of occult (no gross) nodal metastases. However, the therapeutic role of systematic lymphadenectomy has been questioned over the past decade.

Sentinel node mapping, which is already accepted in low- and high-risk endometrial cancer, has emerged as an alternative for nodal staging, even in endometrial carcinosarcoma. Several studies have demonstrated the efficacy and safety of sentinel node mapping in patients with high-risk endometrial cancers, with an acceptable false-negative rate (less than 1%). With particular regard to endometrial carcinosarcoma, in 2016, Schiavone et al reported no significant differences in progression-free survival between patients with endometrial carcinosarcoma undergoing sentinel node mapping versus standard lymphadenectomy (23 vs 23.2 months, respectively; p=0.7). More recently, Zamarrelli et al, compared the oncologic outcomes of 99 patients with endometrial carcinosarcoma who underwent sentinel node mapping with those of 100 patients receiving systematic lymphadenectomy, thus confirming that sentinel node mapping can detect nodal metastasis without compromising oncologic outcomes. However, further prospective studies with longer follow-ups are required to validate these early retrospective results.

The FIRES trial demonstrated that sentinel node mapping with indocyanine green has a high degree of diagnostic accuracy in detecting nodal metastases and can safely replace systematic lymphadenectomy for endometrial cancer staging (any histotype). Recently, the multicenter, prospective SENTOR trial showed that sentinel node mapping (using indocyanine green) in high-risk endometrial cancers, such as endometrial carcinosarcoma, had comparable, if not superior, diagnostic accuracy to those of systematic lymphadenectomy. However, only a few cases of endometrial carcinosarcoma were included in these two latter trials, thus limiting the applicability to this rare histotype. Additional prospective trials (SNEC, ALICE, ENDO-3, ECLAT) are ongoing and will provide further high-quality evidence on nodal staging in high-risk endometrial cancers. To date, there is no consensus on the necessity and extent of lymphadenectomy in patients with early-stage disease who had a hysterectomy without nodal surgical staging and present negative imaging. However, it seems reasonable to avoid another surgery and consider adjuvant radiotherapy in addition to chemotherapy to target the nodal areas at risk.

Adjuvant (Multimodal) Treatment

Owing to the rarity of endometrial carcinosarcoma, no clear consensus exists regarding the optimal adjuvant therapy (after surgery) for patients with endometrial carcinosarcoma. Lacking randomized clinical trials, the benefit of adjuvant therapy is not fully understood and recommendation for subsequent treatment should be considered on a case-by-case basis after multidisciplinary discussion. In general, endometrial carcinosarcoma should be treated as high-risk carcinomas (not as sarcomas). Compared with radiotherapy alone, chemotherapy and, even more, (concurrent or sequential) chemoradiation have been proved to reduce the risk of recurrence and improve survival rates at all stages. Until better treatment options become available, the best approach is multimodal with both chemotherapy and radiotherapy (Table 2). Notably, as for all high-risk histotypes, chemotherapy plays a central role in the management of patients with endometrial carcinosarcoma.

The adjuvant treatment is defined based on both traditional and molecular classifications, which identify different prognostic risk groups (Table 3). FIGO stage IA endometrial carcinosarcoma without myometrial invasion falls within the intermediate-risk group, in the absence of a POLE mutation. The presence of a POLE mutation is rare in endometrial carcinosarcoma but, if present, it determines a subclassification in the low-risk group where adjuvant treatment is not mandatory, at least in the early stages. Endometrial carcinosarcomas with myometrial invasion are considered at high risk, irrespective of the stage and the molecular profile.

The adjuvant treatment usually consists of chemotherapy and radiotherapy, although the optimal sequencing (concurrent vs sequential) remains unclear. Some studies revealed an improvement in survival rates at all stages when using a ‘sandwich approach’ (chemotherapy–radiotherapy–further chemotherapy) compared with alternate sequences (radiotherapy–chemotherapy or chemotherapy–radiotherapy). The rationale behind the greater benefit of sandwich sequencing can probably be explained through the following considerations: (1) chemotherapy is a priority in endometrial carcinosarcoma and should be administered upfront at the maximum dosage; (2) irradiation leads to vascular dysfunction and may impact the tumor delivery of chemotherapeutic agents, thus reducing the efficacy of following systemic treatments; (3) the sequential approach is more tolerable and allows higher dosages of both therapies to be provided separately; (4) administering all six cycles of chemotherapy upfront may increase the risk of toxicity and cause a delay or dose reduction of subsequent radiotherapy, which is itself important for the locoregional control.

Chemotherapy alone may be considered in patients with early-stage and locally advanced endometrial carcinosarcoma receiving surgery. Although patients with endometrial carcinosarcoma were not included in the Gynecologic Oncology Group (GOG) 122 and 258 studies, other experiences reported quite encouraging outcomes following surgery plus chemotherapy. However, it is important to point out that the omission of radiotherapy might correlate with an increased risk of pelvic recurrence. Patients with endometrial carcinosarcoma with residual disease after surgery should be managed with a multimodal approach including chemotherapy and/or radiotherapy. Palliative chemotherapy and the best supportive care should be considered for inoperable advanced endometrial carcinosarcoma. Genetic and molecular differences between non-endometrioid carcinomas and also within every single histotype are gradually emerging and may change therapeutic practices in the future.
## Consensus statement

### Table 2  Most relevant studies investigating the adjuvant treatment for endometrial carcinosarcoma

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerszten et al, 1998&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>60</td>
<td>RT vs observation</td>
<td>RR for local recurrence: 17.54 (p=0.0055)</td>
<td>Adjuvant RT reduced the risk of distant failure and death in patients with disease confined to the uterus but did not impact distant recurrence or survival in stage III patients</td>
</tr>
<tr>
<td>Knocke et al, 1999&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–III ECS</td>
<td>50</td>
<td>RT vs observation</td>
<td>5 year OS, disease-specific survival, local control, and distant control were: 52.9, 57.5, 83.4, and 70.8%, respectively</td>
<td>Adjuvant RT improves local control and disease specific survival in the treatment of ECS</td>
</tr>
<tr>
<td>Callister et al, 2004&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–III ECS</td>
<td>300</td>
<td>RT vs observation</td>
<td>Pelvic recurrence rate: 28% vs 48% (p=0.0002) OS: 36% vs 27% (p=0.10) Distant metastasis rates: 57% vs 54% (p=0.96)</td>
<td>Adjuvant pelvic RT decreased the risk of pelvic recurrence and may delay the appearance of distant metastases after hysterectomy. However, the survival rates remain poor because of a high rate of distant recurrence</td>
</tr>
<tr>
<td>Wolfson et al, 2007 (GOG-150)&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Open-label, multicenter, phase III RCT</td>
<td>Stage I–IV ECS</td>
<td>206</td>
<td>Arm 1 (105): WAI Arm 2 (101): CIM (3 cycles)</td>
<td>Recurrence rate was 21% lower (HR=0.789, 95% CI, 0.530 to 1.176; p=0.245) and death rate 29% lower (HR=0.712, 95% CI: 0.484 to 1.048, p=0.085) for CIM patients</td>
<td>No statistically significant advantage in recurrence rate or survival for CIM over WAI. However, the observed differences favor the use of combination CHT in future trials</td>
</tr>
<tr>
<td>Reed et al, 2008 (EORTC 55874)&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Open-label, multicenter, phase III RCT</td>
<td>Stage I–II uterine sarcomas</td>
<td>224 (92 ECS)</td>
<td>Adjuvant pelvic RT (112 patients) vs observation (112 patients)</td>
<td>Local relapse at 6.8 years (whole cohort): 4% (RT) vs 24% (Observation)</td>
<td>No difference in either OS or PFS was demonstrated but there was an increased local control for ECS patients receiving radiation</td>
</tr>
<tr>
<td>Wright et al, 2008&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–II ECS</td>
<td>1819</td>
<td>RT vs observation</td>
<td>Adjuvant RT reduced the risk of death by 21% in women with ECS (HR=0.79; 95% CI: 0.7 to 0.9). RT reduced mortality rates in patients with ECS who had not undergone LND but had only a marginal effect on survival in node-negative women</td>
<td>Adjuvant RT improves survival for select patients with early-stage ECS</td>
</tr>
</tbody>
</table>

**Continued**
## Table 2  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manzerova et al, 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>2342</td>
<td>RT vs observation</td>
<td>Better OS and CSS in the RT group: 42 vs 22 (p&lt;0.0001) and 57 vs 28 months (p&lt;0.0001), respectively</td>
<td>We observed greater survival rate in the RT group</td>
</tr>
<tr>
<td>Cha et al, 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>97</td>
<td>Adjuvant pelvic RT vs observation</td>
<td>Locoregional recurrence: 17.5% vs 28.5% (p=0.107). RT significantly improved the 5-year LRRFS rate of patients who did not undergo PLND (52.7% vs 18.7%; p&lt;0.001).</td>
<td>Adjuvant RT decreased the risk of locoregional recurrence after hysterectomy for ECS, particularly in patients without surgical nodal staging</td>
</tr>
<tr>
<td>Stokes et al, 2018&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>2357</td>
<td>EBRT vs BRT vs EBRT+BRT vs observation</td>
<td>Survival was significantly improved among patients receiving EBRT+BRT (HR=0.72, 95% CI, 0.58 to 0.89, p&lt;0.01), but not among those receiving EBRT alone (HR=0.93, 95% CI, 0.79 to 1.10, p=0.41) or BRT alone (HR=0.84, 95% CI, 0.68 to 1.03, p=0.09)</td>
<td>EBRT+BRT combination is associated with an overall survival advantage in ECS</td>
</tr>
<tr>
<td>Li et al, 2019&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–III ECS</td>
<td>1069</td>
<td>Adjuvant EBRT and/or BRT</td>
<td>RT significantly reduced the risk of death and cancer-specific death (HR=0.47 and 0.53, respectively; both p&lt;0.05)</td>
<td>Adjuvant RT may provide a survival benefit for ECS</td>
</tr>
<tr>
<td>Nama et al, 2020&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>3706</td>
<td>RT vs observation</td>
<td>The use of RT in ECS patients was independently associated with decreased mortality (OR=0.1, 95% CI, 0.02 to 0.6, p&lt;0.005)</td>
<td>Primary radiotherapy or combination radiotherapy confers a survival advantage to ECS patients</td>
</tr>
</tbody>
</table>

**Chemoradiation (CRT)**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manolitsas et al, 2001&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Single-institution, prospective study</td>
<td>Stage I–IV ECS</td>
<td>38</td>
<td>CRT (sandwich approach: cisplatin/epirubicin → EBRT/BRT → cisplatin/epirubicin) vs observation</td>
<td>PFS (median FU: 55 months): 90% vs 47% (p=0.01)</td>
<td>In this pilot study, patients with clinical stage I–II ECS who received adjuvant RT and CHT had an excellent survival rate</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makker et al, 2008&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>49</td>
<td>CHT±RT vs RT alone</td>
<td>3-year PFS: CHT±RT 35% vs RT 9% for RT alone (HR=1.74, 95% CI, 0.79 to 3.85; p=0.164), 3-year OS: CHT±RT 66% vs RT 34% (HR=2.02, 95% CI, 0.77 to 5.33; p=0.146)</td>
<td>This study corroborates GOG-150 results and shows that paclitaxel–carboplatin appears to be an efficacious adjuvant CHT regimen for completely resected ECS</td>
</tr>
<tr>
<td>Tanner et al, 2011&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage III–IV ECS</td>
<td>44</td>
<td>Adjuvant treatment (CRT or CHT alone) vs observation</td>
<td>OS: 30.1 vs 4.7 months (p&lt;0.001)</td>
<td>Combined adjuvant treatment was associated with better outcomes than observation</td>
</tr>
<tr>
<td>Cantrell et al, 2012&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–II ECS</td>
<td>111</td>
<td>Observation (40%), RT (20%), CHT (25%), CRT (14%)</td>
<td>CHT (±RT) significantly improved the PFS (HR=0.28; p=0.003) compared with CHT-free approaches</td>
<td>In women with FIGO stage I–II ECS, adjuvant CHT is associated with improved PFS compared with RT or observation alone</td>
</tr>
<tr>
<td>Einstein et al, 2012&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Single-institution, phase II prospective study</td>
<td>Stage I–IV ECS</td>
<td>27</td>
<td>Sandwich approach: 3 cycles ifosfamide±cisplatin → EBRT (45 Gy) + BRT (5 Gy) → 3 more cycles ifosfamide±cisplatin</td>
<td>2 year OS: 80.8% (stage I–II); 30.3% (stage III–IV)</td>
<td>Ifosfamide 'sandwiched' with RT appears to be an efficacious regimen for surgically staged ECS patients with no residual disease, even at advanced stage. The addition of cisplatin to the regimen added toxicity without improving efficacy</td>
</tr>
<tr>
<td>Sorbe et al, 2013&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>322</td>
<td>CHT and/or RT or observation</td>
<td>The 5 year LRRFS rate was 63% for patients treated with surgery alone, 68% after addition of adjuvant CHT, 86% after adjuvant RT, and 95% after CRT</td>
<td>RT seems to be the most important constituent of the adjuvant therapy</td>
</tr>
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Continued
### Consensus statement

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Dickson et al, 2015&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–III ECS</td>
<td>303 (195 stage I/II, 108 stage III)</td>
<td>Observation vs CHT vs CRT</td>
<td>Stage I/II: Observation was associated with a fourfold increased risk of death compared with CHT (HR=4.48; p=0.003). Patients receiving CRT had significantly improved PFS compared with those receiving CT alone (HR=0.43; p=0.04), but no difference in OS. Stage III cohort: Observation was associated with worse OS and PFS compared with CHT (OS: HR=2.46, p=0.04; PFS: HR=2.39, p=0.03, respectively). A potential improvement in PFS was seen for those treated with CRT compared with CT alone; however, it was not statistically significant (HR=0.53; p=0.09)</td>
<td>Observation after surgery was associated with poor outcomes in ECS compared with CHT and RT alone. Multimodality therapy for stage I/II disease was associated with improved PFS compared with CHT alone</td>
</tr>
<tr>
<td>Rauh-Hain et al, 2015&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>10 609</td>
<td>CHT and/or RT or observation</td>
<td>Women who received CHT only had a median OS of 22 months (95% CI 19 to 23), RT-only group was 32 months (95% CI 30 to 38), in women who underwent CRT was 65 months (95% CI 56 to 77), and in patients who did not received any adjuvant treatment the median OS was 22 months (95% CI 20 to 22)</td>
<td>Adjuvant CHT and CRT were associated with improved survival</td>
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### Table 2  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gungorduk et al, 2015</td>
<td>Multicenter, retrospective study</td>
<td>Stage I-IV ECS</td>
<td>66</td>
<td>CRT or CHT or RT</td>
<td>In early-stage patients who received CRT, median DFS and OS were 44 months and 55 months, respectively, compared with 34.5 months and 36 months, respectively, in patients who received RT or CT alone (HR=1.4; 95% CI, 0.7 to 3.1 for DFS; p=0.23 and HR=2.2; 95% CI, 0.9 to 5.3 for OS; p=0.03). In advanced-stage patients, the median DFS and OS of patients receiving CRT were 25 months and 38 months, respectively, compared with 23.5 months and 24.5 months, respectively, in patients receiving adjuvant RT or CT alone (HR=3.1; 95% CI, 0.6 to 16.0 for DFS; p=0.03); (HR=3.3; 95% CI, 0.7 to 15.0 for OS; p=0.01)</td>
<td>In patients with early or advanced stage ECS, adjuvant CHT with RT is associated with improved DFS and OS, as compared with CHT or RT alone</td>
</tr>
<tr>
<td>Guttmann et al, 2016</td>
<td>Multicenter, retrospective study</td>
<td>Stage I-II ECS</td>
<td>118</td>
<td>Observation (31%) vs CHT (16%) vs RT (20%) vs CRT (32%)</td>
<td>Adjuvant treatment was associated with improved OS (HR=0.74; 95% CI, 0.58 to 0.96; p=0.02), freedom from vaginal recurrence (HR=0.55; 95% CI, 0.37 to 0.82; p=0.004), and freedom from any recurrence (HR=0.70; 95% CI, 0.54 to 0.92; p=0.01).</td>
<td>In women with early-stage uterine ECS, our data suggest superior survival endpoints with combined RT and chemotherapy. The frequency of vaginal recurrence suggests a role for incorporating vaginal brachytherapy in the adjuvant management</td>
</tr>
<tr>
<td>Wong et al, 2017</td>
<td>Multicenter, retrospective study</td>
<td>Stage I-II ECS</td>
<td>4906</td>
<td>Observation (36.2%), CHT (19.8%), RT 1060 (21.6%), CRT (22.4%)</td>
<td>CRT (HR=0.50; 95% CI, 0.44 to 0.57; p&lt;0.001) and CHT alone (HR=0.78; 95 CI, 0.69 to 0.88; p&lt;0.001) were significantly associated with improved OS, whereas RT alone was not</td>
<td>CRT was associated with significantly improved 5-year OS as compared with no further therapy, RT alone, or CT alone</td>
</tr>
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### Table 2  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
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<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seagle et al., 2017</td>
<td>Multicenter, retrospective study</td>
<td>Stage I ECS</td>
<td>5614</td>
<td>CHT and/or RT or observation</td>
<td>Multagent CHT and VBT were associated with decreased hazard of death (HR=0.62, 95% CI, 0.54 to 0.73), p=1.1x10^-3 and HR=0.83, 95% CI 0.70 to 0.97), p=0.02, respectively. Highest 5-year survival was observed after VBT and multagent CHT (74.1% (68.3–80.3%), p&lt;2.0x10^-16)</td>
<td>Adjuvant BRT and multagent CHT is associated with increased survival</td>
</tr>
<tr>
<td>Matsuo et al., 2017</td>
<td>Multicenter, retrospective study</td>
<td>Stage I ECS</td>
<td>443</td>
<td>CRT vs RT vs CHT</td>
<td>CHT, but not RT, decreased the risk of local (HR=0.46; p=0.01) and distant recurrence (HR=0.41; p&lt;0.001). The CRT group had a lower 5-year cumulative local-recurrence rate vs CHT (HR=0.46; p=0.22)</td>
<td>Adjuvant CHT appears to be effective to control both local and distant recurrences in stage I ECS. Adding RT to CHT may be effective to control local recurrence when the tumor exhibits multiple risk factors</td>
</tr>
<tr>
<td>Versluis et al., 2018</td>
<td>Multicenter, retrospective study</td>
<td>ECS</td>
<td>1140</td>
<td>CRT vs RT vs CHT</td>
<td>CRT significantly improved the OS vs CHT (HR=2.49, 95% CI, 1.24 to 4.99; p=0.01) and RT (HR=2.53, 95% CI, 1.29 to 4.97; p=0.007)</td>
<td>Adjuvant therapy improves survival when LND is omitted or when nodes are positive</td>
</tr>
<tr>
<td>Gunther et al., 2018</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–III ECS</td>
<td>155</td>
<td>CHT and/or RT or observation</td>
<td>Patients treated with EBRT had a higher 5-year pelvic disease control rate (88.3%) than patients treated with VBT only (67.4%) or no radiation (71.2%; p=0.04). In stage III patients, EBRT was associated with higher 5-year pelvic disease control (90.0% vs 55.5%, p=0.046), DSS (64.6% vs 46.4%, p=0.13), and OS (64.6% vs 34.0%, p=0.04)</td>
<td>EBRT improves locoregional control in all stages and may improve survival in stage III patients who are at the highest risk of pelvic relapse</td>
</tr>
</tbody>
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Continued
## Consensus statement

### Table 2  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
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<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odei et al, 2018&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>3538</td>
<td>CRT (1751) vs CHT (1787)</td>
<td>Median survival for the CHT and CRT groups was 24 months and 31.3 months, respectively. When compared with CHT alone, CRT was associated with a benefit in OS (HR=0.65; p&lt;0.01).</td>
<td>When compared with CHT alone, the use of CRT in ECS patients was associated with a significant OS benefit</td>
</tr>
<tr>
<td>Shinde et al, 2018&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage IA EC, unfavorable histotype</td>
<td>5711 (2,701 ECS)</td>
<td>BRT vs observation</td>
<td>BRT was associated with increased survival (HR=0.75, 95% CI, 0.65 to 0.87, p=0.001).</td>
<td>In stage IA EC of unfavorable histology, the use of BRT was associated with improved survival</td>
</tr>
<tr>
<td>Stokes et al, 2018&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>2357</td>
<td>EBRT vs BRT vs EBRT+BRT vs observation</td>
<td>Survival was significantly improved among patients receiving EBRT+BRT (HR=0.72, 95% CI, 0.58 to 0.89, p&lt;0.01), but not among those receiving EBRT alone (HR=0.93, 95% CI, 0.79 to 1.10, p=0.41) or BRT alone (HR=0.84, 95% CI, 0.68 to 1.03, p=0.09) EBRT+BRT combination is associated with an overall survival advantage in ECS.</td>
<td></td>
</tr>
<tr>
<td>Kurnit et al, 2019&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Monocentric, retrospective study</td>
<td>Stage I–II ECS</td>
<td>140</td>
<td>CHT and/or RT or observation</td>
<td>CRT vs observation: for OS, HR=1.01; 95% CI, 0.42 to 2.41; p=0.99; for PFS, HR=0.93; 95%, 0.41–2.09; 0.86</td>
<td>No statistically significant differences in terms of survival rates for adjuvant treatment, including CRT, compared with observation.</td>
</tr>
<tr>
<td>McEachron et al, 2020&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>148</td>
<td>CRT vs CHT alone</td>
<td>Median PFS: 15 vs 11 months; 2-year PFS: 22.5% vs 13.6% (p=0.006). Median OS: 26 vs 20 months; 2-year OS: 50.0% vs 35.6% (p=0.018)</td>
<td>CRT was associated with improvement in both PFS and OS for all staged of ECS compared with CHT alone. Sandwich sequencing was associated with superior OS compared with the alternate sequences.</td>
</tr>
<tr>
<td>van Welden et al, 2020&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Multicenter, retrospective study</td>
<td>Stage IIIC ECS (139 ECS)</td>
<td>1241</td>
<td>CRT vs RT vs CHT</td>
<td>CRT significantly improved the OS vs CHT (HR=1.84, 95% CI, 1.34 to 2.52; p=0.01) and EBRT alone (HR=1.37, 95% CI, 1.05 to 1.79; p=0.007)</td>
<td>In this population-based study, adjuvant EBRT+CT was associated with improved OS compared with CT or EBRT alone in FIGO stage IIIC carcinosarcoma.</td>
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</tbody>
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endometrial carcinosarcoma. However, based on the results from the GOG-232B and GOG-261 trials, the carboplatin/paclitaxel doublet has now been recommended as the preferred first-line treatment for endometrial carcinosarcoma, given the non-inferiority and the better toxicity profile, compared with ifosfamide/paclitaxel. Ifosfamide/paclitaxel and cisplatin/paclitaxel regimens remain alternative options (for instance, in cases of hypersensitivity reactions). Recently, based on the results of several trials, immunotherapy (with or without tyrosine kinase inhibitor) is emerging as the standard treatment modality after the failure of platinum-based chemotherapy. Pembrolizumab plus lenvatinib represents the preferred treatment for non-endometrioid endometrial cancer since they are generally characterized by MSS/pMMR disease. Since MSI-H/dMMR are deserving of treatment with single-agent immunotherapy (eg, dostarlimab, pembrolizumab). Of note, most immunotherapy-based studies (also the KEYNOTE-775) do not include patients with endometrial carcinosarcoma. However, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the use of pembrolizumab and lenvatinib for endometrial cancer recurring after platinum-based chemotherapy, regardless of the histotype (the FDA just for MSS/pMMR disease and the EMA for all types of endometrial cancer). A more detailed description of the evidence for the role of immunotherapy is described below.

Before the adoption of immunotherapy (with or without tyrosine kinase inhibitor), no standard chemotherapeutic treatment has been identified as second-line therapy and the prognosis following recurrence is poor. Rechallenge

<table>
<thead>
<tr>
<th>Author, year</th>
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<th>Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckmann et al, 2021</td>
<td>Multicenter, retrospective study</td>
<td>Stage I–IV ECS</td>
<td>66</td>
<td>CHT and/or RT or observation</td>
<td>DSM was reduced among those who underwent adjuvant CHT (HR=0.39; 95% CI: 0.18 to 0.84) or multimodality treatment (HR=0.11; 95% CI: 0.06 to 0.30)</td>
<td>These findings indicate better survival among those who received CHT and multimodal adjuvant therapy, with the latter applying to early and late-stage disease</td>
</tr>
</tbody>
</table>

Table 3 ECS treatment after surgery and in advanced, metastatic, and recurrent disease

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>Low</td>
<td>I–II POLE-mutated FU</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Stage IA without myometrial invasion (regardless of molecular status)</td>
</tr>
<tr>
<td></td>
<td>▶ CHT (substantial LVSI, high-grade carcinoma) ± RT (sarcoma dominance)</td>
</tr>
<tr>
<td></td>
<td>▶ FU (&lt; 60 years)</td>
</tr>
<tr>
<td>High</td>
<td>Stage I–IVA with myometrial invasion and RT=0 (regardless of molecular status)</td>
</tr>
<tr>
<td></td>
<td>▶ CRT±BRT (→ CHT)</td>
</tr>
<tr>
<td></td>
<td>▶ CHT → EBRT±BRT (→ CHT)</td>
</tr>
<tr>
<td></td>
<td>▶ CHT alone (stage IIa without sarcoma dominance)</td>
</tr>
<tr>
<td>Unresectable, advanced, or metastatic disease</td>
<td>Stage III–IVA with RT&gt;0</td>
</tr>
<tr>
<td></td>
<td>▶ Stage IVB</td>
</tr>
<tr>
<td></td>
<td>▶ CHT+RT (concurrent or sequential)</td>
</tr>
<tr>
<td></td>
<td>▶ NACT → surgery</td>
</tr>
<tr>
<td></td>
<td>▶ CHT alone</td>
</tr>
<tr>
<td></td>
<td>▶ Clinical trials</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Locoregional or oligometastatic</td>
</tr>
<tr>
<td></td>
<td>▶ CHT</td>
</tr>
<tr>
<td></td>
<td>▶ Immunotherapy (with or without TKI) in patients who had prior CHT</td>
</tr>
<tr>
<td></td>
<td>▶ RT-naïve: surgery → CHT and/or EBRT±BRT</td>
</tr>
<tr>
<td></td>
<td>▶ Prior BRT: surgery → CHT and/or EBRT</td>
</tr>
<tr>
<td></td>
<td>▶ Prior EBRT: surgery → CHT</td>
</tr>
<tr>
<td></td>
<td>▶ Clinical trials</td>
</tr>
</tbody>
</table>

BRT, brachytherapy; CHT, chemotherapy; CIM, cisplatin–ifosfamide and mesna; CRT, chemoradiation therapy; CSS, cancer-specific survival; DFS, disease-free survival; DSM, disease-specific mortality; DSS, disease-specific survival; EBRT, external beam radiotherapy; EC, endometrial cancer; ECS, endometrial carcinosarcoma; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up; HR, hazard ratio; LND, lymph node dissection; LRRFS, locoregional recurrence-free survival; N, number of participants; OS, overall survival; PFS, progression-free survival; PLND, pelvic lymph node dissection; RCT, randomized clinical trial; RR, relative risk; VBT, vaginal brachytherapy; WAI, whole abdominal irradiation.
### Table 4 Published prospective trials addressing the efficacy of chemotherapeutic and investigational agents in advanced, persistent, or recurrent ECS

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Identification number</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Treatment arm(s)</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton et al., 1989</td>
<td>–</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Metastatic or recurrent uterine MMT, no prior CHT</td>
<td>28</td>
<td>Ifosfamide 1.5 g/mq d1–5 q28, until PD or unacceptable toxicity</td>
<td>ORR: 32% DCR: 68%</td>
<td>Ifosfamide is an unusually active drug in patients with advanced or recurrent mixed Müllerian tumors of the uterus. Studies with combination regimens incorporating ifosfamide are warranted</td>
</tr>
<tr>
<td>Thigpenet al., 1991</td>
<td>–</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Metastatic or recurrent uterine sarcomas, no prior CHT</td>
<td>96 (23 ECS)</td>
<td>Cisplatin 50 mg/mq q21, until PD or unacceptable toxicity</td>
<td>ORR: 19% DCR: 70%</td>
<td>Cisplatin has definite activity for patients with mixed mesodermal sarcomas who have not received prior CHT</td>
</tr>
</tbody>
</table>
| Sutton et al., 2000 | GOG-108 | Open-label, multicenter, single-arm, phase III RCT | Advanced, persistent, or recurrent ECS, no prior CHT | 194 | ▶ Arm I (102): Ifosfamide 1.5 g/mq d1–5 q21 (VIII cycles)  
▶ Arm II (92): Ifosfamide 1.5 g/mq with cisplatin 20 mg/mq d1–5 q21 (VIII cycles) | PFS: 6 vs 4 months (RR=0.73; 95% upper confidence limit, 0.94; p=0.02). OS: 9.4 vs 7.6 months (RR=0.80, 95% upper confidence limit, 1.03; p=0.07). ORR: 54% vs 36% | The addition of cisplatin to ifosfamide appears to offer a small improvement in PFS, but the added toxicity may not justify use of this combination |
<p>| Van Rijswijk et al., 2003 | EORTC 55923 | Open-label, multicenter, single-arm, phase II trial | Advanced or metastatic ECS, no prior RT or CHT | 41 (22 ECS) | Cisplatin 50 mg/mq IV+ifosfamide 5 g/mq IV+mesna 5 g/mq IV+doxorubicin 45 mg/mq IV | ORR: 56% DCR: 72% OS: 26 months (for all 41 patients) | The results of this study are in line with the hypothesis that carcinosarcomas are chemosensitive, in particular for the currently investigated regimen. Considering the observed toxicities, alternative platinum-based regimens with more favorable toxicity profiles should be explored |
| Ramondetta et al., 2003 | – | Open-label, multicenter, single-arm, phase II trial | Uterine MMMT, no prior CHT | 16 | Cisplatin 75 mg/mq+ifosfamide 1.2 mg/mq+mesna 240 mg/mq q28 | ORR: 33.3% DCR: 50% | The combination of cisplatin, ifosfamide, and mesna in patients with MMMT had moderate activity, but the high toxicity and short response duration suggest that this regimen is disappointing |</p>
<table>
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<tr>
<th>Author, year</th>
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<th>Treatment arm(s)</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton et al, 2005</td>
<td>GOG-117</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Adjuvant treatment after surgery for stage I–II ECS</td>
<td>65</td>
<td>Ifosfamide 1.5 g/mq IV d1–5 q21+cisplatin 20 mg/mq IV q21, for three cycles</td>
<td>2-year PFS: 69%</td>
<td>2-year OS: 82%</td>
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<tr>
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<td></td>
<td>5-year OS: 62%</td>
<td>7-year PFS: 54%</td>
<td>7-year OS: 52%</td>
</tr>
<tr>
<td>Homesley et al, 2007</td>
<td>NCT00003128 GOG-161</td>
<td>Multicentric, phase III RCT</td>
<td>Advanced, persistent, or recurrent ECS, no prior CHT</td>
<td>179</td>
<td>Arm I (91): Ifosfamide 2 g/mq IV d1-3 q21, until PD or unacceptable toxicity</td>
<td>PFS: 5.8 vs 3.6 months (HR=0.71, 95% CI 0.51 to 0.97; p=0.03)</td>
<td>OS: 13.5 vs 8.4 months (HR=0.69, 95% CI 0.49 to 0.97; p=0.03). ORR 45% vs 29% DCR: 67% vs 46%</td>
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<td>Arm II (88): Ifosfamide 1.6 g/mq IV d1–3+Paclitaxel 135 mg/mq d1 q21, until PD or unacceptable toxicity</td>
<td>Survival rates were significantly improved with the combination ifosfamide/paclitaxel, and toxicities were as expected and manageable</td>
<td></td>
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<tr>
<td>Powell et al, 2010</td>
<td>NCT00112489 GOG-232B</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Advanced, persistent, or recurrent ECS, no prior CHT</td>
<td>46</td>
<td>Paclitaxel 175 mg/mq IV+CBDCA AUC 6 q21, until PD or unacceptable toxicity</td>
<td>ORR: 54% (CR: 13%; PR 41%) DCR: 67% PFS: 7.6 months OS: 14.7 months</td>
<td>Paclitaxel plus carboplatin demonstrates antitumor activity against ECS with acceptable toxicity</td>
</tr>
<tr>
<td>Aghajanian et al, 2012</td>
<td>NCT00687687 GOG-232C</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Advanced, persistent, or recurrent ECS, no prior CHT</td>
<td>17</td>
<td>PTX 175 mg/q IV+CBDCA (AUC 5/6) IV d1w21+iniparib 4 mg/kg IV twice weekly beginning on day 1, until PD or unacceptable toxicity</td>
<td>ORR: 23.5% DCR: 58.9% PFS: 3.8 months OS: 11.3 months</td>
<td>Iniparib plus PTX and CBDCA did not show significant activity to warrant further study</td>
</tr>
<tr>
<td>Powell et al, 2022</td>
<td>NCT00954174 GOG-261</td>
<td>Multicentric, phase III, non-inferiority RCT</td>
<td>Newly diagnosed stage I-IV or recurrent chemotherapy-naive ECS</td>
<td>449</td>
<td>Arm I (228): Paclitaxel 175 mg/mq IV+CBDCA (AUC 5/6) IV q21 for 6–10 cycles</td>
<td>PFS: 16 vs 12 months (HR=0.73, 95% CI 0.58 to 0.93; p&lt;0.01)</td>
<td>OS: 37 vs 29 months (HR=0.87, 90% CI 0.70 to 1.075; p&lt;0.01)</td>
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<td>Arm II (221): Ifosfamide 1.6 g/mq d1–3 IV+paclitaxel 135 mg/mq IVd1 q21, for 6–10 cycles</td>
<td>PC was not inferior to the active regimen PI and should be standard treatment for ECS</td>
<td></td>
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<tr>
<td>Further lines chemotherapy</td>
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</tr>
<tr>
<td>Curtin et al, 2001</td>
<td>–</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Persistent or recurrent ECS</td>
<td>44</td>
<td>Paclitaxel 135 or 170 mg/mq</td>
<td>ORR: 18.2%</td>
<td>Paclitaxel had moderate activity in ECS patients</td>
</tr>
<tr>
<td>Miller et al, 2005</td>
<td>NCT00003156 GOG-130D</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Advanced or recurrent ECS, 0–1 prior CHT lines</td>
<td>48</td>
<td>Topotecan 1.5 mg/mq IV QD d1–5 q21, until PD or unacceptable toxicity</td>
<td>ORR: 10% (all CR) SD: 27%</td>
<td>Topotecan does not appear to have major activity in patients with advanced or recurrent ECS</td>
</tr>
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## Table 4  Continued

<table>
<thead>
<tr>
<th>Author, year</th>
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<tbody>
<tr>
<td>Yi-Shin Kuo et al, 2006</td>
<td>NCT00006005</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Recurrent or persistent gynecologic sarcomas or carcinosarcomas</td>
<td>17</td>
<td>Thalidomide 200 mg PO QD (escalated by 100–200 mg every 7 to 14 days), until PD or unacceptable toxicity</td>
<td>PFS: 1.84 months OS: 6.64 months</td>
<td>Thalidomide has no activity in patients with advanced or recurrent gynecologic sarcomas and was not well-tolerated</td>
</tr>
<tr>
<td>Miller et al, 2010</td>
<td>NCT00114218 GOG-130E</td>
<td>Open label, single-arm, phase II trial</td>
<td>Recurrent ECS, one prior CHT</td>
<td>24</td>
<td>Gemcitabine 600 mg/mq+docetaxel 35 mg/mq IV d1,8,15 q28, until PD or unacceptable toxicity</td>
<td>ORR: 8.3% (all PR) PFS: 1.8 months OS: 4.9 months</td>
<td>Docetaxel/gemcitabine is not active in patients with recurrent ECS as second-line CHT</td>
</tr>
<tr>
<td>McMeekin et al, 2012</td>
<td>NCT00025506 GOG-230B</td>
<td>Open-label, single-arm, phase II trial</td>
<td>Recurrent or persistent ECS, up to two prior CHT lines</td>
<td>45</td>
<td>Starting dose of 200 mg thalidomide PO QD that was increased by 200 mg every 2 weeks to a target dose of 1000 mg QD, until PD or unacceptable toxicity</td>
<td>PFS6: 18% PFS: 1.9 months OS: 5.9 months</td>
<td>Treatment with thalidomide met the protocol-specified goal of prolonging PFS6. However, based on results with newer agents, the activity was insufficient to support further investigation</td>
</tr>
<tr>
<td>Harter et al, 2016</td>
<td>NCT0081594 AGO-GYN 7</td>
<td>Open-label, multicentric, single-arm, phase II trial</td>
<td>Newly diagnosed or recurrent gynecologic sarcoma or carcinosarcoma, 0–1 prior CHT lines</td>
<td>40 (20 ECS)</td>
<td>Pegylated liposomal doxorubicin (40 mg/mq) and carboplatin (AUC 6) q28</td>
<td>ORR: 33.3% 1 year PFS: 32.5% 1 year OS: 77.0%</td>
<td>The combination of carboplatin and pegylated liposomal doxorubicin is feasible and has activity.</td>
</tr>
<tr>
<td>George et al, 2009</td>
<td>NCT00474994</td>
<td>Open-label, single-arm, phase II trial</td>
<td>Advanced non-GIST soft tissue sarcomas</td>
<td>48</td>
<td>Sunitinib 37.5 mg PO QD, until PD or unacceptable toxicity</td>
<td>Metabolic PR: 48% Metabolic SD: 52%</td>
<td>Sunitinib demonstrated notable evidence of metabolic response in several patients with non-GIST sarcoma</td>
</tr>
<tr>
<td>Nimeiri et al, 2010</td>
<td>NCT00238121 NCI-2009–00068</td>
<td>Open-label, single-arm, phase II trial</td>
<td>Advanced or recurrent ECS, 0–1 prior CHT lines</td>
<td>16</td>
<td>Sorafenib 400 mg PO twice daily, until PD or unacceptable toxicity</td>
<td>ORR: 0% SD: 25%. PFS6: 13%; OS: 5.0 months</td>
<td>Sorafenib had minimal activity in ECS patients</td>
</tr>
<tr>
<td>Huh et al, 2010</td>
<td>NCT00075400 GOG-230C</td>
<td>Open-label, single-arm, phase II trial</td>
<td>Recurrent or persistent ECS, up to two prior CHT lines</td>
<td>23</td>
<td>Imatinib mesylate 600 mg PO QD, until PD or unacceptable toxicity</td>
<td>PFS6: 4.3%</td>
<td>Imatinib mesylate was generally well tolerated but had minimal activity as a single agent in unscreened patients</td>
</tr>
<tr>
<td>Mackay et al, 2012</td>
<td>–</td>
<td>Multi-institutional non-randomized phase II trial</td>
<td>Recurrent or metastatic uterine carcinosarcomas and leiomyosarcoma, ≤2 prior lines of CHT</td>
<td>22</td>
<td>Aflibercept 4 mg/kg IV d 1q14, until PD or unacceptable toxicity</td>
<td>Two (9%) patients had SD, one lasting &gt;24 weeks Median TTP was 1.6 months (95% CI 1.1 to 1.7) No PR</td>
<td>Single-agent aflibercept has minimal activity in women with carcinosarcoma</td>
</tr>
</tbody>
</table>

**Novel therapeutic agents**

<table>
<thead>
<tr>
<th>Author, year</th>
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<th>Design</th>
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with platinum-based chemotherapy (eg, carboplatin/paclitaxel, carboplatin/pegylated liposomal doxorubicin) can be considered. Other options include ifosfamide±paclitaxel, weekly paclitaxel, pegylated liposomal doxorubicin, docetaxel, gemcitabine, and topotecan. However, if the median response rate and progression-free survival are 37.5% and 5.9 months, respectively, after first-line therapy, the outcomes are far worse in subsequent lines (5.5% and 1.8 months, respectively). Even some studies investigating the efficacy of targeted therapies, such as tyrosine kinase inhibitors (eg, sunitinib, imatinib, sorafenib, pazopanib) have had disappointing results so far. Due to the lack of valid advanced-line therapies, enrollment of patients in future clinical trials is strongly encouraged.

### Table 4 Continued

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<tbody>
<tr>
<td>Alvarez et al, 2013</td>
<td>NCT01010126 NCI-2012–02086</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Recurrent or persistent EC, up to two prior CHT lines</td>
<td>49 (5 ECS)</td>
<td>Bevacizumab 10 mg/kg IV every other week±temsolimus 25 mg IV weekly</td>
<td>ORR: 24.5% PFS6: 46.9% PFS: 5.6 months OS: 16.9 months</td>
<td>Combination of temsolimus and bevacizumab is deemed active in recurrent or persistent EC. However, this treatment was associated with significant toxicity</td>
</tr>
<tr>
<td>Castonguay et al, 2014</td>
<td>NCT00478426 NCI-2009–00210</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Recurrent/metastatic EC or ECS, no more than one prior CHT line</td>
<td>33</td>
<td>Sunitinib 50 mg PO QD (4 weeks on–2 weeks off schedule)</td>
<td>No responses or SD seen among the 3 patients with ECS.</td>
<td>Sunitinib showed promising activity in women with recurrent EC, but no activity was seen against ECS</td>
</tr>
<tr>
<td>Campos et al, 2014</td>
<td>NCT01247571 GOG-230D</td>
<td>Open-label, multicentric, single-arm, phase II trial</td>
<td>Recurrent or persistent ECS, up to two prior CHT lines</td>
<td>19</td>
<td>Pazopanib 800 mg PO QD, until PD or unacceptable toxicity</td>
<td>ORR: 0% PFS6: 15.8% PFS: 2.0 months OS: 8.7 months</td>
<td>Pazopanib demonstrated minimal activity as a second- or third-line treatment for advanced ECS</td>
</tr>
<tr>
<td>McCourt et al, 2017</td>
<td>NCT01168232 GOG-130F</td>
<td>Open-label, multicentric, single-arm, phase II trial</td>
<td>Recurrent or persistent ECS, up to two prior CHT lines</td>
<td>34</td>
<td>Ixabepilone 40 mg/mg IV d1q21, until PD or unacceptable toxicity</td>
<td>ORR: 11.8% (all PR) PFS: 1.7 months OS: 7.7 months PFS6: 20.6%</td>
<td>Single-agent ixabepilone showed modest but insufficient clinical activity within the investigated study cohort</td>
</tr>
<tr>
<td>Dhani et al, 2020</td>
<td>NCT01935934 NCI-2013–00890</td>
<td>Open-label, multicenter, single-arm, phase II trial</td>
<td>Recurrent or metastatic EC, 1–2 prior CHT lines</td>
<td>102 (19 ECS)</td>
<td>Cabozantinib s-malate 60 mg PO QD, until PD or unacceptable toxicity</td>
<td>ORR: 6% 12 weeks PFS: 47%</td>
<td>Cabozantinib has activity in serous and endometrioid histology EC.</td>
</tr>
<tr>
<td>Rubinstein et al, 2020</td>
<td>NCT02549989</td>
<td>Open-label, multicentric, single-arm, phase II trial</td>
<td>Recurrent or persistent EC</td>
<td>28</td>
<td>LY3023414 200 mg PO twice daily</td>
<td>ORR: 16% CBR: was 28% PFS: 2.5 months OS: 9.2 months</td>
<td>In patients with heavily pre-treated advanced EC prospectively selected for tumors with activating PI3K pathway mutations, LY3023414 demonstrated modest single-agent activity and a manageable safety profile</td>
</tr>
</tbody>
</table>

AUC, area under curve; CBDCA, carboplatin; CBR, clinical benefit rate; CHT, chemotherapy; CI, confidence interval; CR, complete response; DCR, disease control rate; EC, endometrial cancer; ECS, endometrial carcinosarcoma; GIST, gastrointestinal stromal tumor; HR, hazard ratio; IV, intravenous; MMTM, malignant mixed Müllerian tumor; ORR, objective response rate; OS, overall survival; PC, carboplatin/paclitaxel; PD, progressive disease; PFS, progression-free survival; PFS6, progression-free survival at 6 months; PI, carboplatin/ifosfamide; PI3K, phosphoinositide 3-kinase; PO, per os; PR, partial response; PTX, paclitaxel; QD, quque die; RCT, randomized clinical trial; RR, response rate; SD, stable disease; TTP, time to progression.
Consensus statement

Radiotherapy

Data on the efficacy of adjuvant radiotherapy (external beam radiation and/or brachytherapy) are limited and mostly retrospective (Table 1). Radiotherapy alone after surgery is not recommended as, despite the reported improvement in local control, it has not demonstrated a clinical benefit for survival compared with observation or chemotherapy alone in all stages. 9,105–107 On the other hand, the rationale for a combined modality with both chemotherapy and radiotherapy is stronger.105–107 In particular, the clinical benefit of adding radiotherapy is particularly evident in the case of positive lymph nodes, unknown nodal status (ie, un-staged patients probably harboring occult metastasis), or sarcoma dominance, where it has been shown to both reduce locoregional recurrence and improve oncologic outcomes.9 28 62 The target volumes include the pelvis and nodal areas at risk as well as the vaginal cuff. The most common dose prescription is 45–50 Gy (1.8–2.0 Gy per fraction) external beam radiation treatment plus 6 Gy x three vaginal brachytherapy. When performed, vaginal brachytherapy should cover only the upper third (or the proximal 3–4 cm) of the vagina.61

Endocrine Therapy

Endocrine therapy may also be an alternative in the metastatic setting, especially in the case of frail, elderly women not suitable to receive further chemotherapy lines. To date, available data on hormone therapy for endometrial carcinosarcoma are still scant, although there is anecdotal evidence on the efficacy of systemic progestins in the estrogen receptor/progestin receptor-positive setting, thus further investigation is suggested. However, since endometrial carcinosarcomas are most frequently high-grade undifferentiated tumors, they generally express low levels of hormone receptors (estrogen receptor: 20–30%; progesterin receptor: 5–40%), and hormonal therapies should probably be reserved for challenging cases where there are no other valuable alternatives.128

FOLLOW-UP

The follow-up program for endometrial carcinosarcoma follows that of high-risk endometrial cancers. For the high-risk groups, physical and gynecological examinations are recommended every 3–4 months for the first 2 years, and then every 6 months until 5 years.9 28 108 Physical and radiological assessment are recommended on a regular basis. A CT scan every 12 months for the first 3–5 years (and then on an individual basis) can be considered, particularly if nodal involvement was present at diagnosis.9 28 108 Routine serum CA125 dosage is not recommended, although it can be useful to guide the decision-making process if it was elevated at diagnosis.9 28 Finally, Pap smears have not been shown to be useful for detecting local recurrences. When there are symptoms (eg, vaginal bleeding or discharge), an appropriate investigation should be carried out to exclude a recurrence.108

RECURRENT TREATMENT

Despite surgical treatment and timely adjuvant multimodal therapy, more than half of the cases of endometrial carcinosarcoma will recur within the first 2 years.19 The management of the recurrent disease is highly personalized and should consider several factors, such as the performance status of the patient, the size and sites of recurrences, and prior therapies.9 10 28 Importantly, it depends on whether the relapse is locoregional, oligometastatic, or disseminated and, second, on whether the patient has already received radiotherapy, as radiotherapy rechallenge is generally avoided for safety reasons (Table 2). Again, the best treatment approach is multimodal. Patients with recurrent disease (including peritoneal and lymph node relapse) should be considered for surgery only if it is anticipated that complete removal of macroscopic disease can be achieved with acceptable morbidity and be treated in specialized centers.9 External beam radiotherapy can be used in radiotherapy-naïve patients or those who had received only prior vaginal brachytherapy. Immunotherapy (with or without tyrosine kinase inhibitor) is the emerging preferred second-line systemic treatment. After the failure of immunotherapy, chemotherapy alone (generally mono-chemotherapy) is the preferred treatment in cases of disseminated metastases.10 33 Due to the poor outcomes associated with standard treatments for relapses, enrollment in clinical trials is highly recommended.

NOVEL THERAPEUTIC AGENTS AND FUTURE PERSPECTIVES

In this era of precision medicine, there is an unmet clinical need to better understand the pathogenesis and molecular landscape of endometrial carcinosarcoma. It is now clear that not all endometrial carcinosarcomas can be managed in the same way, as endometrial carcinosarcoma is not a single entity but instead can display various genetic, molecular, and histologic profiles. The ability to address the molecular characterization of each singular tumor may open new therapeutic horizons for endometrial carcinosarcoma and help to overcome the poor prognosis. In light of the new molecular classification and raised awareness of the pathogenesis, endometrial carcinosarcoma is being progressively included in endometrial cancer clinical trials after being understudied for several years. However, as we know, conducting prospective clinical trials for rare and heterogeneous tumors is challenging while more concrete support can probably come from multicenter retrospective studies or basket trials. Future trials should focus on the efficacy of pattern-specific treatments, selected based on the specific signatures of endometrial carcinosarcoma. Several molecular studies described mutations or alterations of multiple genes and pathways in endometrial carcinosarcoma, including c-KIT, TKR, VEGF, EGFR, Her2/neu, NTRK, PI3K/AKT/mTOR pathway, WEE1, KRAS, EXP, BRCA1/2, and other genes related to cell-cycle regulation (including homologous recombination deficiency), histone modification, and chromatin remodeling, which may all represent potential targets.21–27

New molecular-targeted therapies may play a pivotal role in the treatment of endometrial carcinosarcoma, especially in the recurrence/metastatic setting, and many of these are currently being investigated in prospective clinical trials (Table 5), with the most promising therapeutic agents being immune checkpoint inhibitors, HER2 targeting agents, and WEE1 inhibitors.104

Immune Checkpoint Inhibitors

Immunotherapy is an emerging area of research and treatment for endometrial cancers, especially for patients with advanced/recurrent disease. There are currently two FDA-approved immune checkpoint inhibitors for the treatment of endometrial cancer,
<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT identifier</th>
<th>Design</th>
<th>Setting</th>
<th>Treatment arms</th>
<th>Primary endpoints</th>
<th>Status</th>
<th>Estimated enrollment</th>
<th>ECD</th>
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<tbody>
<tr>
<td>A phase II trial of pembrolizumab plus lenvatinib for the treatment of patients with advanced uterine and ovarian carcinosarcoma</td>
<td>NCT05147558</td>
<td>Open-label, single-center, single-arm, phase II trial</td>
<td>Advanced uterine and ovarian carcinosarcomas, up to three prior CHT lines</td>
<td>Lenvatinib (20 mg once daily OS)+pembrolizumab (200 mg every 3 weeks IV), until PD or unacceptable toxicity</td>
<td>ORR PFS</td>
<td>Recruiting</td>
<td>40</td>
<td>December 23, 2023</td>
</tr>
<tr>
<td>A phase II trial of pembrolizumab plus olaparib for the treatment of patients with persistent/recurrent endometrial cancers</td>
<td>NCT05156268</td>
<td>Open-label, single-center, single-arm, phase II trial</td>
<td>Persistent/recurrent endometrial cancers (serous, grade 3 endometrioid, undifferentiated, ECS)</td>
<td>Olaparib 300 mg PO twice daily+pembrolizumab 200 mg IV q21, until PD or unacceptable toxicity</td>
<td>ORR</td>
<td>Recruiting</td>
<td>25</td>
<td>January, 2024</td>
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<tr>
<td>An open-label, non-randomized multisite phase II trial combining bevacizumab, atezolizumab, and rucaparib for the previously treated recurrent and progressive endometrial carcinoma</td>
<td>NCT03594262 (Endo BARR)</td>
<td>Open-label, single-center, single-arm, phase II trial</td>
<td>Metastatic PD1-high-expressing tumors defined by a single and pre-specified cut-off point</td>
<td>Atezolizumab 1200 mg IV d1+bevacizumab 15 mg/kg IV d1 q21+rucaparib 600 mg orally twice daily, until PD or unacceptable toxicity</td>
<td>ORR</td>
<td>Active, not recruiting</td>
<td>30</td>
<td>June 28, 2026</td>
</tr>
<tr>
<td>Efficacy of spartalizumab across multiple cancer-types in patients with PD1-high mRNA expression tumors defined by a single and pre-specified cut-off point</td>
<td>NCT04802876</td>
<td>Open-label, single-center, single-arm, phase II trial</td>
<td>Metastatic PD1-high-expressing tumors</td>
<td>Spartalizumab (PDR001)400 mg IV q28, until PD or unacceptable toxicity</td>
<td>ORR</td>
<td>Recruiting</td>
<td>141</td>
<td>December 11, 2024</td>
</tr>
<tr>
<td>Phase II trial of single-agent nivolumab in patients with microsatellite unstable/mismatch repair-deficient/hypermutated uterine cancer</td>
<td>NCT03241745</td>
<td>Open-label, single-center, single-arm, phase II trial</td>
<td>Microsatellite unstable/mismatch repair-deficient/hypermutated uterine cancer</td>
<td>Nivolumab 480 mg IV every 4 weeks, until PD or unacceptable toxicity</td>
<td>PFS</td>
<td>Active, not recruiting</td>
<td>35</td>
<td>August, 2023</td>
</tr>
</tbody>
</table>
| A phase II trial of IDO inhibitor, BMS-986205, and PD-1 inhibitor, nivolumab, in patients with recurrent or persistent endometrial cancer or endometrial carcinosarcomas (CA017-056) | NCT04106414           | Open-label, multicenter, phase II RCT | Recurrent or persistent endometrial cancer or endometrial carcinosarcomas | ► Arm 1: Nivolumab 480 mg every 4 weeks.  
► Arm 2: Nivolumab 480 mg every 4 weeks with BMS-986205 100 mg. | ORR               | Active, not recruiting | 24                   | September, 2023     |
| A phase III, randomized, double-blind, multicenter study of dostarlimab (TSR-042) plus carboplatin-paclitaxel vs placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced endometrial cancer (RUBY) | NCT03581796 ENGOT-ENSGO-3031 | Double-blind, multicenter, phase III RCT | Recurrent or primary advanced endometrial cancer | ► Arm 1: Dostarlimab+carboplatin-paclitaxel followed by dostarlimab  
► Arm 2: Dostarlimab+carboplatin-paclitaxel followed by placebo  
► Arm 3: Placebo+carboplatin-paclitaxel followed by placebo  
► Arm 4: Placebo+carboplatin-paclitaxel followed by placebo  
► Arm 5: Dostarlimab+carboplatin-paclitaxel followed by niraparib placebo  
► Arm 6: Placebo+carboplatin-paclitaxel followed by niraparib placebo | PFS OS               | Active, not recruiting | 785                  | December 23, 2026   |
| A multicentric randomized phase II/III evaluating TSR-042 (anti-PD-1 mAb) in combination with niraparib (parp1) vs niraparib alone compared with chemotherapy in the treatment of metastatic or recurrent endometrial or ovarian carcinosarcoma after at least one line of chemotherapy | NCT03651206 (ROCSAN) | Open-label, multicenter, phase II/III RCT | Metastatic or recurrent endometrial or ovarian carcinosarcoma, at least one prior CHT line | ► Arm 1: Niraparib 200 to 300 mg PO QD  
► Arm 2: Niraparib 200 to 300 mg PO QD+dostarlimab 500 mg IV q21 for the first four cycles, followed by 1000 mg IV q42  
► Arm 3: ICT (standard of care) | ORR OS               | Recruiting          | 196                  | June, 2025            |
### A phase II trial of durvalumab(MEDI4736)(anti-PD-L1 antibody) with or without tremelimumab (anti-CTLA-4 antibody) in patients with persistent or recurrent endometrial carcinoma and endometrial carcinosarcoma

**NCT identifier**: NCT03015129  
**Design**: Open-label, multicenter, phase II RCT  
**Setting**: Persistent or recurrent endometrial carcinoma and endometrial carcinosarcoma  
**Treatment arms**:  
- Arm 1: Durvalumab 1500 mg every 4 weeks, until PD or unacceptable toxicity  
- Arm 2: Durvalumab 1500 mg+remelimumab 5 mg IV every 4 weeks for up to four cycles, and then continue durvalumab alone, until PD or unacceptable toxicity  
**Primary endpoints**: ORR  
**Status**: Active, not recruiting  
**Estimated enrollment**: 80  
**ECD**: January 2024

### A phase II study of the WEE1 Inhibitor AZD1775 in women with recurrent or persistent uterine serous carcinoma or uterine carcinosarcoma

**NCT identifier**: NCT0366834  
**Design**: Open-label, multicenter, single-arm, phase II trial  
**Setting**: Recurrent or persistent USC or ECS, at least one prior CHT line  
**Treatment**:  
- Adavosertib 300 mg PO QD d1–5, 8 to 12 q21, until PD or unacceptable toxicity  
**Primary endpoints**: Proportion of patients with completion of 4 cycles  
**Status**: Recruiting  
**Estimated enrollment**: 80  
**ECD**: June 1, 2023

### Feasibility IB trial of paclitaxel/ carboplatin+galunisertib (a small molecule inhibitor of the kinase domain of type 1 TGF-β receptor) in patients with newly diagnosed, persistent or recurrent carcinosarcoma of the uterus or ovary

**NCT identifier**: NCT03206177  
**Design**: Open-label, multicenter, single-arm, phase IB trial  
**Setting**: Newly diagnosed, persistent or recurrent carcinosarcoma of the uterus or ovary  
**Treatment**:  
- Galunisertib 150 mg PO Twice daily d4–17+Paclitaxel 175 mg/m² IV d1+CBDCA AUC 5/6 IV d1 q21, until PD or unacceptable toxicity  
**Primary endpoints**: ORRSOSDLTs  
**Status**: Active, not recruiting  
**Estimated enrollment**: 26  
**ECD**: August 19, 2023

### Phase II trial on trabectedin In the treatment of advanced uterine and ovarian carcinosarcoma

**NCT identifier**: NCT02993705 (MITO26)  
**Design**: Open-label, multicenter, single-arm, phase II trial  
**Setting**: Advanced or recurrent ovarian and uterine carcinosarcoma, up to two prior CHT lines  
**Treatment**: Trabectedin 1.3 mg/m² IV q21, until PD or unacceptable toxicity  
**Primary endpoints**: ORR  
**Status**: Completed (no results posted)  
**Estimated enrollment**: 45  
**ECD**: November 13, 2019

### A phase II study of metformin in combination with doxycycline in patients with localized breast, and uterine, and cervical cancer

**NCT identifier**: NCT02874430  
**Design**: Open-label, multicenter, single-arm, phase II trial  
**Setting**: Localized breast, uterine, and cervical cancer  
**Treatment**: Metformin PO QD d1–3 and twice daily d4+doxycycline PO twice daily d1 q7 for up to two courses  
**Primary endpoints**: Change in the percent of stromal cells expressing caveolin-1 (CAV1) at an intensity of 1+ or greater assessed by immunohistochemistry  
**Status**: Active, not recruiting  
**Estimated enrollment**: 27  
**ECD**: June, 2022

### A phase II/III study of paclitaxel/carboplatin alone or combined with either trastuzumab and hyaluronidase-osykk (HERCEPTIN HYLECTA) or pertuzumab trastuzumab and hyaluronidase-Zzfx (PERJEPZen) in Her2-positive, stage I-IV endometrial serous carcinoma or carcinosarcoma

**NCT identifier**: NCT05256225 (NCI-2022-01540 NRG-GY026)  
**Design**: Multicenter, phase II/III RCT  
**Setting**: Newly diagnosed, HER2 positive endometrial serous carcinoma or carcinosarcoma, no prior CHT  
**Treatment arms**:  
- Arm 1 (comparator): Paclitaxel IV+CBDCA IV q21 for six cycles (± further four cycles, if SD or PR)  
- Arm 2: Paclitaxel IV+CBDCA IV-trastuzumab SC q21 for six cycles (± further four cycles, if SD/PR → Trastuzumab maintenance q21 for up to 1 year (or 3 years, if SD/PR)  
- Arm 3: Paclitaxel IV+CBDCA IV-pertuzumab + Trastuzumab SC q21 for six cycles (± further four cycles, if SD/PR) → pertuzumab+trastuzumab maintenance q21 for up to 1 year (or 3 years, if SD/PR)  
**Primary endpoints**: ORR, PFS, OS, DLTs  
**Status**: Not yet recruiting  
**Estimated enrollment**: 326  
**ECD**: October 31, 2027

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Table 5 Continued
### Table 5 Continued

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT identifier</th>
<th>Design</th>
<th>Setting</th>
<th>Treatment arms</th>
<th>Primary endpoints</th>
<th>Status</th>
<th>Estimated enrollment</th>
<th>ECD</th>
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| Pazopanib vs pazopanib plus gemcitabine in patients with relapsed or metastatic uterine leiomyosarcomas or uterine carcinosarcomas: a multicenter, randomized phase II clinical trial of the NOGGO and AGO | NCT02203760 NOGGO U1 (PazoDoble) | Multicenter, single-arm, phase III RCT | Relapsed or metastatic carcinosarcomas, prior CHT lines | Arm 1: Pazopanib 800 mg PO QD+gemcitabine 1000 mg/mq IV d1,q21, until PD or unacceptable toxicity  
Arm 2 (comparator): Pazopanib 800 mg PO QD, until PD or unacceptable toxicity | PFS6             | Recruiting                | 0                         | December, 2023                                    |
| A dose escalation study of HFB301001 (OX40 agonist antibody) in adult patients with advanced solid tumors | NCT05229601 | Open-label, multicenter, two-stage, phase I trial | Advanced solid tumors (including ECS) | Dose escalation: participants will be administered HFB301001 dose level 1 IV in cohort 1. Participants in cohorts 2 to 4 will receive dose levels 2 to 4, respectively.  
AEs                                      | DLTs           | Recruiting                | 1                         | January, 2024                                     |
| A phase II study of AZD0530 in recurrent or metastatic soft tissue sarcoma | NCT00659360 NCI-2009–01054 | Open-label, multicenter, single-arm, phase II trial | Recurrent, locally advanced or metastatic soft tissue sarcoma | AZD0530 (saracatinib) 175 mg PO QD, until PD or unacceptable toxicity | DCR               | Completed (results posted): ORR: 0%  
ORR: 0%  
OS: 16.1 months  
PFS: 1.7 mos | 17            | November, 2012 (Last update posted: June 29, 2018) |
| A phase II study of VEGF-Trap in recurrent or metastatic gynecologic soft tissue sarcomas | NCT00390234 NCI-2009–00177 | Open-label, multicenter, single-arm, phase II trial | Locally advanced, unresectable, or metastatic gynecologic soft tissue sarcoma | Ziv-afilibercept IV q14, until PD or unacceptable toxicity | ORR               | Completed (results posted): ORR: 0%  
PFS6: 1.6 months | 63             | August, 2013 (Last update posted: December 7, 2015) |
| Phase I study of mirvetuximab soravtansine (IMGN853) and rucaparib for recurrent endometrial, ovarian, fallopian tube or primary peritoneal cancer | NCT03552471 NCI-2018–00438 | Open-label, multicenter, single-arm, phase I trial | Recurrent endometrial, ovarian, fallopian tube, or primary peritoneal cancer | Mirvetuximab soravtansine IV q21+rucaparib PO Twice daily, until PD or unacceptable toxicity | RP2D              | Active, not recruiting          | 25             | December 31, 2022            |
| Targeted complex therapy for advanced melanoma, gynecologic cancers, and other malignancies: Nab-paclitaxel (Abraxane)/bevacizumab complex (AB-complex) | NCT02020707 NCI-2013–01782 | Open-label, multicenter, single-arm, phase I trial | Unresectable stage IV melanoma or gynecological cancers | Nab-paclitaxel/bevacizumab-complex IV d1,8,15 q28, until PD or unacceptable toxicity | MTD               | Recruiting                | 73             | June 1, 2025               |
| A phase I, open-label, multicenter study of INCB123667 as monotherapy in participants with selected advanced solid tumors | NCT05238922 | Open-label, multicenter, single-arm, phase II trial | Advanced or metastatic solid tumors | Part 1 a: dose escalation to identify the RD(s) with a starting dose of INCB123667 of 50 mg QD.  
Part 1B: dose expansion | Part 1A: DLTs, AEs  
Part 1B: PK parameters, ORR, DOR, DOR | Recruiting | 155            | July 30, 2026                                |
<p>| A Phase II study evaluating the efficacy and safety of DKN-01 as a monotherapy or in combination with paclitaxel in patients with recurrent epithelial endometrial epithelial ovarian cancer, or carcinosarcoma | NCT033995080 | Open-label, multicenter, phase II trial | Recurrent epithelial endometrial or epithelial ovarian cancer or carcinosarcoma | DKN-01 600 mg IV±PTX IV in ECS | ORR, CTOAEs, PK parameters | Completed (no results posted) | 111           | January 27, 2021            |</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Setting</th>
<th>Treatment arms</th>
<th>Primary endpoints</th>
<th>Status</th>
<th>Estimated enrollment</th>
<th>ECD</th>
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<tr>
<td>A 3-arm randomized phase II evaluation of cediranib in combination with weekly paclitaxel or olaparib vs weekly paclitaxel chemotherapy for advanced endometrial carcinoma or for disease relapse within 18 months of adjuvant carboplatin-paclitaxel chemotherapy.</td>
<td>Open-label, multicenter, phase II RCT</td>
<td>Advanced or recurrent endometrial carcinoma or carcinosarcoma, at least one prior CHT</td>
<td>• Arm 1: Paclitaxel 80 mg/m² IV d1,8,15 + Q28 for up to six cycles • Arm 2: Paclitaxel 80 mg/m² IV d1,8,15+Q28 for up to six cycles + cediranib 20 mg PO QD, until PD or unacceptable toxicity • Arm 3: Cediranib 20 mg PO QD + olaparib 300 mg PO Twice daily, until PD or unacceptable toxicity</td>
<td>PFS</td>
<td>Active, not recruiting</td>
<td>124</td>
<td>June 30, 2023</td>
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<tr>
<td>Dose escalation and expansion clinical study to evaluate the safety and efficacy of ELU001 in subjects who have advanced, recurrent or refractory FRα overexpressing tumors</td>
<td>Open-label, multicenter, single-arm, two-stage, phase II trial</td>
<td>Advanced, recurrent, or refractory FRα-overexpressing tumors</td>
<td>Dose escalation: escalating doses of ELU001 Dose expansion: RP2D</td>
<td>MTD</td>
<td>Recruiting</td>
<td>166</td>
<td>March 15, 2025</td>
</tr>
<tr>
<td>A phase II trial of ZW25 in HER2 overexpressed advanced endometrial cancers and carcinosarcomas (ZW25-IST-2)</td>
<td>Open-label, multicenter, single-arm, two-stage, phase II trial</td>
<td>Recurrent or persistent HER2 overexpressing endometrial cancer or endometrial carcinosarcoma, 1-2 prior CHT</td>
<td>ZW25 (Zanidatamab) 20 mg/kg IV every 2 weeks</td>
<td>ORR</td>
<td>Recruiting</td>
<td>25</td>
<td>April 12, 2023</td>
</tr>
<tr>
<td>SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma</td>
<td>A single-arm phase II trial</td>
<td>Recurrent or persistent HER2 overexpressing endometrial cancer, 1 prior platinum-based CHT</td>
<td>SYD985, Intravenous, every 3 weeks (Q3W)</td>
<td>ORR</td>
<td>Active, not recruiting</td>
<td>60</td>
<td>December, 2022</td>
</tr>
<tr>
<td>A phase I/II study of T-DXd in patients with selected HER2 expressing tumors (DPT02)</td>
<td>Open-label, multicenter, single-arm, two-stage, phase II trial</td>
<td>Seven cohorts of urothelial bladder cancer, biliary tract cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and rare tumors.</td>
<td>Trastuzumab deruxtecan by intravenous infusion</td>
<td>ORR</td>
<td>Active, not recruiting</td>
<td>268</td>
<td>June 16, 2023</td>
</tr>
<tr>
<td>Phase I trial of intravenous administration of vesicular stomatitis virus genetically engineered to express thyroid sodium iodide symporter (NIS) and human interferon β, in patients with metastatic or recurrent endometrial cancer</td>
<td>Open-label, multicenter, phase I RCT</td>
<td>Metastatic or recurrent endometrial cancer</td>
<td>VSV-hIFNbeta-NIS with or without ruxolitinib phosphate</td>
<td>MTD</td>
<td>Recruiting</td>
<td>77</td>
<td>July 15, 2023</td>
</tr>
<tr>
<td>A phase I/II study to evaluate the safety, pharmacokinetics, and efficacy of BLU-222 as a single agent and in combination therapy for patients with advanced solid tumors</td>
<td>Open-label, multicenter, phase II trial</td>
<td>Advanced solid tumors</td>
<td>• Arm 1: BLU-222 • Arm 2: BLU-222 + carboplatin • Arm 3: BLU-222 + ribociclib + fulvestrant • Arm 4: BLU-222 + fulvestrant</td>
<td>MTD</td>
<td>Recruiting</td>
<td>366</td>
<td>September 2026</td>
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<tr>
<td>ATARI: ATR Inhibitor in combination With olaparib in gynecological cancers with ARId1A loss</td>
<td>Open-label, multicenter, two-stage, phase II trial</td>
<td>Progressive or recurrent gynecological cancers with ARId1A loss</td>
<td>AZD6738 + olaparib</td>
<td>ORR</td>
<td>Recruiting</td>
<td>40</td>
<td>March 2023</td>
</tr>
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</table>
Phase I study of the CDK4/6 inhibitor palbociclib (PD-0332991) in combination with the PI3K/mTOR inhibitor gedatolisib (PF-05212384) for patients with advanced squamous cell lung, pancreatic, head and neck, and other solid Tumors

NCT03065062

Open-label, multicenter, two-stage, phase I trial

Advanced solid tumors

Palbociclib PO QD on days 1 to 21 for each of the 4-week cycles Gedatolisib IV once weekly on the first day for each of the 4 weeks during the 4-week cycles.

MTD

RP2D

CTCAEs

Recruiting

96

January, 2024

Estimated enrollment

ECD

*Data extracted by clinicaltrials.gov.104

AE, adverse events; AUC, area under curve; CBDCA, carboplatin; CHT, chemotherapy; CTCAEs, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DLT, dose-limiting toxicities; DOR, duration of response; EC, endometrial cancer; EGD, estimated completion date; EGS, endometrial carcinosarcoma; HER2, human epidermal growth factor receptor 2; ICT, investigator choice of therapy; IV, intravenous; MTD, maximum tolerated dose; OIR, objective response rate; OS, overall survival; PD, progressive disease; PFS6, progression-free survival at 6 months; PFS, progression-free survival; PK, pharmacokinetics; PO, per os; PR, partial response; PTX, paclitaxel; RCT, randomized clinical trial; RDE, recommended dose of expansion; RP2D, recommended phase 2 dose; SD, stable disease; TGF-β, transforming growth factor β; USC, uterine serous carcinoma.
under investigation in dedicated clinical trials, alone or in combination (Table 5): pembrolizumab plus lervatinib (NCT05147558), pembrolizumab plus olaparib (NCT05156268), atezolizumab plus bevacizumab and rucaparib (NCT03694262/EndoBARR), spartalizumab (NCT04802876), nivolumab (NCT03241745), nivolumab plus IDO1 inhibitor (NCT04106414), dostarlimab plus niraparib (NCT03981796/ENGOT-EN6-GOG-3031, NCT03651206/ROCSAN), durvalumab plus tremelimumab (NCT03015129).104

HER2 Targeting Agents

HER2/neu is a tyrosine kinase membrane receptor encoded by the ERBB2 gene and a member of the epidermal growth factor receptor family.111 112 Its role has been well-acknowledged in breast and gastric cancers, where HER2 overexpression has been reported in approximately 15–30% and 7–34% of cases, respectively, leading to the introduction of the monoclonal antibody trastuzumab as a standard treatment in the HER2-positive adjuvant (breast tumors) and metastatic setting (breast and gastric tumors).113 114

To date, the adoption of trastuzumab in uterine serous carcinoma is supported by the NCCN guidelines.28 Trastuzumab can be added (8 mg/kg for the first dose and 6 mg/kg in subsequent cycles) to chemotherapy in HER2-positive uterine serous carcinoma.115 Importantly, a consensus definition for HER overexpression/amplification in endometrial carcinosarcoma is lacking for endometrial cancer. Generally, HER2-positive tumors are defined as 3+ by immunohistochemistry or 2+ by immunohistochemistry with confirmatory in situ hybridization testing.113 114

Several trials are currently investigating the role of HER2 as a molecular target in other solid tumors harboring HER2 amplification, including endometrial carcinosarcoma.104 Pre-clinical research has suggested the efficacy of trastuzumab and another monoclonal antibody, pertuzumab, in endometrial carcinosarcoma.113 115 The rate of HER2 amplification in endometrial carcinosarcoma is 10–20% and reaches nearly 50% in high-grade and recurrent diseases, making it a promising therapeutic target.113 114 Significantly improved survival rates have been recently demonstrated when adding trastuzumab to carboplatin/paclitaxel in recurrent/metastatic HER2-positive uterine serous carcinoma (17.9 vs 9.3 months for advanced-stage disease and 9.2 vs 6.0 months for recurrent disease).113 114 Since serous carcinoma and endometrial carcinosarcoma share a similar molecular background, this treatment strategy has gained increasing attention also in endometrial carcinosarcoma.104

Two clinical studies are currently investigating the intriguing role of HER2 targeting agents specifically in endometrial carcinosarcoma and results are excitedly awaited (Table 5). A multicenter phase II/III trial (NCT05256225) is currently addressing the efficacy of paclitaxel/carboplatin alone or combined with either trastuzumab or pertuzumab/trastuzumab, in newly diagnosed, HER2-positive uterine serous carcinoma and endometrial carcinosarcoma.104 A possible synergistic effect for the combination of the two monoclonal antibodies has been suggested in gynecological malignancies.115 The phase II trial NCT04513665 is investigating the efficacy of another monoclonal antibody, zanidatamab (ZW25), in recurrent or persistent HER2-overexpressed endometrial cancer (including endometrial carcinosarcoma), with one to two prior lines of chemotherapy.104 Moreover, antibody drug conjugates are under evaluation even in HER2-low solid tumors (including endometrial carcinosarcoma).104 The phase II STATICE trial tested trastuzumab deruxtecan (T-DXd) in HER2-positive 1+ by immunohistochemistry endometrial carcinosarcomas. The trial enrolled 34 patients. The preliminary data of this trial is very exciting, with an estimated overall response rate of about 60%.116

WEE1 Inhibitors

WEE1 is a kinase protein that plays a key role in the correct functioning of the G2/M cell-cycle checkpoint, where the cell has the opportunity to further grow and repair the DNA damage before starting the mitotic phase.117 Its role is even more important in the presence of a TP53 mutation, which determines the loss of the G1/S cell-cycle checkpoint and so an increased cell dependency on the regulation of the G2/M checkpoint by WEE1. Since almost all endometrial carcinosarcomas harbor a p53 mutation, these tumors are characterized by cell-cycle dysregulation and high replication stress and so might be particularly vulnerable to WEE1 blockade. Adavosertib is a potent and selective oral WEE1 inhibitor, that has already shown encouraging and durable evidence of activity in women with uterine serous carcinoma, with an overall response rate of 29%, and is now being further investigated in the phase Ib ADAGIO trial.117 A phase II trial (NCT03668340) is currently investigating its efficacy also in the setting of recurrent or persistent endometrial carcinosarcoma after one or more lines of chemotherapy (Table 5).104

Targeting Epithelial–Mesenchymal Transition

The epithelial–mesenchymal transition is the process by which epithelial cells lose their polarity and intercellular junctions and become multipotent mesenchymal cells with invasion and metastatic properties and the ability to differentiate in several cell types. The epithelial–mesenchymal transition is crucial in nearly all cancers and, notably, plays a key role in the pathogenesis of sarcomatous trans-differentiation from carcinomatous elements in endometrial carcinosarcoma.118 119 Endometrial carcinosarcomas with sarcoma dominance and heterologous sarcomatous component display a higher epithelial–mesenchymal transition and have been associated with poorer outcomes than homologous ones. Therefore, the pathogenesis of epithelial–mesenchymal transition has gained increasing attention as its blockage could be a valid therapeutic strategy for patients with endometrial carcinosarcoma. In particular, by blocking epithelial–mesenchymal transition, endometrial carcinosarcomas would maintain their original carcinomatous prevalence and hence be more responsive to the standard treatments used for carcinomas. A clinical trial (the GYNecological Cancers Treated With NETrin mAbs in Combination With Chemotherapy and/or Pembrolizumab (GYNET, NCT04652076)) is ongoing to explore such mechanism of action in gynecological cancers.104 The epithelial–mesenchymal transition is regulated by complex networks involving transcriptional factors, growth factors, and cytokine signaling pathways, such as the transforming growth factor TGF-β1, Wnt, JAK/STAT, and MAPK cascade. In particular, TGF–β regulates a key pathway in the epithelial–mesenchymal transition process and may be a potential target.118 119 A phase IB trial (NCT03206177) is currently investigating the feasibility of combining galunisertib (TGF–β1 inhibitor) with the paclitaxel/carboplatin doublet in patients with newly diagnosed, persistent, or recurrent endometrial carcinosarcoma (Table 5).104
CONCLUSIONS
Endometrial carcinosarcoma is now regarded, and consequently staged and treated, as a primary endometrial carcinoma. Despite its rarity, the incidence of endometrial carcinosarcoma is slowly growing while the prognosis has remained extremely poor, despite current available multimodal treatment strategies. Historically, endometrial carcinosarcoma has been underinvestigated and mostly in retrospective series or in unspecific clinical trials designed for uterine sarcomas and endometrial carcinomas. Over the past years, there has been a raised awareness and understanding of endometrial carcinosarcoma pathogenesis and molecular landscape. In the era of tumor-agnostic therapies, researchers should be encouraged to design ad hoc endometrial carcinosarcoma-oriented studies to develop new practice-changing targeted therapies and provide specific guidelines for the management of endometrial carcinosarcoma. In the wake of the new insights in endometrial carcinosarcoma treatment, immunotherapy (plus tyrosine kinase inhibitor) and HER2-targeting antibodies seem to be the most promising agents for the future, and results from ongoing trials are expectedly awaited.

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Contributors Substantial contributions to the conception or design of the work; All authors. Drafting the work or revising it critically for important intellectual content: All authors. Final approval of the version to be published: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

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Consensus statement

Consensus statement


