ENDOMETRIAL CANCER

CHI Formulary Indication Review

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Contents

List of Tables

List of Figures

Abbreviations

BGCS	British Gynecological Cancer Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete Blood Count
CrCl	Creatinine Clearance
CT	Computer Tomography
dMMR	Mismatch Repair Deficient
EBRT	External Beam Radiotherapy
EC	Endometrial Cancer
ER	Estrogen Receptor
ESGO	European Society of Gynecological Oncology
ESMO	European Society of Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FIGO	International Federation of Gynaecology and Obstetrics
GFR	Glomerular Filtration Rate
HAS	Haute Autorité de Santé
HR	Hazard Ratio
HrQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICI	Immune Checkpoint Inhibitor
IHC	Immunohistochemistry
IQWIG	Institute for Quality and Efficiency in Healthcare
IORT	Intra-Operative Radiotherapy
IUD	Intrauterine Device
JSGO	Japan Society of Gynecologic Oncology
KSA	Kingdom of Saudi Arabia
LVSI	Lymphovascular Space Invasion
MSI-H	Microsatellite Instability High
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSMP	No Specific Molecular Profile
ORR	Objective Response Rate
OS	Overall Survival
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Peritoneal Dialysis
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand-1
pERC	pan-Canadian Oncology Drug Review Expert Review Committee

PET	Positron Emission Tomography
PFS	Progression-Free Survival
pMMR	Mismatch Repair Proficient
POLEmut	POLE ultramutated
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
RT	Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SITC	Society for Immunotherapy of Cancer
SLN	Sentinel Lymph Node
TMBH	Tumor Mutational Burden High

Executive Summary

Uterine cancer is the most common gynecologic malignancy in high-income countries and the second most common in low- and middle-income countries (where cervical cancer is more dominant)[1]. **Adenocarcinoma of the endometrium** (also known as **endometrial cancer** (EC), or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common cancer malignancy of the female genital tract in the United States[1]. With 400,000 new cases and over 80,000 deaths a year worldwide, endometrial cancer is the tumor with the highest increase in incidence, a unique trend among gynecological cancers[2].

Risk factors for uterine neoplasms include **increased levels of estrogen** (caused by obesity, diabetes, and high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, ages between 55 and 64 years, and tamoxifen use[3,4,5]. Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity. Most endometrial cancer (95%) is caused by sporadic (somatic mutations. However, **genetic mutations** cause endometrial cancer in about **5% of patients**, which occurs 10 to 20 years before sporadic cancer[3,4].

Abnormal uterine bleeding (AUB) is the **cardinal symptom** of endometrial cancer. A minority of patients present with abnormal findings on cervical cytology. Most patients are diagnosed when disease is still confined to the uterus and thus have a greater than 90% 5-year survival rate[6,7].

Screening – As per the American Cancer Society (ACS) guidance, for most patients, performing screening tests (e.g., imaging, tissue sampling, and cervical cytology) is not preferred for endometrial carcinoma; all patients should be asked about and told to report AUB[8]. The exception is patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer) and Cowden syndrome who have a lifetime risk of endometrial cancer between 13 and 71% compared with 3% in the general population. Strategies for screening and prevention of endometrial cancer in these patients include endometrial sampling and risk-reducing hysterectomy[8].

Clinical findings – Pelvic examination is usually normal in patients with early-stage disease. In more advanced disease, the uterus may be enlarged and/or fixed in the pelvis. In postmenopausal patients, uterine imaging may show a thickened endometrium[1,9].

Diagnosis – Endometrial carcinoma is a **histologic diagnosis** based upon the results of evaluation of an **endometrial biopsy**, curettage sample, or hysterectomy specimen[9].

Initial Workup – Prior to treatment, patients with endometrial cancer should have a complete evaluation, including history and physical examination, complete blood count (including platelets), expert pathology review with additional endometrial

biopsy as indicated, imaging, recommendation of genetic evaluation of tumor and for inherited cancer risk, consideration of liver function tests (LFTs)/renal function tests or chemistry profile[10,11,12,13,14,15,16].

- An **expert pathology review** will determine whether a patient has a malignant epithelial tumor (epithelial tumor types include pure endometrioid cancer and carcinomas with high-risk endometrial histology or a stromal/malignant mesenchymal tumor[10].
- A **chest radiograph** should be performed as part of the initial assessment to exclude lung metastases. Abdominal and pelvic imaging is rarely performed in patients with nonaggressive ECs but is often used to exclude metastasis from aggressive ECs[10].
- **Sources of estrogen** – In postmenopausal patients, development of endometrial carcinoma requires assessment of endogenous and exogenous sources of estrogen. In the absence of common sources of estrogen (e.g., estrogen therapy, obesity, selective estrogenic receptor modulators, or some herbs), such patients should be evaluated with pelvic ultrasound or other imaging for an adnexal mass, which could be an estrogen-producing sex cord-stromal tumor of the ovary[17].

Surgical staging – EC is **surgically** staged. The standard surgical procedure for patients with endometrial carcinoma is **total hysterectomy with bilateral salpingo-oophorectomy (TH/BSO)** and **lymph node assessment** (except in patient candidates for fertility-sparing options) [11-16,19].

The **FIGO** (International Federation of Gynecology and Obstetrics) system is most commonly used for **staging uterine cancer**[19] (table 1). This grading system applies only to endometrioid and mucinous carcinomas. It excludes high-grade cases such as serous, clear cell, transitional, and neuroendocrine carcinomas; undifferentiated/dedifferentiated carcinomas; and carcinosarcomas[14].

Table 1. 2023 FIGO Staging of Cancer of the Endometrium

Stage	Description
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium

	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa

IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Abbreviations: EEC, endometrioid carcinoma; LVSI, lymphovascular space involvement.

Approach to lymph node evaluation – The approach to lymph node evaluation in patients with EC is a subject of debate and no option has emerged as superior based on the available data. Options for management of retroperitoneal lymph nodes (in the absence of grossly metastatic disease) include no lymph node dissection (LND), systematic LND only if the risk of lymph node metastasis exceeds a certain threshold, routine sentinel lymph node dissection (SLND) following lymphatic mapping, or systematic LND in all patients[10-16].

In the **Kingdom of Saudi Arabia,** cancer of the corpus uteri was the 9th most common cancer among Saudi nationals in 2020 and the 4th most common cancer in females, with 1016 new cases (7.5% of all cancer cases among females), 293 deaths, and a 5-year prevalence of 25.06 cases per 100,000 (ranking 3rd after breast and thyroid cancer)[20]. Endometrial adenocarcinoma was the most common morphologic type of cancer of the corpus uteri in KSA in 2018, accounting for 377 cases (66.8% of all cancers of the corpus uteri)[21]. In a retrospective study conducted in King Abdulaziz University Hospital in Jeddah from 2011 to 2020, 263 female patients underwent uterine resection surgery with an age range from 30 to 95 years old (median age of 61 years)[22]. The majority (71%) presented with abnormal uterine bleeding. The most common histopathological diagnosis was endometrioid carcinoma (70%), followed by serous carcinoma (13.7%). About half (45.6%) did not have previous radiological images, (38.8%) had endometrial thickening, (10.6%) showed uterine mass and (4.9%) had other findings[22]. Histopathological diagnosis revealed type 1 as the most common type in 70% of the patients, type 2 among 22%, and other findings among 8%[22]. Different management methods were used among the participants and the majority have had total abdominal hysterectomy (89.7%), while some have had dilation and curettage (4.6%), and other methods (6.1%)[22].

Prognosis – Most patients with endometrial carcinoma have a favorable prognosis. Prognosis is determined primarily by disease stage, grade, histology, and molecular classification (if known)[1,5].

This report compiles all clinical and economic evidence related to endometrial cancer and associated complications according to the relevant sources. The ultimate objective of issuing endometrial cancer guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to endometrial cancer patients in Saudi Arabia.** The main focus of the

review was on Saudi, North American, and European guidelines issued within the last five years in addition to recent systematic reviews and Meta-Analysis.

Treatment strategies for patients with endometrial cancer are outlined in the below sections[11-16]:

A. Primary Treatment

Most patients with endometrial cancer have stage I disease at presentation, and **surgery (with or without adjuvant therapy) is recommended for medically operable patients** (Recommendation Level A, Evidence Level II)[11-16]. As a general principle, endometrial carcinoma should be removed ***en bloc*** to optimize outcomes; intraperitoneal morcellation should be avoided[11-16]. Pure endometrioid cancer can be divided into **three categories** for defining treatment:

- **Disease limited to the uterus** – For EC staging in patients with disease apparently confined to the uterus (based on physical examination, with or without pelvic imaging) who are surgical candidates and in whom the procedure is expected to be able to be completed without conversion to laparotomy, both NCCN and European guidelines agree on a **minimally invasive surgical approach** (MIS; laparoscopy or robotic surgery), even in patients with high-risk endometrial carcinoma rather than laparotomy (Recommendation Level A, Evidence Level II)[11-16].
  - Conventional **total laparoscopic hysterectomy** with **BSO** is the preferred option for most patients, with use of robotic surgery if this makes MIS possible in patients who have a high risk of conversion to laparotomy (e.g., patients with obesity)[11-16].
  - Patients with apparent uterine-confined endometrial carcinoma are candidates for **SLN mapping**, which assesses the pelvic nodes bilaterally and may be less morbid than complete lymphadenectomy[11-16].
  - For *patients not eligible for primary surgery*, **external beam radiotherapy (EBRT) and/or brachytherapy is the preferred treatment approach** (Recommendation Level A, Evidence Level II); progestational agents can be an alternative in select patients[11-16].
- **Suspected or Gross Cervical Involvement** – For patients with clinically apparent extension of EC to the cervix, **cervical biopsy** or **pelvic MRI** should be performed if not done previously[11-16].
  - If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described, although a radical hysterectomy may be performed when necessary to obtain negative margins.

- It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for patients suitable for primary surgery, **TH or radical hysterectomy** is recommended along with **BSO, cytology** (peritoneal lavage), and **evaluation of lymph nodes** if indicated (Recommendation Level A, Evidence Level II) [11-16].
- Alternatively, the patient may undergo **EBRT and brachytherapy** (Recommendation Level B, Evidence Level II) followed by **TH/BSO** and **surgical staging**[11-16].
- For *patients who are not suited for primary surgery*, **EBRT and brachytherapy** is an effective alternative; it may be administered **with or without platinum-based chemosensitization**, depending on the clinical situation and medical fitness of the patient (Recommendation Level A, Evidence Level II)[11-16].
    - **Cisplatin** is the preferred chemosensitizing agent (Recommendation Level A, Evidence Level II)[11-16].
    - If rendered operable, local treatment consisting of **surgery** should follow.
    - **Systemic therapy alone** is also a primary treatment option (category 2B) but should be followed by EBRT + brachytherapy if the patient remains inoperable[11-16].

- **Suspected Extrauterine Disease** – If extrauterine disease is suspected, **imaging studies** are recommended along with **CA-125 testing**. **Estrogen Receptor** (ER) testing is recommended in the setting of stage III or IV endometrioid tumors, alongside with progesterone receptor (PR) testing when clinically indicated[11-16].
    - Patients with abdominal- or pelvic-confined disease require surgical intervention using **TH/BSO with surgical staging** and **surgical debulking** with the goal to have no measurable residual disease (Recommendation Level A, Evidence Level II); several studies support debulking[11-16].
    - Consider preoperative chemotherapy.
    - Patients with *unresectable extrauterine pelvic disease* (i.e., vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with **EBRT with (or without) brachytherapy with (or without) systemic therapy**, followed by re-evaluation of tailored surgery[11-16].
        - Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT.

- For distant visceral metastasis (e.g., liver involvement), recommended options include systemic therapy with (or without) EBRT with (or without) TH/BSO and with (or without) stereotactic body RT (SBRT). Ablative radiation can be considered for 1 to 5 metastatic lesions if disease is otherwise controlled (Recommendation Level B, Evidence Level II) [11-16].

- **Fertility-Sparing Therapy**: Conservative management may be considered in highly selected patients with **grade 1, stage IA non-invasive endometrioid endometrial carcinoma** who wish to preserve their fertility[11-16].
  - **Continuous progestin-based therapy** is used in that setting and may include megestrol acetate, medroxyprogesterone, or an intrauterine device (IUD) containing levonorgestrel[11-16].
  - Patient-specific factors should be carefully considered, including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking.
  - TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs[11].

B. Adjuvant therapy

B.1 Disease Limited to the Uterus

Thorough **surgical staging** provides important information to assist in selection of adjuvant therapy for endometrial tumors.

- Patients with **stage I** endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (i.e., age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement).
  - **Observation** is preferred for patients with **stage IA, grade 1/2 disease**, but **treatment with adjuvant vaginal brachytherapy** is strongly suggested for patients **≥60 years** and/or with **LVSI** (Recommendation Level A, Evidence Level II) [11-16].
  - For **patients with stage IA, grade 3 tumors**, especially those who have been surgically staged, **vaginal brachytherapy** is the **preferred** option, or observation can be considered if no myometrial invasion is present (Recommendation Level A, Evidence Level II) [11-16].
  - If higher risk factors are present, i.e., age ≥70 years or LVSI, **EBRT** can be considered (Recommendation Level B, Evidence Level II) [11-16].
- For **patients with stage IB, grade 1–2 disease**, **vaginal brachytherapy is preferred** although observation can be considered if no adverse risk factors are present (Recommendation Level A, Evidence Level II) [11-16].

- **EBRT** can be considered in grade 2 tumors if additional risk factors are present such as age ≥60 years and/or if LVSI is present.
- For **stage IB, grade 3 disease with adverse risk factors**, **systemic therapy** in addition to **EBRT** and/or **vaginal brachytherapy** can be considered (Recommendation Level B, Evidence Level II) [11-16].

- For patients with an **invasive cervical component**, **adjuvant therapy** is to be considered if extrafascial hysterectomy is performed.
- Patients with **deeply invasive, grade 3, uterine-confined disease** (2009 FIGO stage IB, grade 3) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have a significant risk of distant metastases, and an optimal adjuvant therapy is still sought[11-16].
  - Adding **systemic therapy** to **adjuvant RT** may provide added therapeutic benefit (i.e., decrease in distant metastases) (Recommendation Level B, Evidence Level II) [11-16].

B.2 Advanced Stage/Extrauterine Disease

- Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field **RT alone or with chemotherapy** (radiation is targeted to sites of nodal disease)[11-16].
- However, **systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease** (Recommendation Level A, Evidence Level II)[11-16].
- International guidelines include **carboplatin/paclitaxel as the preferred systemic therapy** option in the **primary/adjuvant setting** for advanced-stage disease or high-risk histologies (Recommendation Level A, Evidence Level II)[11-16].
- Recently, the **pembrolizumab/carboplatin/paclitaxel** and **dostarlimab carboplatin/paclitaxel** triplet regimens are added as **preferred, primary therapy options for stage III or IV disease** based on the data from phase III NRG-GY018 and RUBY trials, respectively (Recommendation Level A, Evidence Level I)[11,16].
  - The **pembrolizumab/carboplatin/paclitaxel** regimen is recommended for **stage III or IVA with measurable disease or for stage IVB with or without measurable disease**. Since the NRG-GY018 trial did not include patients with carcinosarcoma histology, it is not recommended for patients with carcinosarcoma disease[11,16].
  - The **dostarlimab carboplatin/paclitaxel** option is recommended for patients with stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1

with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV disease regardless of the presence of measurable disease[11,16].

- For **stages III and IV disease**, **systemic therapy forms the mainstay of treatment** and can be combined with **EBRT with (or without) vaginal brachytherapy**. The combination of therapies depends on assessment of both locoregional and distant metastatic risk. Combination therapy can be considered for stages IIIB and IIIC disease (Recommendation Level A, Evidence Level II) [11-16].

C. High-Risk EC Histologies

- **Uterine serous carcinomas**, **clear cell carcinomas**, **carcinosarcomas**, and **undifferentiated/dedifferentiated carcinomas** are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation[11].
- Even patients with apparent early-stage disease may have distant metastases.
- Thus, **fertility-sparing therapy is not recommended** for these aggressive tumors.
- If done, SLN mapping should proceed with particular caution.
- Serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/dedifferentiated carcinomas are all considered high-risk histologies and **high grade by default**, although they are staged using the same FIGO/AJCC staging system as endometrial cancers.
- Patients may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding.
- **CA-125** and **MRI** or **chest/abdominal/pelvic CT** may be useful before surgery to assess if extrauterine disease is present; **PET** may also be useful (Recommendation Level A, Evidence Level II).

C.1 Patients suitable for primary surgery

- **Multimodality therapy** is typically recommended for these histologically aggressive tumors. Primary treatment includes **TH/BSO with surgical staging**, **peritoneal lavage** for cytology, **omental and peritoneal biopsies**, and consideration of **maximal tumor debulking** for gross disease (Recommendation Level A, Evidence Level II)[11].
- **Minimally invasive surgery** is the preferred approach when technically feasible (Recommendation Level A, Evidence Level II)[11].
- For patients with *clear cell* or *serous carcinomas* with *no residual disease* in the hysterectomy specimen, **observation** is the recommended option.

- For **stage IA disease** without myometrial invasion with negative peritoneal washings, options include **vaginal brachytherapy** with (or without) **systemic therapy** (Recommendation Level A, Evidence Level II; Recommendation Level B, Evidence Level II for systemic therapy) or **observation**. If the washings are positive, both systemic therapy and vaginal brachytherapy are recommended[11].
- For patients with **invasive stage IA, IB, or II**, options include **systemic therapy** with (or without) **EBRT** with (or without) **vaginal brachytherapy**; or EBRT with (or without) vaginal brachytherapy (Recommendation Level A, Evidence Level II)[11].
- For patients with clear cell or serous carcinoma at a more advanced stage (i.e., **stage III or IV**), or with undifferentiated/dedifferentiated histology, **systemic therapy** with (or without) **EBRT** with (or without) **vaginal brachytherapy** is recommended (Recommendation Level A, Evidence Level II)[11].

- For the patients with *carcinosarcoma* histology at stage IA, **systemic therapy** and **vaginal brachytherapy** are recommended with an option for **EBRT**, if it has high-grade epithelial components and is sarcoma dominant (>50% of sarcoma component in uterine tumor) (Recommendation Level A, Evidence Level II) [11].

C.2 Patients Not Suitable for Primary Surgery

- The primary treatment option is **EBRT** with (or without) **brachytherapy** with (or without) **systemic therapy** and then re-evaluation for surgery (Recommendation Level A, Evidence Level II)[11-16].
- Alternatively, **systemic therapy** could be given first, and then patients can be re-evaluated for surgery before giving RT based on the tumor response[11-16].
- For patients with carcinosarcoma histology with unresectable tumor that has metastasized, the panel recommends systemic therapy with (or without) EBRT or best supportive care[11-16].

D. Recurrent or Metastatic Disease

D.1 Disease Limited to the Uterus

For recurrences confined to the vagina or the pelvis alone, **second-line treatment** (typically with RT and/or surgery or systemic therapy) can be effective and selection depends on **prior therapy**.

- For patients with *no prior RT exposure* at the recurrence site, **EBRT** with (or without) **brachytherapy** and **systemic therapy**, or **surgery** with (or without)

intraoperative RT (IORT) and **systemic therapy** are recommended options (Recommendation Level A, Evidence Level II)[11].

- For patients *previously treated with brachytherapy* only at the recurrence site, **surgery** with (or without) **IORT** is recommended (Recommendation Level A, Evidence Level II; Recommendation Level C, Evidence Level III for IORT)[11].
- For patients *previously treated with EBRT* at the recurrence site, recommended therapy for isolated relapse includes **surgery** with (or without) **IORT** (Recommendation Level A, Evidence Level II; Recommendation Level C, Evidence Level III for IORT) plus or minus **systemic therapy**[11].

D.2 Distant Metastasis

- For *resectable isolated metastases*, **surgical resection** and/or **EBRT**, or **ablative therapy** are to be considered (Recommendation Level A, Evidence Level II). **Ablative RT** can be considered for 1 to 5 metastatic lesions if the primary cancer has been controlled (Recommendation Level B, Evidence Level II)[11].
- Providers can also consider **systemic therapy** (Recommendation Level B, Evidence Level II)[11].
- Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Treatment options for disseminated metastases are **systemic therapy** with (or without) **palliative EBRT**. For persistent progression of disseminated metastases (Recommendation Level A, Evidence Level II), **best supportive care** is recommended[11-16].

D.3 Hormonal Therapy

- Hormonal therapy is typically used for **lower-grade endometrioid histologies**, preferably in patients with small tumor volume or an indolent growth pace[11-16].
- Hormonal agents for treating **metastatic disease** include **megestrol acetate with alternating tamoxifen**, **everolimus/letrozole** combination, **progestational agents** (such as medroxyprogesterone acetate and megestrol acetate), **aromatase inhibitors**, **tamoxifen** alone, or **fulvestrant** (Recommendation Level A, Evidence Level II)[11-15].
- No drug, dose, or schedule has been found to be superior.

D.4 Systemic Therapy

- The combination **carboplatin/paclitaxel for 6 cycles [with pembrolizumab (for up to 2 years**; except in patients with carcinosarcoma histology) or **dostarlimab (for up to 3 years) in patients with MSI-H/dMMR disease]** are the preferred first-line therapy options for metastatic or recurrent endometrial

carcinoma, based on the results from the NRG-GY018 and RUBY trials (Recommendation Level A, Evidence Level I)[11-16].

- It is to note that the NCCN guidelines recommend the three-drug combination with immunotherapy regardless of the MSI-I/dMMR status (based on the mentioned trials)[11], which can be considered.
- The **NRG-GY018**, randomized, phase III trial evaluated the benefits of **pembrolizumab/carboplatin/paclitaxel** regimen over the **carboplatin/paclitaxel regimen** in 816 patients with stage III or IVA endometrial carcinoma with measurable disease, or stage IVB or recurrent disease of any histologic subtype, except for carcinosarcoma[23].
  - The PFS was 74% versus 38% in the dMMR cohort for the triplet regimen versus the chemotherapy arm, respectively (HR, 0.30; 95% CI, 0.19–0.48; P < .001). In pMMR tumors, the median PFS was 13.1 months in the pembrolizumab arm versus 8.7 months in the chemotherapy arm (HR, 0.54; 95% CI, 0.41–0.71; P < .001)[23].
- Another phase III, randomized trial **(RUBY)** showed benefits of **adding dostarlimab** to the **carboplatin/paclitaxel** regimen in 494 patients with stage III or IV or recurrent disease, including all histologies[24].
  - At 24 months, PFS was 36.1% versus 18.1% (HR, 0.64; 95% CI, 0.51–0.80; P < .001) and OS was 71.3% versus 56% (HR, 0.64; 95% CI, 0.46–0.87) in the dostarlimab-based arm versus the chemotherapy arm, respectively[24].
  - Significantly more benefits were observed in patient with dMMR/MSI-H tumors with PFS of 61.4% versus 15.7% (HR, 0.28; 95% CI, 0.16–0.50; P < .001) in the triplet versus the doublet therapy arms, respectively[24].
- **Biomarker-Directed Therapies:**
  - **Pembrolizumab** is a recommended treatment option for patients with **recurrent endometrial cancer with MSI-H/dMMR disease** that has *progressed on or following prior treatment with a platinum-containing regimen* in any setting including neoadjuvant or adjuvant therapy (Recommendation Level A, Evidence Level II)[11-16].
  - **Dostarlimab** is recommended by international guidelines for the treatment of patients with **recurrent dMMR/MSI-H endometrial cancer** that has *progressed on or following prior treatment with a platinum-containing regimen* in any setting including neoadjuvant or adjuvant therapy (Recommendation Level A, Evidence Level II)[11-16].
  - **Nivolumab** and **avelumab** are included in the NCCN guidelines as biomarker-directed **subsequent therapy options for recurrent**

dMMR/MSI-H endometrial tumors (Recommendation Level A, Evidence Level II)[11].

- **Larotrectinib** or **entrectinib** are included in the NCCN guidelines for **NTRK gene fusion-positive** endometrial tumors as a subsequent therapy option (Recommendation Level B, Evidence Level II)[11].

- Other multiagent regimens such as **carboplatin/paclitaxel**, **carboplatin/docetaxel**, and **carboplatin/paclitaxel/bevacizumab** are alternative first-line therapy options for the recurrent disease setting (Recommendation Level A, Evidence Level II)[11-15].
- Other combination therapies such as **cisplatin/doxorubicin**, **cisplatin/doxorubicin/paclitaxel**, **ifosfamide/paclitaxel** (for carcinosarcoma), and **cisplatin/ifosfamide** (for carcinosarcoma) are recommended as **subsequent therapy options** (Recommendation Level A, Evidence Level II)[11-15].
- **Bevacizumab** can be considered as a single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy (Recommendation Level A, Evidence Level II)[11-15].
- If multiagent chemotherapy regimens are contraindicated, then **single-agent therapy** options for recurrent disease include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, temsirolimus, cabozantinib, and docetaxel (Recommendation Level A, Evidence Level II)[11].
- **Systemic Therapy Options for High-Risk Endometrial Histologies:**
  - The previously mentioned systemic therapy options can be used for all carcinoma histologies.
  - Among these, **carboplatin/paclitaxel is a preferred** option for patients with **carcinosarcoma** histology (Recommendation Level A, Evidence Level I)[11].
  - The triplet therapy regimen **carboplatin/paclitaxel/trastuzumab** is recommended by the NCCN guidelines as a preferred option for **HER2-positive uterine serous carcinoma** or **HER2-positive carcinosarcoma** as: 1) primary therapy for stage III/IV disease; or 2) a first-line option for recurrent disease (Recommendation Level A, Evidence Level II; Recommendation Level B, Evidence Level II for HER2-positive carcinosarcoma in both disease settings)[11].
  - In **subsequent therapy**, the NCCN Panel has included **ifosfamide**, **ifosfamide/paclitaxel**, and **ifosfamide/cisplatin** as options for **carcinosarcoma** treatment only (Recommendation Level A, Evidence Level II)[11].

A **summary of drugs used** for the management of endometrial cancer is illustrated in tables 1, 2, and 3[11-16].

Table 2. Drugs Used in the Management of Newly Diagnosed Endometrial Cancer

Management of Newly Diagnosed Endometrial Cancer				
Medication	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Carboplatin	Treatment of Endometrial Cancer as first-line adjuvant or primary therapy; preferred for advanced-stage disease or high-risk histologies	**1st**	A	II
Paclitaxel	Treatment of Endometrial Cancer as first-line adjuvant or primary therapy; preferred for advanced-stage disease or high-risk histologies	**1st**	A	II
Pembrolizumab	Treatment of Endometrial Cancer as first-line adjuvant or primary therapy in combination with carboplatin/paclitaxel; preferred for stage III or IV disease except in patients with carcinosarcoma disease	**1st**	A	I
Trastuzumab	Treatment of Endometrial Cancer as first-line	**1st**	A	II II

	adjuvant or primary therapy in combination with carboplatin/paclitaxel in patient with stage III/IV HER2-positive uterine serous carcinoma OR in patients with for stage III/IV HER2-positive carcinosarcoma		B (carcinosarcoma)	
Cisplatin	First-line treatment of Endometrial Cancer as part of chemoradiation therapy	**1st**	A	II

Table 3. Drugs Used in the Management of Recurrent or Metastatic Endometrial Cancer

Management of Recurrent or Metastatic Endometrial Cancer				
Medication	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Carboplatin	First and second-line treatment of recurrent/metastatic Endometrial Cancer (preferred)	**1st, 2nd**	A	I II
Paclitaxel	First and second-line treatment of recurrent/metastatic Endometrial Cancer (preferred)	**1st, 2nd**	A	I II
Pembrolizumab	First and second-line treatment of recurrent/metastatic Endometrial Cancer in combination with carboplatin/paclitaxel; preferred therapy	**1st, 2nd**	A	I II

	except in patients with carcinosarcoma disease **OR** as a single agent in patients with for TMB-H or MSI-H/dMMRm tumors **OR** in combination with Lenvatinib in patients with for mismatch repair proficient (pMMR) tumors			
Trastuzumab	First-line treatment of recurrent/metastatic Endometrial Cancer in combination with carboplatin/paclitaxel in patient with HER2-positive uterine serous carcinoma OR in patients with for HER2-positive carcinosarcoma	**1st**	A B (carcinosarcoma)	II II
Lenvatinib	Second-line treatment of recurrent/metastatic Endometrial Cancer in combination with pembrolizumab after prior platinum-based therapy in patients with for mismatch repair proficient (pMMR) tumors	**2nd**	A	I
Docetaxel	First (in patients not eligible for paclitaxel) and second-line treatment of recurrent/metastatic Endometrial Cancer	**1st, 2nd**	A B	II II

Cisplatin	Second-line treatment of recurrent/metastatic Endometrial Cancer	**2nd**	A	II
Doxorubicin	Second-line treatment of recurrent/metastatic Endometrial Cancer	**2nd**	A	II
Bevacizumab	Second-line treatment of recurrent/metastatic Endometrial Cancer for patients who have progressed on previous cytotoxic chemotherapy	**2nd**	A	II
Topotecan	Second-line treatment of recurrent/metastatic Endometrial Cancer	**2nd**	A	II
Ifosfamide	Second-line treatment of recurrent/metastatic Endometrial Cancer for carcinosarcoma histologies	**2nd**	A	II

Table 4. Hormonal Therapy for Endometrial Cancer

Hormonal Therapy for Endometrial Cancer				
Medication	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Megestrol acetate	Hormonal therapy for recurrent or metastatic Endometrial Carcinoma OR for Uterine Limited Disease Not Suitable for Primary Surgery (or	**1st, 2nd**	A	II

	as part of a fertility-sparing approach)			
Tamoxifen	Hormonal therapy for recurrent or metastatic Endometrial Carcinoma	**2nd**	A	II
Medroxy-progesterone acetate	Hormonal therapy for for Uterine Limited Disease Not Suitable for Primary Surgery (or as part of a fertility-sparing approach)	**1st, 2nd**	A	II
Levonorgestrel intrauterine device (IUD)	Hormonal therapy for for Uterine Limited Disease Not Suitable for Primary Surgery (or as part of a fertility-sparing approach)	**2nd**	A	II

Other Drugs:

- **Dostarlimab** is mentioned in the international guidelines as a first-line treatment for patients with advanced or recurrent endometrial carcinoma, used in combination with carboplatin and paclitaxel (followed by single-agent dostarlimab) in patients with dMMR or MSI-H tumors; or as a single agent in patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation. The approval in the combination setting is based on the results of the phase III, randomized RUBY trial,that showed OS and PFS benefits of **adding dostarlimab** to the **carboplatin/paclitaxel** regimen in 494 patients with stage III or IV or recurrent disease, including all histologies, with more pronounced benefits in dMMR/MSI-H tumors. Dostarlimab is not currently available in the Saudi Market, and some Health Technology Assessment (HTA) recommendations have evaluated its use (cf. table 5 below)[11-16].
- **Nivolumab** and **Avelumab** are mentioned in the NCCN guidelines as other recommended treatment alternatives for the second-line treatment of

recurrent/metastatic endometrial cancer in patients with dMMR/MSI-H tumors[11]. Knowing that only Phase II trial data is available and no FDA or EMA approval has been issued for nivolumab and avelumab in endometrial cancer, with no HTA recommendations in this regard, the inclusion of these drugs in the formulary would be too early to consider at the moment.

- **Albumin-bound paclitaxel** (for patients with a hypersensitivity to paclitaxel if the skin testing to paclitaxel is negative), **liposomal doxorubicin**, and **topotecan** are mentioned only in the NCCN guidelines as other recommended treatment options[11]; however, since there is no FDA/EMA approval, strong clinical trial data, or HTA recommendations in this setting they were not included in the analysis.
- Everolimus, letrozole, aromatase inhibitors, and fulvestrant are mentioned only in the NCCN guidelines as other recommended treatment options for hormonal therapy[11]; however, since there is no FDA/EMA approval, strong clinical trial data, or HTA recommendations in this setting they were not included in the analysis.

All the medications in the standard of care therapy are available in the Saudi Market, except dostarlimab. Section 3 provides a full description of each treatment protocol with a final statement on the place in therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA), reflecting specific drug class role in the endometrial cancer therapeutic landscape.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in endometrial cancer were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations is shown in Section 3.

The summary of the HTA recommendations for pembrolizumab, lenvatinib, bevacizumab, and dostarlimab are shown in table 5 below[25-38].

Table 5. HTA Recommendations Endometrial Cancer

Medication	Agency	HTA Recommendation
Pembrolizumab + Lenvatinib	HAS[25,26]	03/2022: **Favorable opinion for reimbursement** in the indication extension: **pembrolizumab, in combination with lenvatinib**, is indicated in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. - **Therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma. - **Moderate clinical added value** (CAV III) - Demonstration in a randomized, open-label phase 3 study of the superiority of pembrolizumab and lenvatinib combination compared to single-agent chemotherapy with doxorubicin or paclitaxel, particularly in terms of: ▪ Progression-free survival (PFS) (absolute increase of 3.4 months, HR=0.56 [CI95%: 0.47- 0.66]): ▪ Overall survival (OS) (absolute increase of 6.9 months, HR=0.62 [CI95%: 0.51-0.75]) - Safety profile for the pembrolizumab and lenvatinib combination less favorable than that for single-agent chemotherapy, marked by additional toxicity with, in particular, more serious adverse events (53% versus 30%) - Absence of any formal conclusion that can be drawn based on the quality of life results

	NICE[27]	06/2023: Pembrolizumab plus lenvatinib is **recommended**, within its marketing authorization, for treating **advanced or recurrent endometrial cancer** in adults: whose **cancer has progressed** on or after **platinum-based chemotherapy** and who **cannot have curative surgery or radiotherapy**. - There is no standard second-line treatment for advanced or recurrent endometrial cancer. - Key evidence for pembrolizumab with lenvatinib comes from the KEYNOTE-775 trial: ▪ **Pembrolizumab plus lenvatinib improves OS and PFS compared with doxorubicin or paclitaxel monotherapy**. ▪ Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. - Pembrolizumab plus lenvatinib **meets NICE's criteria to be considered a life-extending treatment at the end of life**. - There is some uncertainty in the economic model about how long the effect of treatment lasts after people stop taking pembrolizumab at 2 years. - But the **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**. - The most plausible ICER is less than £50,000 per QALY gained
	CADTH[28]	04/2023: pERC recommends that pembrolizumab be **reimbursed** as monotherapy for the treatment of adult patients with **unresectable or metastatic MSI-H or dMMR endometrial cancer** whose tumors have **progressed following prior**

		therapy and who have **no satisfactory alternative treatment options**.
		- Single-arm, phase II, open-label, nonrandomized trial (KEYNOTE-158 [KN-158], N = 94).
		  ▪ The median OS was 65.4 months (95% confidence interval [CI], 29.5 to not reported [NR]) and the OS rate of patients treated with pembrolizumab at 12 months was 70.0%.
		  ▪ The median PFS was 13.1 months (95% CI, 4.3 months to 25.7 months) and the PFS rate at 12 months was 50.3%.
		- The cost-effectiveness of pembrolizumab relative to physician's choice of chemotherapy is unknown in patients with dMMR or MSI-H endometrial cancer owing to the lack of direct comparative clinical effectiveness data.
		- The committee considered an exploratory analysis conducted by CADTH that produced an incremental cost-effectiveness ratio of $61,200 per QALY gained when compared with chemotherapy.
		- Based on this exploratory finding, a price reduction is needed for pembrolizumab to be cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold.
		12/2022: pERC recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced endometrial carcinoma** that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are

		not candidates for curative surgery or radiation. - One multicenter, randomized, open-label phase III trial (KEYNOTE-775; N = 697 for patients with pMMR disease) demonstrated that treatment with pembrolizumab/lenvatinib resulted in added clinical benefit when compared with treatment of physicians' choice in that setting. - Pembrolizumab/lenvatinib was associated with statistically significant and clinically meaningful improvements in OS (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.56 to 0.84; P< 0.0001) and PFS (HR = 0.60; 95% CI, 0.50 to 0.72; P < 0.0001). - Pembrolizumab/lenvatinib was **unlikely to worsen health-related quality of life (HRQoL)**. - Pembrolizumab/lenvatinib **is not considered cost-effective** when compared to physician's choice of chemotherapy. - Economic evidence suggests that even at a 100% price reduction in the cost of pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. - Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**.
	IQWIG[29,30]	07/2022: Pembrolizumab + Lenvatinib in adult patients with **advanced or recurrent endometrial cancer** whose disease has **progressed during or after prior platinum-based therapy** at any stage of the disease

		when surgery or radiation to cure the cancer is not an option: - *Patients for whom doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **indication of a considerable added benefit**; OS clearly prolonged - *Patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **added benefit not proven** 10/2022: Adult patients with **advanced or recurrent microsatellite instability high or mismatch repair deficient endometrial carcinoma**, who have **disease progression** on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation **Added benefit not proven**
	PBAC[31]	03/2023: **Pembrolizumab plus lenvatinib** (combination therapy) is **recommended** for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following prior systemic therapy **regardless of biomarker status** - The claim of superior efficacy of pembrolizumab plus lenvatinib versus chemotherapy, based on the results of the comparative KN775 trial, was reasonable. - The PBAC noted that the superior efficacy was observed in the intention to treat population comprising both dMMR and pMMR patients, with a substantial OS gain observed (ITT HR: 0.62 (95% CI: 0.51, 0.75)), and a 6.9 month increase in median survival (18.3 versus 11.4 months).

		- The PBAC considered that an ICER of $75,000 to < $95,000/QALY or lower was reasonable for pembrolizumab plus lenvatinib in the all-comer population given the level of OS benefit observed in the KN775 trial, and the high clinical need in this patient population in which there have been no recent advances in therapy.
Pembrolizumab	CADTH[32]	04/2023: pERC recommends that pembrolizumab be **reimbursed** as monotherapy for the treatment of adult patients with **unresectable or metastatic MSI-H or dMMR endometrial cancer** whose tumors have **progressed following prior therapy** and who have **no satisfactory alternative treatment options**. - Single-arm, phase II, open-label, nonrandomized trial (KEYNOTE-158 [KN-158], N = 94). ▪ The median OS was 65.4 months (95% confidence interval [CI], 29.5 to not reported [NR]) and the OS rate of patients treated with pembrolizumab at 12 months was 70.0%. ▪ The median PFS was 13.1 months (95% CI, 4.3 months to 25.7 months) and the PFS rate at 12 months was 50.3%. - The cost-effectiveness of pembrolizumab relative to physician's choice of chemotherapy is unknown in patients with dMMR or MSI-H endometrial cancer owing to the lack of direct comparative clinical effectiveness data. - The committee considered an exploratory analysis conducted by CADTH that produced an incremental cost-effectiveness ratio of $61,200 per

		QALY gained when compared with chemotherapy. - Based on this exploratory finding, a price reduction is needed for pembrolizumab to be cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold.
	IQWIG[33]	10/2022: Adult patients with **advanced or recurrent microsatellite instability high or mismatch repair deficient endometrial carcinoma**, who have **disease progression** on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation **Added benefit not proven**
	PBAC[34]	03/2023: Pembrolizumab monotherapy in the dMMR population **not recommended** in patients with deficient DNA mismatch repair (dMMR) endometrial cancer. - The PBAC considered that the clinical benefit of monotherapy, which was based on a relatively small single arm study, was **uncertain** with a **high-risk of bias** in the naïve side-by-side comparison of point estimates of OS observed in KN158 versus the chemotherapy arm of the dMMR subgroup in KN775. - The submission **did not specifically assess the cost-effectiveness** of pembrolizumab monotherapy versus chemotherapy.
Bevacizumab	PBAC[35]	07/2020: The PBAC **recommend** the listing of the biosimilar brand of bevacizumab, Zirabev for all the indications for which the reference brand, Avastin, is currently PBS-listed, including **advanced FIGO Stage IIIB, IIIC or Stage IV epithelial ovarian**, fallopian tube or primary peritoneal **cancer**

		The PBAC recommended listing Zirabev on a **cost-minimization** basis to the Avastin brand of bevacizumab
Dostarlimab	NICE[36]	**Recommended** for use within the Cancer Drugs Fund as an option for treating advanced or recurrent endometrial cancer that is MSI-H/dMMR in adults who have had platinum-based chemotherapy. - There is an unmet need and no standard treatment for previously treated advanced or recurrent endometrial cancer with MSI-H/dMMR, where patients are offered further chemotherapy. - The main clinical evidence comes from a single-arm study, the GARNET trial. - Matching-adjusted indirect treatment comparisons suggest that dostarlimab improves survival, but these are highly uncertain. - Dostarlimab has the potential to be cost effective, but more long-term evidence is needed to address the clinical uncertainties. - More data from the dostarlimab trial would help address uncertainties about its clinical effectiveness. Dostarlimab is therefore recommended for use in the Cancer Drugs Fund so that more data can be collected.
	CADTH[37]	Dostarlimab **should not be reimbursed** by public drug plans for monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. - The ongoing multicentre, phase I dose escalation and cohort expansion study (part 2B of the GARNET trial, A1 cohort) evaluated dostarlimab in patients with

		advanced or recurrent dMMR or MSI-H EC that had progressed on or following prior treatment with a platinum-containing regimen. - An interim analysis (IA-2) of 105 patients showed an objective response rate (ORR) of 44.8% (95% confidence interval (CI), 35.0% to 54.8%). - However, there was a high degree of **uncertainty regarding the magnitude of clinical benefit directly attributable to dostarlimab** due to the non-randomized, non-comparative, open-label study design and the small sample size and short follow-up in the study.
	IQWIG[38]	Patients with MSI-H/dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen: **added benefit not proven**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, no guidelines issued by Saudi bodies have been published for the management of endometrial carcinoma.

1.2 North American Guidelines

1.2.1 National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of Uterine Cancer in April 2023, including recommendations for the diagnosis, evaluation, treatment, and follow-up of Endometrial Carcinoma.

a) Clinical Presentation and Workup

Currently, there is no validated screening test for endometrial carcinoma. About 90% of patients with endometrial carcinoma have **metrorrhagia**, most commonly in the postmenopausal period. Table 6 summarizes the workup recommendations for patients with suspicion of EC as per NCCN guidelines.

Table 6. Workup Recommendations for Patients with Endometrial Carcinoma (NCCN Guidelines)

Initial Workup
Non–Fertility-Sparing Treatment
▪ Consider chest imaging (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed. ▪ Consider pelvic MRI to establish the origin of the tumor (endocervical vs. endometrial) and assess local disease extent. ▪ Consider preoperative pelvic ultrasound if uterine size is not clear on exam. ▪ For high-grade carcinoma, consider chest/abdomen/pelvis CT (preferred) to evaluate for metastatic disease. ▪ For patients who underwent TH with incidental finding of endometrial cancer or whose cancer was incompletely staged with uterine risk factors, consider chest/abdomen/pelvis CT to evaluate for metastatic disease.

- Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if metastasis is suspected in select patients.
- Other initial imaging should be based on symptomatology and clinical concern for metastatic disease

Fertility-Sparing Treatment

- Pelvic MRI (preferred) to exclude myoinvasion and assess local disease extent; pelvic transvaginal ultrasound if MRI is contraindicated.
- Consider chest imaging (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.
- Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if metastasis is suspected in select patients.
- Other imaging should be based on symptomatology and clinical concern for metastatic disease

Follow-up/Surveillance

Non–Fertility-Sparing Treatment

- Imaging should be guided by patient symptoms, risk assessment, and clinical concern for recurrent or metastatic disease.

Fertility-Sparing Treatment

- Repeat pelvic MRI (preferred) for patients with persistent endometrial carcinoma after 6–9 months of failed medical therapy, especially if considering further fertility-sparing approaches.
- Other imaging should be based on symptomatology and clinical concern for metastatic disease

Suspected Recurrence or Metastasis

- Abdomen/pelvis and/or chest CT is recommended based on symptoms or physical exam findings.
- Consider whole body FDG-PET/CT and/or abdomen/pelvis MRI in select patients as clinically indicated.

Diagnosis can usually be made by an **office endometrial biopsy**, with a false-negative rate of about 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage under anesthesia. **Hysteroscopy** may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent bleeding.

Consideration of preoperative **chest imaging (chest x-ray)** is recommended. Based on the fertility-sparing or non–fertility-sparing treatment criteria, other imaging tests such as **CT, MRI, ultrasound (US), and/or FDG-PET/CT** may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical

symptoms, physical findings, or abnormal laboratory findings. In patients with extrauterine disease, a serum **CA-125** assay may be helpful in monitoring clinical response. However, serum CA-125 levels can be falsely increased in patients who have peritoneal inflammation/infection or radiation injury, may be normal in patients with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.

b) Staging

- The FIGO (International Federation of Gynecology and Obstetrics) system is most commonly used for staging uterine cancer (Table 1).
- **Pathology**: An expert pathologic review determines the specific epithelial histology of the tumor (endometrioid, serous, clear cell, carcinosarcoma, or undifferentiated).
  - The assessment of the uterus includes the hysterectomy type, specimen integrity, tumor site and size, histologic type and grade if applicable, myometrial invasion (depth of invasion in mm/myometrial thickness in mm), cervical stromal involvement, and lymphovascular space invasion (LVSI).
  - The pathologic assessment should also include assessment of involvement by other tissues such as the fallopian tubes, ovaries, vagina, parametrium, peritoneum, and omentum. The assessment of peritoneal/ascitic fluid cytology should also be obtained. If nodal resection was performed, the level of nodal involvement (ie, pelvic, common iliac, para-aortic) should be determined.
  - Estrogen receptor (ER) testing is recommended in the setting of stage III, IV, or recurrent endometrioid carcinoma. Evaluation of human epidermal growth factor receptor 2 (HER2) overexpression should also be considered.
- **Lymphadenectomy**: Previously, a full standard lymphadenectomy (i.e., dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, to decrease side effects, **a more selective and tailored nodal evaluation** approach that includes the SLN algorithm is recommended by the NCCN Panel.
  - Decisions about whether to perform lymphadenectomy, and, if done, to what extent (e.g., pelvic nodes only or both pelvic and para-aortic nodes), can be made based on preoperative and intraoperative findings.
  - Criteria have been suggested as indicative of low risk for nodal metastases: 1) less than 50% myometrial invasion; 2) tumor less than 2 cm; and 3) well or moderately differentiated histology.

- **Sentinel Lymph Node (SLN) Mapping**: SLN mapping may be considered for patients without suspicion of metastatic disease by preoperative imaging and no obvious extrauterine disease at exploration.
- **Minimally Invasive Procedures**: Over the past decade, practice has trended towards minimally invasive approaches to total abdominal hysterectomy (TH)/BSO and lymph node assessment in patients with early-stage endometrial cancer.
    - Although these procedures may be performed by any surgical route (e.g., laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach.

c) Primary Treatment

The NCCN Guidelines divide pure endometrioid cancer into **three categories** for delineating treatment:

1. Disease limited to the uterus
2. Suspected or gross cervical involvement
3. Suspected extrauterine disease.

Most patients with endometrial cancer have stage I disease at presentation, and **surgery (with or without adjuvant therapy) is recommended for medically operable patients**. As a general principle, endometrial carcinoma should be removed ***en bloc*** to optimize outcomes; intraperitoneal morcellation should be avoided.

c.1. Disease limited to the uterus

- To **stage** medically operable patients with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes **removal of the uterus and bilateral tubes and ovaries with lymph node and abdominal assessment**.
- **Ovarian preservation** may be safe in select premenopausal patients with stage I endometrioid cancer.
- **Minimally invasive surgery** is the preferred approach when technically feasible and is considered a quality measure by the SGO and the American College of Surgeons.
- Patients with apparent uterine-confined endometrial carcinoma are candidates for **SLN mapping**, which assesses the pelvic nodes bilaterally and may be less morbid than complete lymphadenectomy.

- **Incomplete Surgical Staging:**
  - For patients with incomplete surgical staging and high-risk intrauterine features, imaging is recommended, especially in patients with higher grade histologies.
  - Surgical restaging, including lymph node dissection, can also be done.
  - Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided.
- **Fertility-Sparing Therapy:**
  - Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered **for highly selected patients with grade 1, stage IA (noninvasive) disease who wish to preserve fertility**. The criteria established by NCCN for fertility-sparing therapy are:
    - Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
    - Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound
    - Absence of suspicious or metastatic disease on imaging
    - No contraindications to medical therapy or pregnancy
    - Patients should undergo counseling that fertility sparing option is NOT standard of care for the treatment of endometrial carcinoma
    - Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation.
  - **TH/BSO with surgical staging is recommended after childbearing is complete**, if therapy is not effective, or if progression occurs.
  - Fertility-sparing therapy is **not recommended for high-risk patients** (e.g., those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and uLMS).
  - **Continuous progestin-based therapy** may include **megestrol acetate, medroxyprogesterone, or an intrauterine device (IUD) containing levonorgestrel**.
  - The use of progestin-based therapy should be carefully considered in the context of other patient-specific factors, including **contraindications** such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking. The panel also recommends counseling for weight management and lifestyle modification.

c.2 Suspected or Gross Cervical Involvement

- For patients with suspected or gross cervical involvement (endometrioid histologies), **cervical biopsy** or **pelvic MRI** should be performed if not done previously.
- If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described, although a radical hysterectomy may be performed when necessary to obtain negative margins.
- It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for patients suitable for primary surgery, TH (preferred) or radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and evaluation of lymph nodes if indicated.
- In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.
- Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging.

c.3 Suspected Extrauterine Disease

- If extrauterine disease (endometrioid histologies) is suspected, **imaging studies** are recommended along with **CA-125 testing**.
- **ER testing** is recommended in the setting of stage III or IV endometrioid tumors.
- Patients with abdominal- or pelvic-confined disease require surgical intervention using TH/BSO with surgical staging and surgical debulking with the goal of having no measurable residual disease; several studies support debulking.
- Consider preoperative chemotherapy.
- For distant visceral metastasis (e.g., liver involvement), recommended options include systemic therapy with (or without) EBRT with (or without) TH/BSO and with (or without) stereotactic body RT (SBRT). Ablative radiation can be considered for 1 to 5 metastatic lesions if disease is otherwise controlled (category 2B).

c.4 Patients Not Suited for Primary Surgery

- For *uterine-confined disease* not suitable for primary surgery, **EBRT and/or brachytherapy is the preferred treatment approach**.
  - Alternatively, **progestational agents** (such as **medroxyprogesterone acetate** and **megestrol acetate**) and **levonorgestrel IUD** can also be

considered for select patients (e.g., estrogen and progesterone receptor–positive [ER/PR positive]).

- Patients receiving hormonal therapy alone should be closely monitored by endometrial biopsy (e.g., consider endometrial biopsies every 3–6 months).

- For suspected *gross cervical involvement* in patients who are not suited for primary surgery, **EBRT and brachytherapy** is an effective treatment that can provide pelvic control and long-term progression-free survival (PFS).
  - EBRT with or without brachytherapy may be administered, depending on the clinical situation and medical fitness of the patient.
  - If rendered operable 4–12 weeks post RT, local treatment consisting of **surgery** should follow.
  - **Systemic therapy alone** is also a primary treatment option (category 2B) but should be followed by EBRT + brachytherapy if the patient remains inoperable.
- Patients with *unresectable extrauterine pelvic disease* (i.e., vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with **EBRT with (or without) brachytherapy with (or without) systemic therapy**, followed by re-evaluation of tailored surgery.
  - Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT.

d) Adjuvant therapy

d.1 Uterine-Confined Disease

- Thorough **surgical staging** provides important information to assist in selection of adjuvant therapy for endometrial tumors.
- Patients with stage I endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (i.e., age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement).
- Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer. The practice of **surgical staging** has led to a **decrease in the use of adjuvant therapy for stage I endometrial carcinoma**, which is reflected in the option of **observation** in the NCCN Guidelines.
  - The NCCN Panel prefers **observation** for patients with **stage IA, grade 1/2 disease**, but strongly **suggests treatment with adjuvant vaginal brachytherapy** for those **≥60 years** and/or those with **LVSI**.

- For **patients with stage IA, grade 3 tumors**, especially in those who have been surgically staged, **vaginal brachytherapy** is the **preferred** option, or observation can be considered if no myometrial invasion is present.
- If higher risk factors are present, i.e., age ≥70 years or LVSI, **EBRT** can be considered as a category 2B option.
- For **patients with stage IB, grade 1–2 disease**, **vaginal brachytherapy is preferred** although observation can be considered if no adverse risk factors are present. **EBRT** can be considered in grade 2 tumors if additional risk factors are present such as age ≥60 years and/or if LVSI is present.
- For **stage IB, grade 3 disease with adverse risk factors**, **systemic therapy** is added as a category 2B option (in addition to EBRT and/or vaginal brachytherapy).

- The NCCN Panel generally agrees on the role of **adjuvant therapy** for patients with an **invasive cervical component** if extrafascial hysterectomy is performed.
- Adjuvant Systemic Therapy
  - Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have a significant risk of distant metastases, and an optimal adjuvant therapy is still sought.
  - Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (i.e., decrease in distant metastases).
  - However, the NCCN Panel feels that **adjuvant systemic therapy is a category 2B recommendation** in this setting of uterine-confined disease because an OS advantage has not been shown.

d.2 Advanced Stage/Extrauterine Disease

- Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone or with chemotherapy (radiation is targeted to sites of nodal disease).
- However, **systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease**.
- The NCCN Guidelines include **carboplatin/paclitaxel as the preferred systemic therapy** option in the **primary/adjuvant setting** for advanced-stage disease or high-risk histologies.

- The NCCN Guidelines recently added the **pembrolizumab/carboplatin/paclitaxel** and **dostarlimab carboplatin/paclitaxel** triplet regimens as **Category 1, preferred, primary therapy options for stage III or IV disease** based on the data from phase III NRG-GY018 and RUBY trials, respectively.
  - The **pembrolizumab/carboplatin/paclitaxel** regimen is recommended for **stage III or IVA with measurable disease or for stage IVB with or without measurable disease**. Since the NRG-GY018 trial did not include patients with carcinosarcoma histology, the NCCN Panel do not recommend the pembrolizumab/carboplatin/paclitaxel treatment option for patients with carcinosarcoma disease.
  - The **dostarlimab carboplatin/paclitaxel** option is recommended for patients with stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV disease regardless of the presence of measurable disease.
- For stages **III and IV disease**, **systemic therapy forms the mainstay of treatment** and can be combined with **EBRT** with (or without) **vaginal brachytherapy**. The combination of therapies depends on assessment of both locoregional and distant metastatic risk. Combination therapy can be considered for stages IIIB and IIIC disease.
- Recommendations for primary/adjuvant therapy for EC according to the NCCN guidelines are outlined in table 7 below.

Table 7. Systemic Therapy for Primary of Adjuvant Treatment of Endometrial Carcinoma (NCCN guidelines)

Primary or Adjuvant Therapy (Stage I-IV)	
Chemoradiation therapy	**Systemic therapy**
Preferred Regimens ▪ Cisplatin plus RT followed by carboplatin/paclitaxel **Other Recommended Regimens (if cisplatin and carboplatin are unavailable)** ▪ Capecitabine/mitomycin ▪ Gemcitabine ▪ Paclitaxel	**Preferred Regimens** ▪ Carboplatin/paclitaxel ▪ Carboplatin/paclitaxel/pembrolizumab (for stage III-IV tumors, except for carcinosarcoma) (category 1)[1] ▪ Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV tumors) (category 1)[2]

	▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[3] ▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (category 2B)

[1] For stage III or IVA with measurable disease or stage IVB with or without measurable disease.
[2] For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease

e) High-Risk Endometrial Carcinoma Histologies

- **Uterine serous carcinomas**, **clear cell carcinomas**, **carcinosarcomas**, and **undifferentiated/dedifferentiated carcinomas** are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.
- Even patients with apparent early-stage disease may have distant metastases.
- Thus, **fertility-sparing therapy is not recommended** for these aggressive tumors.
- If done, SLN mapping should proceed with particular caution.
- Serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/dedifferentiated carcinomas are all considered high-risk histologies and **high grade by default**, although they are staged using the same FIGO/AJCC staging system as endometrial cancers.
- Patients may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding.
- Both the NCCN Panel and the SGO recommend that **CA-125** and **MRI** or **chest/abdominal/pelvic CT** may be useful before surgery to assess if extrauterine disease is present; **PET** may also be useful.
- **Primary Treatment:**

  Suitable for Primary Surgery

  - **Multimodality therapy** is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease.
  - Minimally invasive surgery is the preferred approach when technically feasible.

- For patients with **clear cell** or **serous carcinomas** with no residual disease in the hysterectomy specimen, **observation** is the recommended option.
    - For stage IA disease without myometrial invasion with negative peritoneal washings, options include vaginal brachytherapy with (or without) systemic therapy (category 2B for systemic therapy) or observation. If the washings are positive, both systemic therapy and vaginal brachytherapy are recommended.
    - For patients with invasive stage IA, IB, or II, options include systemic therapy with (or without) EBRT with (or without) vaginal brachytherapy; or EBRT with (or without) vaginal brachytherapy.
    - For patients with clear cell or serous carcinoma at a more advanced stage (ie, stage III or IV), or with undifferentiated/dedifferentiated histology, systemic therapy with (or without) EBRT with (or without) vaginal brachytherapy is recommended.
- For the patients with **carcinosarcoma histology** at **stage IA**, **systemic therapy** and **vaginal brachytherapy** are recommended with an option for EBRT, if it has high-grade epithelial components and is sarcoma dominant (>50% of sarcoma component in uterine tumor).

  Not Suitable for Primary Surgery

- The primary treatment option is **EBRT with (or without) brachytherapy with (or without) systemic therapy** and then re-evaluation for surgery.
- Alternatively, **systemic therapy** could be given first, and then patients can be re-evaluated for surgery before giving RT based on the tumor response. For patients with carcinosarcoma histology with unresectable tumor that has metastasized, the panel recommends systemic therapy with (or without) EBRT or best supportive care.

f) Treatment of Recurrent or Metastatic Disease

f.1 Uterine-Confined Disease

- For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or systemic therapy) can be effective and selection depends on **prior therapy**.
- For patients with *no prior RT exposure* at the recurrence site, the panel recommends EBRT with (or without) brachytherapy and systemic therapy, or surgery with (or without) intraoperative RT (IORT) and systemic therapy.
- For patients *previously treated with brachytherapy* only at the recurrence site, surgery with (or without) IORT is recommended (category 3 for IORT).

- For patients *previously treated with EBRT* at the recurrence site, recommended therapy for isolated relapse includes surgery with (or without) IORT (category 3 for IORT) plus or minus systemic therapy.

f.2 Distant Metastases

- For resectable isolated metastases, consider surgical resection and/or EBRT, or ablative therapy. Ablative RT can be considered for 1 to 5 metastatic lesions if the primary cancer has been controlled (category 2B).
- Providers can also consider systemic therapy (category 2B).
- Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Treatment options for disseminated metastases are systemic therapy with (or without) palliative EBRT. For persistent progression of disseminated metastases, best supportive care is recommended.

f.3 Hormonal Therapy

- Hormonal therapy is typically used for **lower-grade endometrioid histologies**, preferably in patients with small tumor volume or an indolent growth pace.
- Hormonal agents for treating **metastatic disease** include **megestrol acetate with alternating tamoxifen**, **everolimus/letrozole** combination, **progestational agents** (such as medroxyprogesterone acetate and megestrol acetate), **aromatase inhibitors**, **tamoxifen** alone, or **fulvestrant**.
- No particular drug, dose, or schedule has been found to be superior.
- Hormonal therapy recommendations for EC according to NCCN guidelines are outlined in table 8 below.

Table 8. Hormonal Therapy for Endometrial Carcinoma (NCCN guidelines)

Hormonal Therapy	
Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma	
Preferred Regimens ▪ Megestrol acetate/tamoxifen (alternating) ▪ Everolimus/letrozole	**Other Recommended Regimens** ▪ Medroxyprogesterone acetate/tamoxifen (alternating) ▪ Progestational agents o Medroxyprogesterone acetate o Megestrol acetate ▪ Aromatase inhibitors ▪ Tamoxifen ▪ Fulvestrant

Hormonal Therapy for Uterine Limited Disease Not Suitable for Primary Surgery	
Preferred Regimens ▪ **Progestational agents** o **Medroxyprogesterone acetate** o **Megestrol acetate**	**Useful in Certain Circumstances** ▪ Levonorgestrel intrauterine device (IUD)

f.4 Systemic Therapy

- Based on the current data, multiagent regimens are preferred for advanced disease, if tolerated.
- Based on the results from the NRG-GY018 and RUBY trials, the NCCN Panel has added **pembrolizumab/carboplatin/paclitaxel** (except for carcinosarcoma histology) and **dostarlimab/ carboplatin/paclitaxel as Category 1, preferred, first-line therapy options for recurrent endometrial carcinoma**.
- The **NRG-GY018**, randomized, phase III trial evaluated the benefits of **pembrolizumab/carboplatin/paclitaxel** regimen over the **carboplatin/paclitaxel regimen** in 816 patients with stage III or IVA endometrial carcinoma with measurable disease, or stage IVB or recurrent disease of any histologic subtype, except for carcinosarcoma[23].
  - The PFS was 74% versus 38% in the dMMR cohort for the triplet regimen versus the chemotherapy arm, respectively (HR, 0.30; 95% CI, 0.19–0.48; P < .001). In pMMR tumors, the median PFS was 13.1 months in the pembrolizumab arm versus 8.7 months in the chemotherapy arm (HR, 0.54; 95% CI, 0.41–0.71; P < .001)[23].
- Another phase III, randomized trial **(RUBY)** showed benefits of **adding dostarlimab** to the **carboplatin/paclitaxel** regimen in 494 patients with stage III or IV or recurrent disease, including all histologies[24].
  - At 24 months, PFS was 36.1% versus 18.1% (HR, 0.64; 95% CI, 0.51–0.80; P < .001) and OS was 71.3% versus 56% (HR, 0.64; 95% CI, 0.46–0.87) in the dostarlimab-based arm versus the chemotherapy arm, respectively[24].
  - Significantly more benefits were observed in patient with dMMR/MSI-H tumors with PFS of 61.4% versus 15.7% (HR, 0.28; 95% CI, 0.16–0.50; P < .001) in the triplet versus the doublet therapy arms, respectively[24].
- Other multiagent regimens such as **carboplatin/paclitaxel**, **carboplatin/docetaxel**, and **carboplatin/paclitaxel/bevacizumab** are included as first-line therapy options for the recurrent disease setting.

- Other combination therapies such as **cisplatin/doxorubicin**, **cisplatin/doxorubicin/paclitaxel**, **ifosfamide/paclitaxel** (for carcinosarcoma), and **cisplatin/ifosfamide** (for carcinosarcoma) are added as **subsequent therapy options**.
- If multiagent chemotherapy regimens are contraindicated, then **single-agent therapy** options for recurrent disease include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, temsirolimus, cabozantinib, and docetaxel (category 2B for docetaxel).
- The NCCN Panel considers **bevacizumab** as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.
- **Biomarker-Directed Therapies:**
  - **Pembrolizumab** is included as a treatment option for patients with **recurrent endometrial cancer with MSI-H/dMMR disease** that has progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy.
  - The NCCN Panel recommends **dostarlimab** for the treatment of patients with **recurrent dMMR/MSI-H endometrial cancer** that has progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy.
  - **Nivolumab** and **avelumab** are included as biomarker-directed **subsequent therapy options for recurrent dMMR/MSI-H endometrial tumors**.
  - The NCCN Panel also recommends **larotrectinib** or **entrectinib** for **NTRK gene fusion-positive** endometrial tumors as a category 2B subsequent therapy option.
- **Systemic Therapy Options for High-Risk Endometrial Histologies:**
  - The NCCN Panel notes that the systemic therapy options recommended in the NCCN Guidelines can be used for all carcinoma histologies.
  - Among these, **carboplatin/paclitaxel is included as a category 1, preferred** option for patients with **carcinosarcoma** histology.
  - The triplet therapy regimen **carboplatin/paclitaxel/trastuzumab** is recommended by the NCCN Panel as a preferred option for **HER2-positive uterine serous carcinoma** or **HER2-positive carcinosarcoma** as: 1) primary therapy for stage III/IV disease; or 2) a first-line option for recurrent disease.

The NCCN Panel has designated the regimen a category 2B option for HER2-positive carcinosarcoma in both disease settings.

- In **subsequent therapy**, the NCCN Panel has included **ifosfamide**, **ifosfamide/paclitaxel**, and **ifosfamide/cisplatin** as options for **carcinosarcoma** treatment only.

- Systemic therapy regimens for recurrent EC according to NCCN guidelines are outlined in table 9 below.

Table 9. Systemic Therapy for Recurrent Endometrial Carcinoma (NCCN Guidelines)

Recurrent Disease	
First-Line Therapy	**Second-Line Therapy**
Preferred Regimens ▪ Carboplatin/paclitaxel (category 1 for carcinosarcoma)[1] ▪ Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1) ▪ Carboplatin/paclitaxel/dostarlimab-gxly (category 1) ▪ Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma) ▪ Carboplatin/paclitaxel/trastuzumab (for HER2-positive carcinosarcoma) (category 2B) **Other Recommended Regimens** ▪ Carboplatin/docetaxel[2] ▪ Carboplatin/paclitaxel/bevacizumab **Useful in Certain Circumstances (Biomarker directed: after prior platinum-based therapy including neoadjuvant and adjuvant)** ▪ Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors	**Other Recommended Regimens** ▪ Cisplatin/doxorubicin ▪ Cisplatin/doxorubicin/paclitaxel ▪ Cisplatin ▪ Carboplatin ▪ Doxorubicin ▪ Liposomal doxorubicin ▪ Paclitaxel ▪ Albumin-bound paclitaxel[3] ▪ Topotecan ▪ Bevacizumab[4] ▪ Temsirolimus ▪ Cabozantinib ▪ Docetaxel (category 2B) ▪ Ifosfamide (for carcinosarcoma) ▪ Ifosfamide/paclitaxel (for carcinosarcoma) ▪ Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker directed therapy)** ▪ Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors ▪ Pembrolizumab for TMB-H or MSI-H/dMMR tumors

▪ Pembrolizumab for TMB-H or MSI-H/dMMRm tumors ▪ Dostarlimab-gxly for dMMR/MSI-H tumors	▪ Dostarlimab-gxly for dMMR/MSI-H tumors ▪ Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B) ▪ Avelumab for dMMR/MSI-H tumors ▪ Nivolumab for dMMR/MSI-H tumors

[1] Carboplatin/paclitaxel is preferred only for patients who have not received any prior systemic therapy. Can be considered as an option under the "Other Recommended Regimens" list if or when re-use is appropriate in the first-line setting for recurrent disease.
[2] Docetaxel may be considered for patients in whom paclitaxel is contraindicated.
[3] Albumin-bound paclitaxel is a reasonable substitute for patients with a hypersensitivity to paclitaxel if the skin testing to paclitaxel is negative. If the patient has a positive skin test to paclitaxel then the patient requires desensitization to paclitaxel.
[4] Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy

g) Follow-up and Surveillance

- History and physical exam is recommended every 3 to 6 months for the first 2 to 3 years, and then every 6 to 12 months thereafter for up to the 5th year, then annually.
- For *non-fertility sparing treatment*, imaging should be guided by patient symptoms, risk assessment, and clinical concern for recurrent or metastatic disease. The indications of metastatic disease may include abnormal physical exam finding, bulky uterine tumor, vaginal or extrauterine involvement, delay in presentation or treatment, and abdominal or pulmonary symptoms.
- For *fertility-sparing treatment*, the panel recommends repeat pelvic MRI (preferred) for patients with persistent endometrial carcinoma after 6 to 9 months of failed medical therapy, especially if considering further fertility-sparing approaches.
- Abdominal/pelvic MRI and/or chest CT is recommended based on symptoms or physical exam findings. Whole body FDG-PET/CT and/or abdomen/pelvis MRI can be considered in select patients as clinically indicated.

1.3 European Guidelines

1.3.1 European Society for Medical Oncology (ESMO)

The European Society for Medical Oncology (ESMO) released in 2022 clinical practice guidelines for diagnosis, treatment, and follow up of endometrial cancer. The key recommendations of the guideline are outlined in the following sections:

a) Diagnosis and pathology/Molecular biology

The diagnosis and pathology recommendations for endometrial cancer according to the ESMO guidelines are shown in table 10.

Table 10. Diagnosis and Pathology Recommendations for Endometrial Cancer (ESMO Guidelines)

Recommendations	Strength
Diagnosis and pathology	
▪ Histological type, FIGO grade, myometrial invasion and LVSI (focal/substantial) should be described for all EC pathology specimens.	V,A
▪ Molecular classification through well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) in combination with targeted tumor sequencing (POLE hotspot analysis) should be carried out for all EC pathology specimens regardless of histological type.	IV,A

b) Staging and Risk assessment

The staging and risk assessment recommendations for endometrial cancer according to the ESMO guidelines are shown in table 11.

Table 11. Staging and Risk Assessment Recommendations for Endometrial Cancer (ESMO Guidelines)

Recommendations	Strength
Staging and Risk Assessment	
▪ Obtaining endometrial sampling by biopsy or D&C are acceptable initial approaches to histological diagnosis of EC.	IV,A
▪ The preoperative work-up should include clinical and gynecological examination, transvaginal ultrasound, pelvic MRI, a full blood count and liver and renal function profiles.	IV,B

▪ Additional imaging tests (e.g. thoracic and abdominal CT scan and/or FDG-PET-CT) may be considered in those patients at high risk of extrapelvic disease.	IV,C

c) Management of local and regional disease

ESMO uses The Cancer Genome Atlas (TCGA) classification to stratify patients into risk categories and recommend an appropriate treatment approach (table 12).

Table 12. Endometrial Cancer Risk Groups (TCGA Classification)

Risk group	Description
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI
	Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI
	Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI
	Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI
	Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI
	Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI
	Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI
	Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion
	All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion
	All stage III and IVA with no residual tumor, regardless of histology and regardless of molecular subtype

dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated.

The treatment recommendations for patients with local/locoregional endometrial cancer according to the ESMO guidelines are shown in table 13.

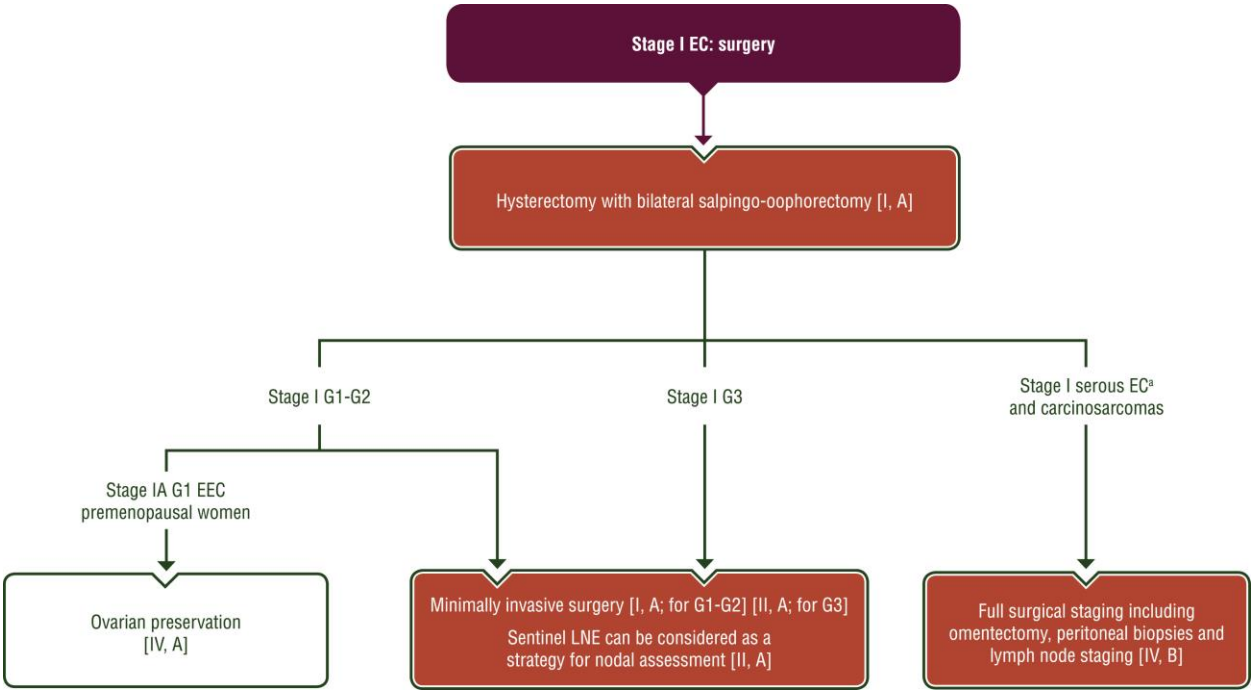
Table 13. Treatment Recommendations for Patients with Local/Locoregional Endometrial Cancer (ESMO Guidelines)

Recommendations	Strength
General Recommendations	
▪ Hysterectomy with bilateral salpingo-oophorectomy is the standard surgical procedure in early-stage EC.	I,A
▪ Minimally invasive surgery is the recommended approach in stage I G1-G2 EC [I, A]. Minimally invasive surgery may also be the preferred surgical approach in stage I G3.	II,A
▪ Ovarian preservation can be considered in premenopausal women with stage IA G1 EEC.	IV,A
▪ Sentinel LNE can be considered as a strategy for nodal assessment in low-risk/intermediate-risk EC (e.g. stage IA G1-G3 and stage IB G1-G2).	II,A
▪ It can be omitted in cases without myometrial invasion. Systematic LNE is not recommended in this group.	II,D
▪ Surgical lymph node staging should be carried out in patients with high-intermediate-risk/high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic LNE for lymph node staging in intermediate-risk/high-risk stage I-II.	III,B
▪ Full surgical staging including omentectomy, peritoneal biopsies and lymph node staging should be considered in serous ECs and carcinosarcomas.	IV,B
▪ When feasible, and with acceptable morbidity, cytoreductive surgery to a maximal surgical extent should be considered in stage III and IV.	IV,B
Low-Risk EC	
▪ For patients with stage IA (G1 and G2) with endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant treatment is not recommended.	I,E

▪ For patients with stage IA non-endometrioid type (and/ or p53-abn), without myometrial invasion and no or focal LVSI, adjuvant treatment is not recommended.	III,E
▪ For patients with stage I-II cancers with pathogenic variations in the exonuclease domain of DNA polymerase epsilon (POLE)-ultramutated (*POLEmut* cancers) adjuvant treatment is not recommended.	III,D
▪ For patients with stage III POLEmut cancers, treatment within the scope of clinical trials is recommended but no adjuvant treatment is also an option.	III,C
Intermediate-Risk EC	
▪ For patients with stage IA G3 endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence	I,A
▪ For patients with stage IB G1-G2 endometrioid (dMMR and NSMP) type and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence	I,A
▪ For patients with stage II G1 endometrioid cancer (dMMR and NSMP) and no or focal LVSI, adjuvant VBT is recommended to decrease vaginal recurrence	II,B
▪ Omission of adjuvant VBT can be considered (especially for patients aged < 60 years) for all above stages, after patient counseling and with appropriate follow-up	III,C
High-intermediate-risk EC with lymph node staging (pN0)	
▪ For patients with stage IA and IB with substantial LVSI, stage IB G3, stage II G1 with substantial LVSI and stage II G2-G3 (dMMR and NSMP): - Adjuvant EBRT is recommended	I,A
- Adding (concomitant and/or sequential) chemotherapy to EBRT could be considered, especially for G3 and/or substantial LVSI	II,C
- Adjuvant VBT (instead of EBRT) could be recommended to decrease vaginal recurrence, especially for those without substantial LVSI	II,C
- With close follow-up, omission of any adjuvant treatment is an option following shared decision making with the patient	IV,C
High-intermediate-risk EC without lymph node staging.	

▪ For patients with stage IA and IB with substantial LVSI, stage IB G3, stage II G1 with substantial LVSI and stage II G2-G3 (dMMR and NSMP): - Adjuvant EBRT is recommended	I,A
- Adding (concomitant and/or sequential) chemotherapy to EBRT could be considered especially for substantial LVSI and G3	II,C
- Adjuvant VBT could be considered for IB G3 without substantial LVSI to decrease vaginal recurrence	II,C
High-Risk EC	
▪ Adjuvant EBRT with concurrent and adjuvant Chemotherapy is recommended.	I,A
▪ Sequential chemotherapy and RT can be used.	I,C
▪ Chemotherapy alone is an alternative option.	I,B

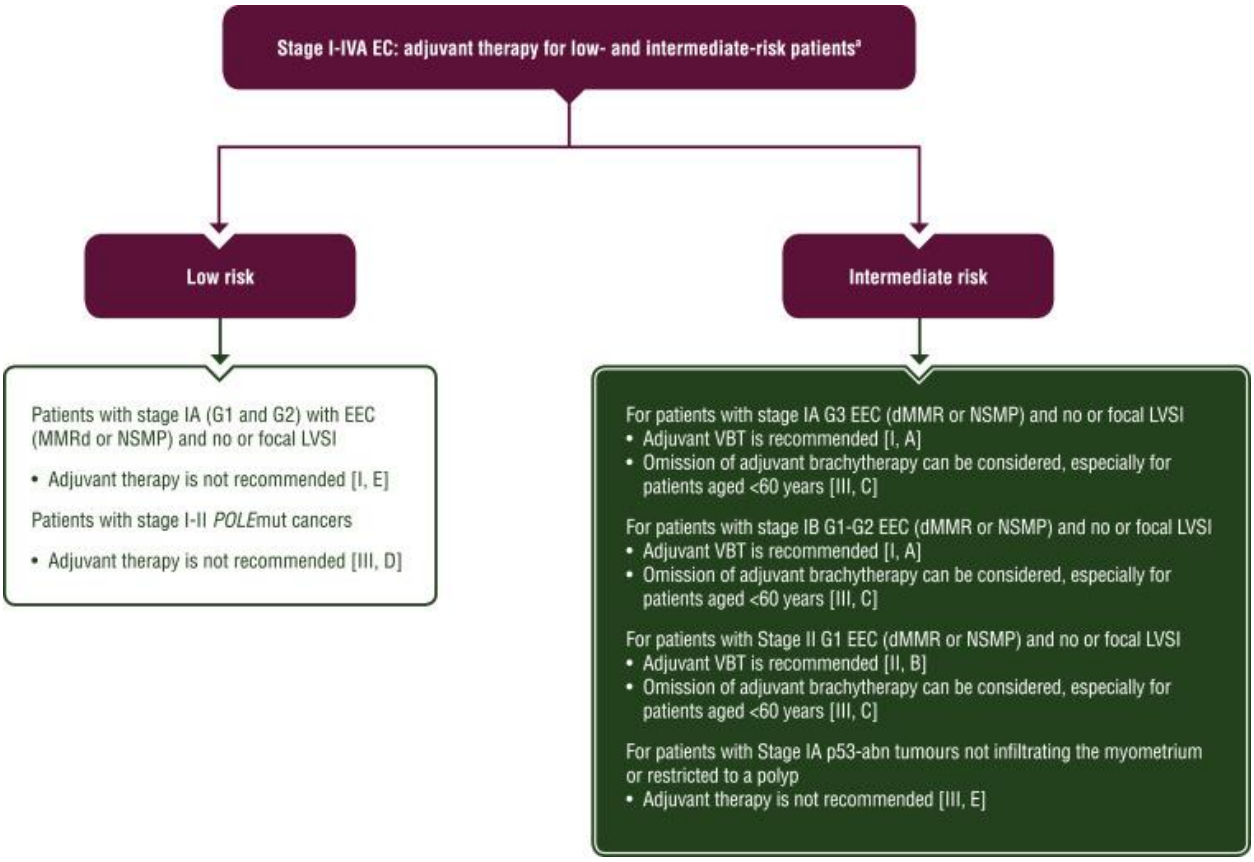
A proposed algorithm for the surgery recommendations for Stage I endometrial cancer is shown in figure 1.



Purple: general categories or stratification; red: surgery; white: other aspects of management; EC, endometrial cancer; EEC, endometrioid-type endometrial cancer; LNE, lymphadenectomy

Figure 1. Stage I EC: surgery (ESMO guidelines). Retrieved from Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009.

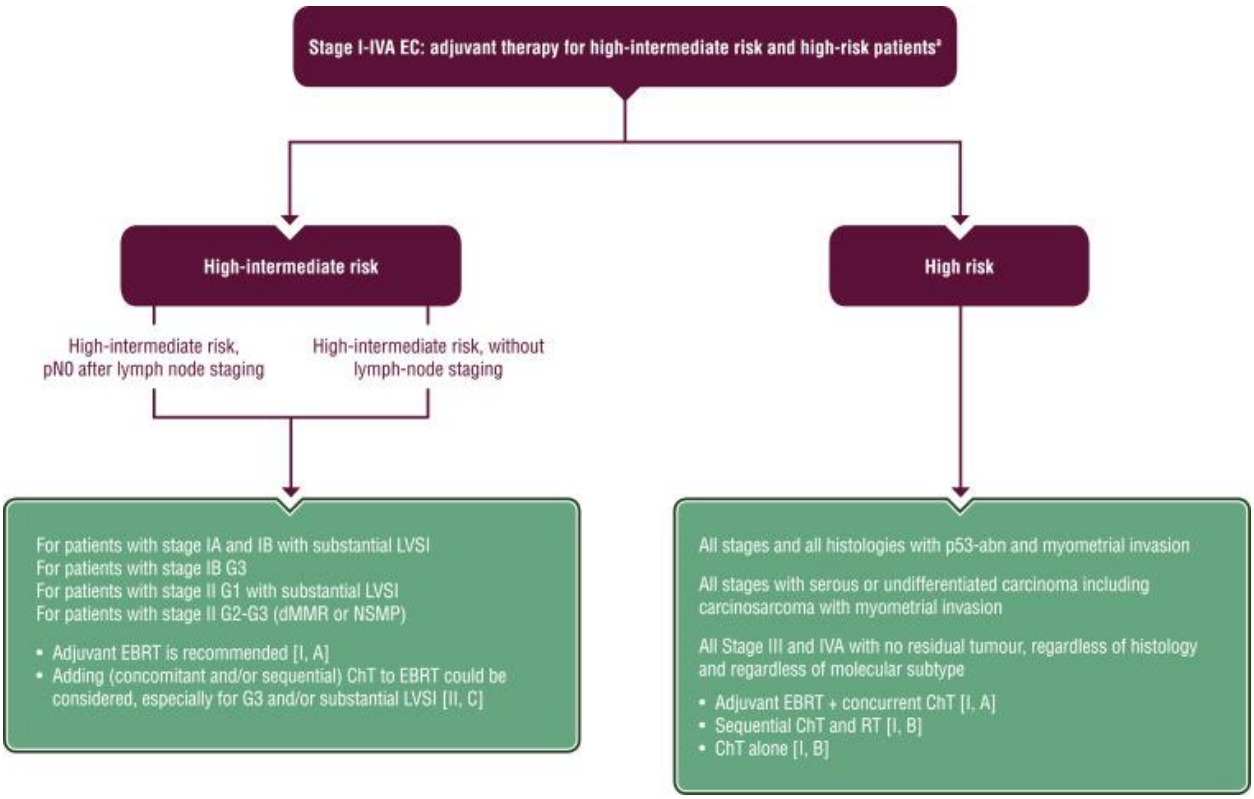
A proposed algorithm for adjuvant therapy for low- and intermediate-risk EC is shown in figure 2.



dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid-type endometrial cancer; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated; RT radiotherapy; VBT, vaginal brachytherapy.

Figure 2. Stage I-IVA EC: adjuvant therapy for low- and intermediate-risk patients (ESMO guidelines). Retrieved from Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009.

A proposed algorithm for adjuvant therapy for intermediate- and high-risk EC is shown in figure 3.



dMMR, mismatch repair deficient; EC, endometrial cancer; EEC, endometrioid-type endometrial cancer; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated; RT radiotherapy; VBT, vaginal brachytherapy.

Figure 3. Stage I-IVA EC: adjuvant therapy for intermediate- and high-risk patients (ESMO guidelines). Retrieved from Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009.

d) Recurrent/Metastatic Disease

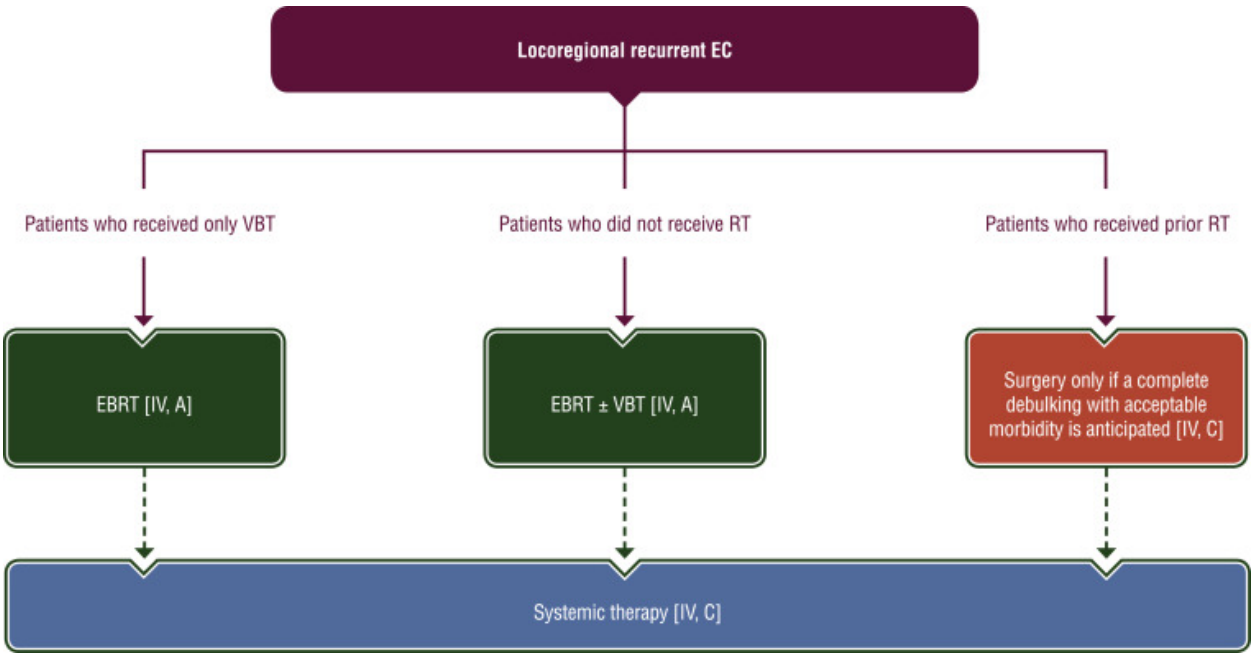
The recurrent/metastatic disease treatment recommendations for patients with EC according to the ESMO guidelines are shown in table 14[13].

Table 14. Treatment Recommendations for Patients with Recurrent/Metastatic Endometrial Cancer (ESMO Guidelines)

Recommendations	Strength
Recurrent/Metastatic EC	
▪ For patients with locoregional recurrence following primary surgery alone, the preferred primary therapy should be RT with vaginal brachytherapy.	IV,A

▪ Adding systemic therapy to salvage RT could be considered.	IV,C
▪ For patients with recurrent disease following RT, surgery should be considered only if a complete debulking with acceptable morbidity is anticipated.	IV,C
▪ Complementary systemic therapy after surgery could be considered.	IV,C
▪ The first-line standard chemotherapy treatment is **carboplatin AUC 5-6 plus paclitaxel 175 mg/m²** every 21 days for six cycles.	I,A
▪ **Hormone therapy** could be considered as front-line systemic therapy for patients with low-grade carcinomas endometrioid histology.	III,A
▪ **Progestins** (medroxyprogesterone acetate 200 mg and megestrol acetate 160 mg) are the recommended agents.	II,A
▪ Other options for hormonal therapies include AIs, tamoxifen and fulvestrant.	III,C
▪ There is no standard of care for second-line chemotherapy. **Doxorubicin** and **weekly paclitaxel** are considered the most active therapies.	IV,C
▪ Immune-checkpoint blockade monotherapy could be considered after platinum-based therapy failure in patients with MSI-H/dMMR EC.	III,B
▪ **Dostarlimab** has recently been approved by both the EMA and the FDA for this indication [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3].	III,B
▪ **Pembrolizumab** is FDA approved for the treatment of TMBH solid tumors (as determined by the FoundationOne CDx assay) that have progressed following prior therapy for EC [ESMO-MCBS v1.1 score: 3; not EMA approved].	III,B
▪ **Pembrolizumab-lenvatinib** is approved by the EMA for EC patients who have failed a previous platinum-based chemotherapy, and who are not candidates for curative surgery or RT. FDA approval is for EC patients whose tumors are not dMMR/MSI-H [ESMO-MCBS v1.1 score: 4].	I,A

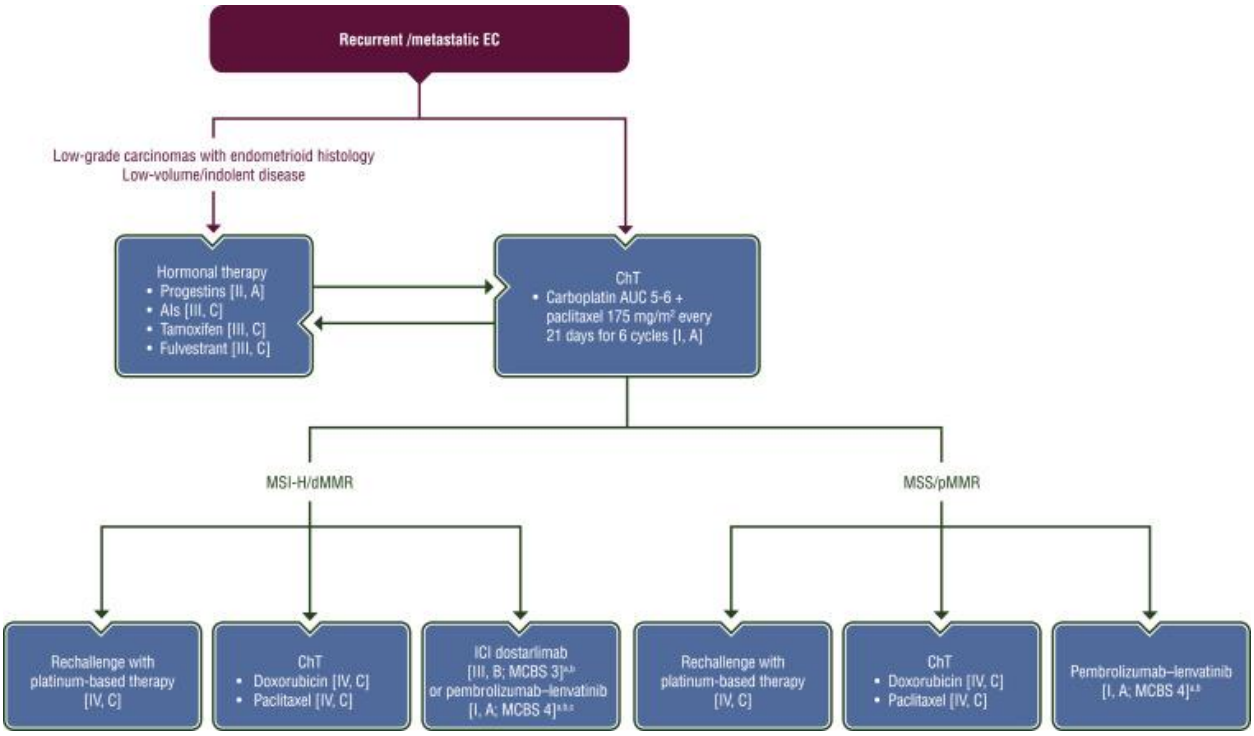
A proposed algorithm for the treatment recommendations for locoregional recurrent endometrial cancer is shown in figure 4.



EBRT, external beam radiotherapy; EC, endometrial cancer; RT radiotherapy; VBT, vaginal brachytherapy.

Figure 4. Locoregional Recurrent EC (ESMO Guidelines). Retrieved from Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009

A proposed algorithm for the treatment recommendations for metastatic endometrial cancer is shown in figure 5.



AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; dMMR, mismatch repair deficient; EC, endometrial cancer; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient.

Figure 5. Metastatic EC (ESMO guidelines). Retrieved from Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009.

e) Follow-up, Long-Term Implications, and Survivorship

The follow-up, long-term implications, and survivorship recommendations for patients with EC according to the ESMO guidelines are shown in table 15[13].

Table 15. Follow-up, Long-Term Implications, and Survivorship Recommendations (ESMO Guidelines)

Recommendations	Strength
Follow-up, Long-Term Implications, and Survivorship	
▪ For low-risk EC, the proposed surveillance is every 6 months, with physical and gynecological examination for the first 2 years and then yearly until 5 years.	V,C
▪ In the low-risk group, phone follow-up can be an alternative to hospital-based follow-up consultation.	II,B

▪ For the high-risk groups, physical and gynecological examinations are recommended every 3 months for the first 3 years, and then every 6 months until 5 years.	V,C
▪ A CT scan or PET-CT could be considered in the high-risk group, particularly if node extension was present.	V,D
▪ Regular exercise, healthy diet and weight management should be promoted with all EC survivors.	II,B

1.3.2 European Society of Gynecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP)

The European Society of Gynecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP) released in 2021, their joint guidelines for the management of patients with endometrial carcinoma. The key management recommendations of the guideline are outlined in table 16.

Table 16. Management Recommendations for Endometrial Cancer (ESGO/ESTRO/ESP Guidelines)

Recommendations	Strength
General Recommendations	
▪ Planning of staging and treatment should be made on a multi-disciplinary basis (generally at a tumor board meeting, composed according to local guidelines) and based on the comprehensive and precise knowledge of prognostic and predictive factors for outcome, morbidity, and quality of life.	V,A
▪ Patients should be carefully counseled about the suggested diagnostic and treatment plan and potential alternatives, including risks and benefits of all options.	V,A
▪ Treatment should be undertaken in a specialized center by a dedicated team of specialists in the diagnosis and management of gynecological cancers, especially in high-risk and/or advanced stage disease.	V,A
Identification and surveillance of women with a pathogenic germline variant in a Lynch syndrome associated gene	
▪ To identify patients with Lynch syndrome and triage for germline mutational analysis, MMR IHC (plus analysis of MLH1 promotor methylation status in case of immunohistochemical loss of	III,B

MLH1/PMS2 expression) or MSI tests should be performed in all endometrial carcinomas, irrespective of histologic subtype of the tumor.	
▪ Endometrial carcinoma patients identified as having an increased risk of Lynch syndrome should be offered genetic counseling.	III,B
▪ Surveillance for endometrial carcinoma in Lynch syndrome mutation carriers should in general start at the age of 35 years; however, individual factors need to be taken into consideration (tailored surveillance programs). The decision on the starting age of surveillance should integrate knowledge on the specific mutation and history of onset of events in the family.	IV,B
▪ Surveillance of the endometrium by annual transvaginal ultrasound (TVUS) and annual or biennial biopsy until hysterectomy should be considered in all Lynch syndrome mutation carriers.	IV,B
▪ Hysterectomy and bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer should be performed at the completion of childbearing and preferably before the age of 40 years. All the pros and cons of prophylactic surgery must be discussed including the risk of occult gynecological cancer detection at prophylactic surgery. Estrogen replacement therapy should be suggested if bilateral salpingo-oophorectomy is performed in pre-menopausal women.	IV,B
Molecular markers for EC diagnosis and treatment decisions	
▪ Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors. ▪ POLE mutation analysis may be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology.	IV,B IV,C
Pre-and Intra-operative workup	
▪ Histopathologic tumor type and grade in endometrial biopsy is required.	IV,A
▪ Pre-operative mandatory work-up includes family history; general assessment and inventory of co-morbidities; geriatric assessment, if appropriate; clinical examination, including pelvic examination; expert transvaginal or transrectal ultrasound or pelvic MRI.	IV,C
▪ Depending on clinical and pathologic risk, additional imaging modalities (thoracic, abdominal and pelvic CT scan, MRI, PET scan,	IV,C

or ultrasound) should be considered to assess ovarian, nodal, peritoneal, and other sites of metastatic disease.	
▪ Intra-operative frozen section is not encouraged for myometrial invasion assessment because of poor reproducibility and interference with adequate pathologic processing.	IV,A
Early-stage disease	
Minimally invasive approach	
▪ Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma.	I,A
▪ Any intra-peritoneal tumor spillage, including tumor rupture or morcellation (including in a bag), should be avoided.	III,B
▪ If vaginal extraction risks uterine rupture, other measures should be taken (e.g., mini-laparotomy, use of endobag).	III,B
▪ Tumors with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contraindications for minimally invasive surgery.	III,B
Standard surgical procedures	
▪ Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff resection.	II,A
▪ Staging infracolic omentectomy should be performed in clinical stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma. It can be omitted in clear cell and endometrioid carcinoma in stage I disease.	IV,B
▪ Surgical re-staging can be considered in previously incompletely staged patients with high– intermediate-risk/high-risk disease if the outcome might have an implication for adjuvant treatment strategy.	IV,B
Lymph node staging	
▪ Sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group.	I,A
▪ Surgical lymph node staging should be performed in patients with high–intermediate-risk/high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II.	III,B
▪ If sentinel lymph node biopsy is performed:	II,A

- Indocyanine green with cervical injection is the preferred detection technique. - Tracer re-injection is an option if sentinel lymph node is not visualized upfront. - Side-specific systematic lymphadenectomy should be performed in high–intermediate-risk/high-risk patients if sentinel lymph node is not detected on either pelvic side. - Pathologic ultrastaging of sentinel lymph nodes is recommended.	
▪ When a systematic lymphadenectomy is performed, pelvic and para-aortic infrarenal lymph node dissection is suggested.	III,B
▪ Presence of both macrometastases and micrometastases (<2mm, pN1(mi)) is regarded as a metastatic involvement.	IV,C
▪ The prognostic significance of ITCs, pN0(i+), is still uncertain.	IV,C
▪ If pelvic lymph node involvement is found intra-operatively, further systematic pelvic lymph node dissection should be omitted. However, debulking of enlarged lymph nodes and para-aortic staging can be considered.	IV,B
Ovarian preservation	
▪ Ovarian preservation can be considered in pre-menopausal patients aged < 45 years with low-grade endometrioid endometrial carcinoma with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease.	IV,A
▪ In cases of ovarian preservation, salpingectomy is recommended.	IV,B
▪ Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (eg, BRCA mutation, Lynch syndrome, etc.).	IV,B
Fertility preservation	
▪ Hysteroscopic resection prior to progestin therapy can be considered.	III,B
▪ Medroxyprogesterone acetate (400–600mg/day) or megestrol acetate (160–320 mg/day) is the recommended treatment. Treatment with levonorgestrel intrauterine device in combination with oral progestins with or without gonadotropin-releasing hormone analogs can also be considered.	IV,B
▪ In order to assess response, hysteroscopic guided biopsy and imaging at 3–4 and 6 months must be performed. If no response is	IV,B

achieved after 6 months, standard surgical treatment is recommended.	
▪ Continuous hormonal treatment should be considered in responders who wish to delay pregnancy.	IV,B
▪ Strict surveillance is recommended every 6 months with TVUS and physical examination. During follow-up, hysteroscopic and endometrial biopsy should be performed only in case of abnormal uterine bleeding or atypical ultrasound findings.	IV,B
▪ Fertility-sparing treatment can be considered for intrauterine recurrences only in highly selected cases under strict surveillance.	IV,C
▪ Hysterectomy and bilateral salpingo-oophorectomy is recommended after childbearing due to a high recurrence rate. Preservation of the ovaries can be considered depending on age and genetic risk factors.	IV,B
Adjuvant Chemotherapy	
Low-risk	
▪ If all WHO 2020 criteria are met and the ovarian carcinoma is pT1a, no adjuvant treatment is recommended	III,B
▪ For patients with low-risk endometrial carcinoma, no adjuvant treatment is recommended.	I,A
▪ When molecular classification is known: - For patients with endometrial carcinoma stage I–II, low-risk based on pathogenic POLE-mutation, omission of adjuvant treatment should be considered.	III,A
- For the rare patients with endometrial carcinoma stage III–IVA and pathogenic POLE-mutation, there are no outcome data with the omission of the adjuvant treatment. Prospective registration is recommended.	IV,C
Intermediate-risk	
▪ Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (I, A).	I,A
▪ Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged < 60 years (II,A).	-
▪ When molecular classification is known, POLEmut and p53abn with myometrial invasion have specific recommendations.	-
▪ For p53abn carcinomas restricted to a polyp or without myometrial invasion, adjuvant therapy is generally not recommended.	III,C

High–intermediate risk (pN0 after lymph node staging)	
▪ Adjuvant brachytherapy can be recommended to decrease vaginal recurrence.	II,B
▪ EBRT can be considered for substantial LVSI and for stage II.	I,B
▪ Adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI.	II,C
▪ Omission of any adjuvant treatment is an option.	IV,C
▪ When molecular classification is known, POLEmut and p53abn have specific recommendations.	-
High–intermediate risk cN0/pNx (lymph node staging not performed)	
▪ Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II.	I,A
▪ Additional adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI.	II,B
▪ Adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas.	II,B
▪ When molecular classification is known, POLEmut and p53abn have specific recommendations.	-
High–risk	
▪ EBRT with concurrent and adjuvant chemotherapy or alternatively sequential chemotherapy and radiotherapy is recommended.	I,A
▪ Chemotherapy alone is an alternative option.	I,B
▪ Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas).	IV,B
▪ When the molecular classification is known, p53abn carcinomas without myometrial invasion and POLEmut have specific recommendations.	III,C
Advanced disease	
▪ In stage III and IV endometrial carcinoma (including carcinosarcoma), surgical tumor debulking including enlarged lymph nodes should be considered when complete macroscopic resection is feasible with an acceptable morbidity and quality of life profile, following full pre-operative staging and discussion by a multi-disciplinary team.	IV,B
▪ Primary systemic therapy should be used if upfront surgery is not feasible or acceptable.	IV,A

▪ In cases of a good response to systemic therapy, delayed surgery can be considered.	IV,C
▪ Only enlarged lymph nodes should be resected. Systematic lymphadenectomy is not recommended.	IV,B
▪ Residual lymph node disease should be treated with a combination of chemotherapy and EBRT (III, B) or chemotherapy alone.	IV,B
▪ EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost.	IV,B
Recurrent disease	
▪ 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. Systemic and/or radiation therapy should be considered post-operatively depending on the extent and pattern of relapse and the amount of residual disease.	IV,C
▪ For locoregional recurrence, the preferred primary therapy should be EBRT±chemotherapy with brachytherapy.	IV,A
▪ Systemic treatment can be considered before or after radiotherapy.	IV,C
Systemic treatment for recurrent disease	
▪ **Hormone therapy** is the preferred front-line systemic therapy for patients with **low-grade carcinomas without rapidly progressive disease**.	II,A
▪ **Progestogens** (medroxyprogesterone acetate 200 (–300) mg and megestrol acetate 160mg) are recommended.	III,A
▪ Alternative options for hormonal therapies include **aromatase inhibitors, tamoxifen, fulvestrant**.	III,C
▪ The **standard chemotherapy treatment** is **carboplatin AUC 5–6 + paclitaxel 175mg/m² every 21 days for six cycles**.	I,A
▪ There is no standard of care for second-line chemotherapy. Doxorubicin and paclitaxel are considered the most active therapies.	IV,C
▪ In patients with a long platinum-free interval, re-introduction of platinum can be considered.	IV,C
▪ Anti-PD1-based immune therapy with **pembrolizumab** could be considered for **second-line therapy of MSI/MMRd carcinomas**. The combination of **pembrolizumab** and the multi-tyrosinekinase	III,B

	inhibitor **lenvatinib** could be considered for second-line treatment of microsatellite-stable carcinomas. However, its use may be limited due to regulatory approvals or reimbursement in different countries. Clinical trial participation should be offered to all patients with relapse disease.	

1.3.3 British Gynecological Cancer Society (BGCS)

The British Gynecological Cancer Society (BGCS) released in 2021, their updated guidelines for uterine cancer. The key treatment recommendations of the guideline are outlined in the below sections.

a) Primary treatment – Surgical Management

- Enhanced recovery after surgery (ERAS) programs improve outcomes following gynecological oncology surgery and should be standard of care. (Grade A)
- Standard surgery is a total hysterectomy and BSO without vaginal cuff or parametrectomy (Grade D).
- Hysterectomy/salpingectomy with ovarian conservation can be considered in pre-menopausal patients with grade 1 endometrioid EC, < 50% myometrial invasion and no extra-uterine disease on imaging (MRI/CT) with low-risk disease. (Grade D)
- Minimal access surgery has not been shown to have adverse oncological outcomes on EC, as compared to open surgery, is associated with a significantly lower risk of post-operative morbidity and is therefore the preferred route in suitable patients. (Grade A)
- Robotic-assisted surgery appears to be non-inferior to laparoscopy and laparotomy for the treatment of endometrial cancer, although long-term oncological outcome data are lacking. (Grade B)
- Lymphadenectomy of non-bulky nodes is a diagnostic procedure and has not been shown to reduce the risk of recurrence or improve survival. (Grade A)
- Lymphadenectomy for non-bulky nodes is not recommended, especially for low-risk EC. (Grade A)
- Sentinel lymph node biopsy (SLNB) has a high diagnostic test accuracy and should replace lymphadenectomy of non-bulky nodes for staging. (Grade B)
- Surgical staging, including sentinel lymph node biopsy and omental biopsy, may be appropriate for women with disease greater than low risk. (Grade C)

- Recruitment of patients with high grade disease and non-endometrioid endometrial cancers into trials investigating the role of sentinel node surgery in clinical management pathways is strongly recommended. (Grade C)
- In patients with overt stage II endometrial cancer, total hysterectomy with bilateral salpingo-oophorectomy is adequate. Radical hysterectomy should only be considered to obtain tumor-free margins. (Grade B)

b) Primary treatment – Non-Surgical Management

b.1 Patients unfit for surgical management

- Women who are unfit for standard surgical management may be treated by vaginal hysterectomy, definitive pelvic radiotherapy or progestin/aromatase inhibitors. The choice of treatment depends on patient characteristics and local preferences. (Grade D)
- Vaginal hysterectomy may be considered for women who cannot undergo abdominal or laparoscopic hysterectomy. (Grade C)
- Combined external beam radiation therapy (EBRT) and intra-cavitary brachytherapy may be considered for women with high grade tumors, deep myometrial invasion and/or stage II disease. Intra-cavitary brachytherapy alone may be considered for women with low grade, stage I tumors without deep myometrial invasion. (Grade B)
- Progestin therapy may be considered in women with low grade tumors to postpone standard surgical management for 3-6 months for temporary or reversible medical reasons. (Grade B)
- Progestin (and/or aromatase inhibitors in postmenopausal women) may be considered in women in whom surgery/radiotherapy is not an option. (Grade B)

b.2 Fertility-preserving management

- Women wishing to preserve their fertility should be managed in specialist centers. Assessment should include specialist pathology review, imaging by MRI scan and fertility clinic referral to confirm eligibility. (Grade A)
- Women with atypical hyperplasia or Stage 1A grade 1 endometrial cancer without myometrial invasion may be suitable for fertility-sparing management. Women should be carefully counseled regarding success rates, the need for close surveillance before/after treatment, recurrence rates and the need for hysterectomy if treatment fails/once childbearing is complete. (Grade A)
- Treatment is by medroxyprogesterone acetate (400-600 mg/day) or megestrol acetate (160- 320mg/day) and/or levonorgestrel-releasing

intrauterine system (LNG-IUS) for 6-12 months. Hysteroscopic resection prior to progestin therapy may be considered. Additional prescription of gonadotrophin-releasing hormones may be considered. (Grade B) Strict surveillance during treatment includes endometrial biopsy and repeat imaging at 3 monthly intervals to exclude progressive disease. (Grade B)

- Women should be supported to maximize their chances of pregnancy after successful fertility-sparing treatment because recurrence is common and their window of opportunity may be short. (Grade A)
- After 6-months of proven disease regression, maintenance progestin therapy should be considered in responders wishing to delay pregnancy. Endometrial surveillance by biopsy and/or scan at 3-6 monthly, then 6-12 monthly intervals is appropriate during follow up. Progestin therapy may be considered for intrauterine recurrence. Hysterectomy and bilateral salpingectomy is indicated if conservative management fails and once childbearing is complete. Ovarian preservation may be considered in young women who do not have Lynch syndrome. (Grade B)

b.3 Surgery for more advanced disease at presentation

- In FIGO stage III/IV EC, debulking surgery, including bulky nodes, should be considered if complete macroscopic resection is feasible, and, if the patient is deemed fit for radical surgery with acceptable morbidity and quality of life, as limited evidence shows that this may improve survival. However, more limited surgery with hysterectomy for palliation of symptoms, or other palliative treatment options are alternatives and should be discussed with the patient (Grade D)
- Routine systematic pelvic and para-aortic lymph node dissection of non-suspicious nodes is not recommended (Grade D)
- Surgery may be appropriate for patients with advanced disease at presentation who have responded to neoadjuvant chemotherapy (NACT). (Grade D)
- Debulking palliative surgery has a role in providing symptom relief. (Grade C)

c) Primary treatment – adjuvant treatment

c.1 General recommendations

c.1.1 Low-risk EC

- No adjuvant treatment is recommended for those with low-risk EC. (Grade A) If molecular classification is available, consider omitting adjuvant treatment in those with stage I-II and POLEmut. (Grade C)

c.1.2 Intermediate-risk EC

- Vaginal vault brachytherapy (VBT) can be recommended to reduce the risk of vaginal recurrence (Grade A)
- Omission of adjuvant brachytherapy can be considered especially for patients aged less than 60 years (Grade A)
- Where molecular classification is available, those with POLEmut EC may be considered as low risk and those with p53abn EC with myometrial invasion considered high risk (see relevant sections for recommendations). (Grade C)
- For those with p53abn EC restricted to a polyp or without myometrial invasion, there are no RCT data to guide treatment and any adjuvant therapy should be individualized. (Grade D)

c.1.3 High-intermediate-risk endometrial cancer

- When surgical staging of lymph nodes has been performed:
  - Consider adjuvant vaginal brachytherapy alone, if no LVSI. (Grade A)
  - EBRT is recommended for substantial LVSI and for Stage II tumors with high grade or deep myometrial invasion. (Grade A)
- When surgical staging of lymph nodes has not been performed:
  - Adjuvant EBRT is recommended. (Grade A)
  - Adjuvant chemotherapy can be considered, when substantial LVSI is present. (Grade B)
  - Adjuvant brachytherapy alone can be considered for stage II low grade endometrioid cancers without deep invasion. (Grade B)
- If molecular classification is known, those with POLEmut and p53abn consider management as per low and high-risk disease sections. (Grade C)

c.1.4 High-risk EC

- EBRT with concurrent and adjuvant chemotherapy or alternatively sequential chemotherapy and radiotherapy is recommended. (Grade A)
- Chemotherapy alone or with VBT may be an alternative option, if systematic lymphadenectomy has been performed. (Grade B)

c.2 Adjuvant chemotherapy

- Postoperative carboplatin-paclitaxel chemotherapy is associated with a FIGO stage and histological/ molecular subtype dependent improvement in progression-free survival and overall survival irrespective of radiotherapy treatment. (Grade A)

- The use of a four-group molecular classifier provides robust prognostic information and predicts benefit from adjuvant chemotherapy. Centers should work towards adopting this into routine practice. (Grade C)
- If molecular subtyping has not been performed:
  - Adjuvant chemotherapy is a recommended treatment option for:
    - Women with stage III/IVA endometrial adenocarcinoma of all histological subtypes (Grade A)
    - Women with myoinvasive stage I or II serous endometrial carcinoma (Grade B)
    - Women with myoinvasive stage I or II clear cell or undifferentiated endometrial carcinoma or carcinosarcoma. (Grade C)
  - Adjuvant chemotherapy can be discussed as a potential treatment option with:
    - Women with stage IB or II grade 3 endometrioid endometrial carcinoma where lymphadenectomy has not been performed or there is substantial lymphovascular space invasion. (Grade B)
- If molecular subtyping has been performed:
  - Women with POLEmut endometrial cancer do not require adjuvant chemotherapy. (Grade C)
  - Adjuvant chemotherapy is recommended for:
    - Women with stage I (myoinvasive)–IVA p53abn endometrial cancer;(Grade C)
    - Women with stage III/IVA endometrial cancer with no specific molecular profile (NSMP). (Grade C)
  - Adjuvant chemotherapy can be discussed as a potential treatment option with:
    - Women with stage III/IVA MMRd endometrioid endometrial cancer. (Grade C)
    - Women with myoinvasive stage I-II non-endometrioid high grade histological subtypes that are NSMP or MMRd. (Grade C)
  - Entry into molecularly stratified adjuvant trials should be actively considered. (Grade D)
- Concurrent cisplatin-radiotherapy followed by carboplatin-paclitaxel or sequential carboplatin/paclitaxel and radiotherapy are appropriate treatment regimens, if combined modality adjuvant treatment is necessary. (Grade A)

c.3 Adjuvant hormonal therapy

- There is no role for adjuvant hormonal therapy outside clinical trials. (Grade A)

c.4 Adjuvant RT

- IMRT technique should be used to reduce the risk of acute and long-term toxicity. (Grade B)

d) Primary treatment – chemotherapy

- Neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) may be an alternative approach in the treatment of selected patients with advanced EC who are considered poor candidates for primary debulking surgery (PDS). Generally, NACT should be reserved for patients where it would be expected that PDS would not achieve complete macroscopic resection. Prospective studies investigating this approach are strongly recommended. (Grade D)
- Carboplatin-paclitaxel is the recommended standard first-line chemotherapy regimen for the treatment of advanced/recurrent endometrial cancer regardless of histologic subtype (Grade A)
- Progestogens are a suitable alternative for the treatment of low-grade hormone-receptor positive advanced/recurrent endometrioid endometrial cancer (Grade B)
- Patients with advanced/recurrent endometrial cancer should be considered for entry into first-line clinical trials evaluating targeted therapies. (Grade D)

e) Management of recurrent disease

- Patients with recurrent endometrial cancer should be managed by MDTs with expertise in the management of recurrent cancers (Grade D).
- All patients should undergo baseline cross-sectional imaging (Grade B).
- Where possible, a biopsy, for re-assessment of estrogen and progesterone receptor status and molecular profile, should be considered. (Grade D)
- All patients who are candidate for surgical resection or radiotherapy should undergo PET-CT scan to exclude multisite disease (Grade B).
- Patients with isolated vaginal recurrence who are radiotherapy naïve should be considered for radical radiotherapy. (Grade B)
- Patients with isolated vaginal vault recurrence, who have received pelvic/vault radiotherapy previously, should only be considered for surgery, if resection is achievable with clear margins (Grade D)

- Relapse that on CT scanning appears to be confined and amenable to radical therapy, particularly, if exenteration is considered, should be staged using a PET/CT scan prior to starting radical therapy. (Grade C)
- For patients treated surgically for pelvic recurrence, those with positive margins/residual disease, post-operative radiotherapy or brachytherapy should be considered, if normal tissue tolerance allows. (Grade D)
- Pelvic exenteration can be considered for patients with single-site, central pelvic recurrence and is performed with the aim to achieve margins clear of microscopic disease. (Grade D)
- Following local therapy for recurrence, additional chemotherapy is of uncertain benefit, but can be considered. (Grade D)
- Chemotherapy-naïve patients who relapse with systemic disease or those who relapse more than 6 months after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel. (Grade A)
- For patients who relapse more than 6 months after carboplatin and paclitaxel, further platinum-based chemotherapy can be considered. [Grade C]
- For patients who relapse less than 6 months after carboplatin and paclitaxel, there is no treatment that could be considered standard of care. (Grade D)
- Patients requiring second-line systemic therapy should be offered PD-1/PD-L1 inhibitors if the cancer is mismatch repair deficient, or carries a POLE mutation, or has a high tumor mutational burden. (Grade B)
- Hormonal therapy can be the first choice in those with low grade, hormone receptor positive, disease. Selected cases with long disease-free interval, well-differentiated tumors, lung only metastases and high progesterone receptor expression in the tumor may be candidates for primary hormonal therapy. (Grade C)

1.4 International Guidelines

1.4.1 Japan Society of Gynecologic Oncology (JSGO)

The Japan Society of Gynecologic Oncology (JSGO) released in 2018 clinical practice guidelines for treatment of uterine body neoplasms.

The algorithm for the initial treatment of patients with endometrial cancer considered to be stage I or II preoperatively according to the JSGO guidelines is illustrated in figure 6.

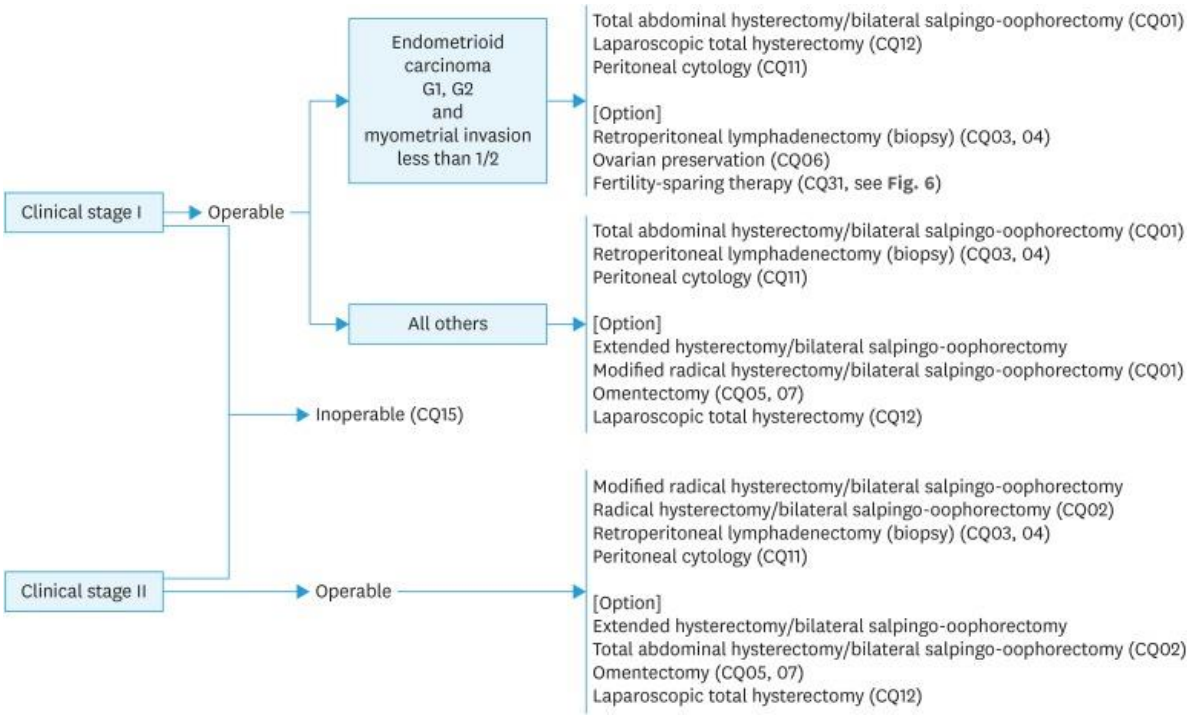


Figure 6. Initial treatment for patients with endometrial cancer considered to be stage I or II preoperatively. Retrieved from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. *J Gynecol Oncol.* 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18

The algorithm for the initial treatment for patients who are confirmed to be EC after hysterectomy and patients diagnosed with an intermediate to high risk of recurrence after surgery performed with a presumed low risk of recurrence according to the JSGO is illustrated in figure 7.

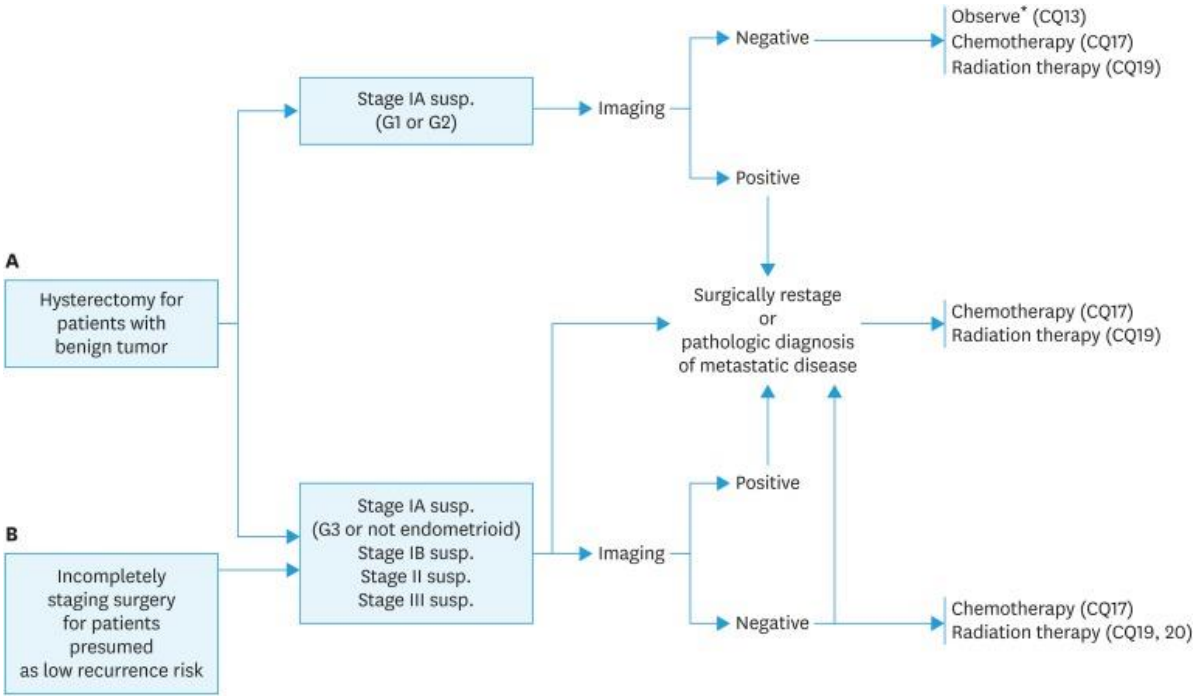


Figure 7. Initial treatment for (A) patients who are confirmed to be endometrial cancer after hysterectomy, and (B) patients diagnosed with an intermediate to high risk of recurrence after surgery performed with a presumed low risk of recurrence. Retrieved from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18

The algorithm for the initial treatment for patients with endometrial cancer considered to be stage III or IV preoperatively according to the JSGO is illustrated in figure 8.

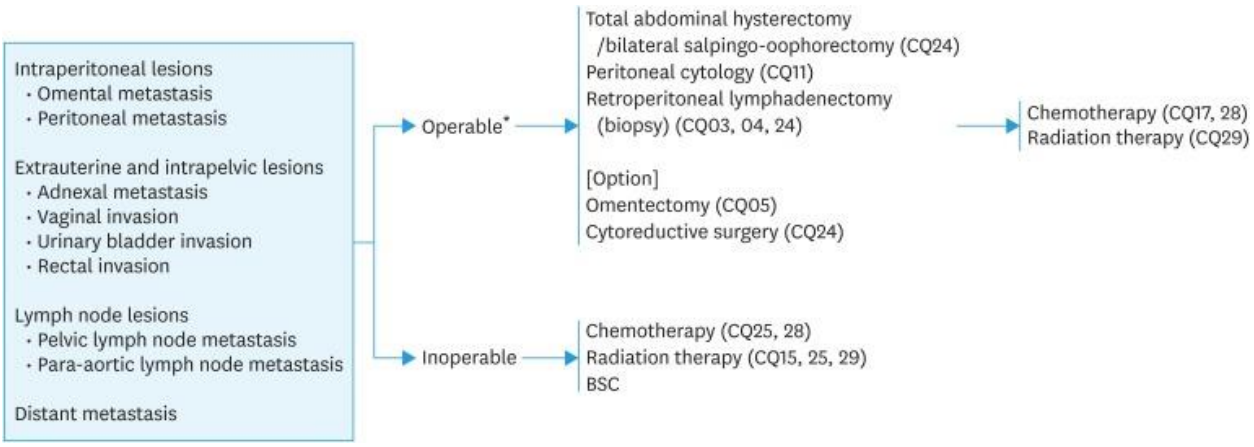


Figure 8. Initial treatment for patients with endometrial cancer considered to be stage III or IV preoperatively. Retrieved from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18

The algorithm for postoperative adjuvant treatment for endometrial cancer according to the JSGO is illustrated in figure 9.

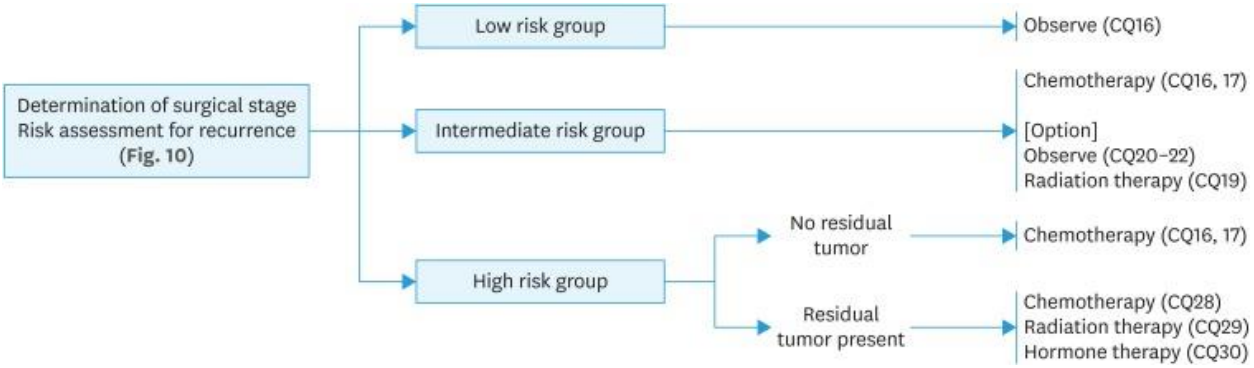


Figure 9. Postoperative adjuvant treatment for endometrial cancer. Retrieved from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18

The algorithm for the treatment of recurrent endometrial cancer according to the JSGO is illustrated in figure 10.

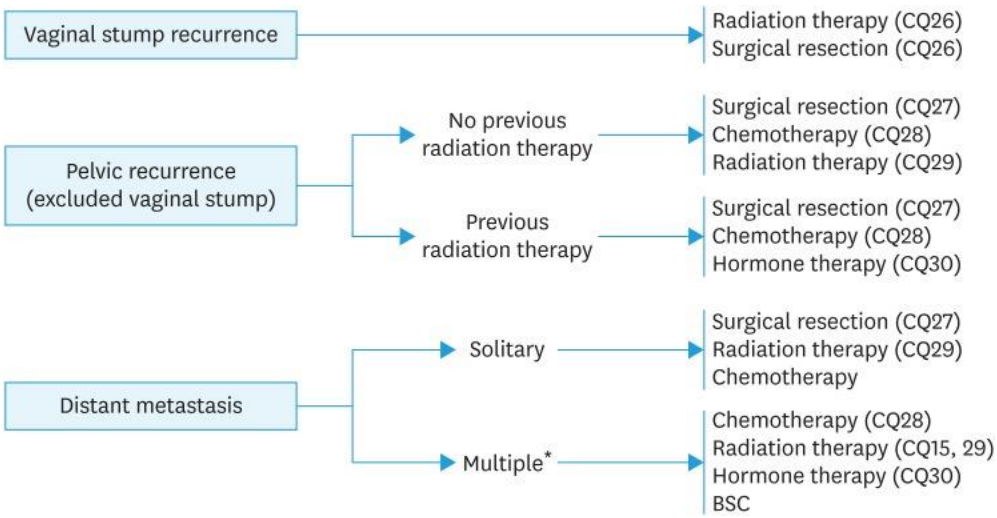


Figure 10. Treatment of recurrent endometrial cancer. Retrieved from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18.

The algorithm for fertility-sparing therapy for atypical endometrial hyperplasia and endometrioid adenocarcinoma according to the JSGO is illustrated in figure 11.

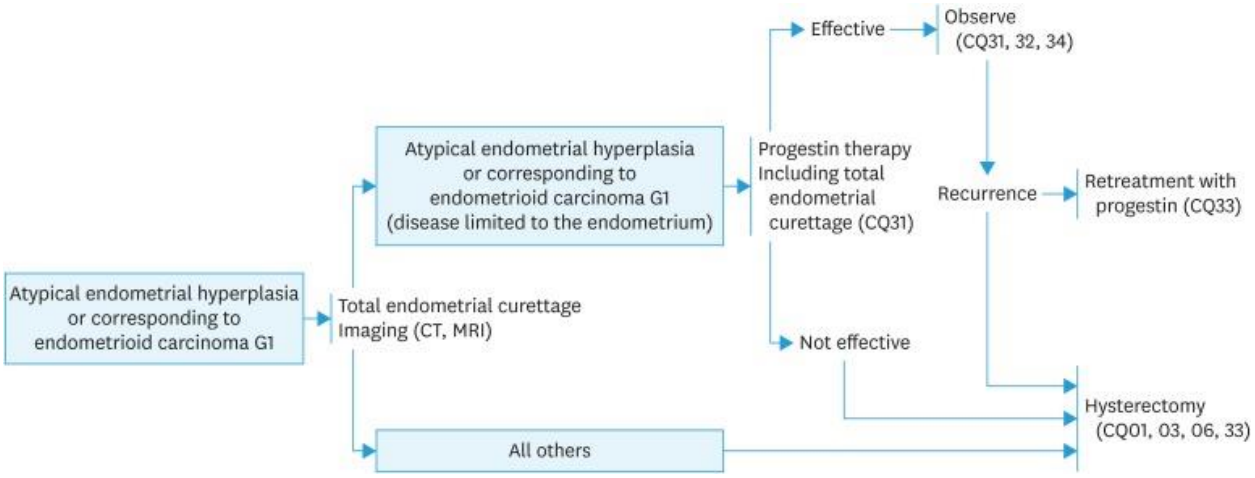


Figure 11. Strategies for fertility-sparing therapy for atypical endometrial hyperplasia and endometrioid adenocarcinoma. from Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18

The key treatment recommendations of the JSGO guideline for EC are outlined below:

a) Initial treatment for EC

- Abdominal total hysterectomy or extended hysterectomy (extrafascial technique) are recommended (Grade B).
- Modified radical hysterectomy is also suggested (Grade C1).
- Radical hysterectomy or modified radical hysterectomy is suggested (Grade C1).
- Required to determine the exact surgical staging (Grade A).
- Suggested for intermediate-risk or high-risk patients (Grade C1).
- Omission of this procedure is suggested for some low-risk patients (Grade C1).
- Required to determine the exact surgical staging (Grade A).
- Suggested for intermediate-risk or high-risk patients (Grade C1).
- Omission of this procedure is suggested for low-risk patients (Grade C1).
- Searching the omentum by careful ocular inspection and palpation is necessary in all cases (Grade A).
- Strongly recommended for cases with suspected omentum metastasis during surgery (Grade A).
- Suggested if deeper myometrial invasion, cytology, Grade 3 endometrioid carcinoma or non-endometrioid carcinoma is expected, or positive intraoperative peritoneal cytology or macroscopic extrauterine disease is found during surgery, even if no gross omentum metastasis is detected (Grade C1).
- In principle, bilateral salpingo-oophorectomy is conducted to determine the exact surgical staging during initial treatment (Grade A).
- Ovarian preservation is considered after the risks are explained to young patients with G1 endometrioid carcinoma and superficial myometrial invasion (Grade C1).
- Total hysterectomy with bilateral salpingo-oophorectomy is recommended (Grade B).
- Pelvic and para-aortic lymphadenectomy (lymph node biopsy) and omentectomy are also recommended (Grade C1).
- Evaluation of myometrial invasion and cervical invasion by preoperative MRI is strongly recommended (Grade A).
- Evaluation of lymph node metastases or distant metastases by preoperative imaging such as computed tomography (CT), magnetic resonance imaging

(MRI) or positron emission tomography (PET)/CT is strongly recommended (Grade A).

b) Post-operative adjuvant therapy

- **Postoperative adjuvant chemotherapy** is **recommended** for **high-risk patients** (Grade B).
- Postoperative adjuvant chemotherapy is suggested for intermediate-risk patients (Grade C1).
- Postoperative adjuvant chemotherapy is not recommended for low-risk patients (Grade D).
- Chemotherapy with **adriamycin** (doxorubicin hydrochloride) **and cisplatin** is recommended for high-risk patients (Grade B).
- **Taxane-based and platinum-based drug combination therapy** are also suggested (Grade C1).
- Regimens for high-risk patients are also recommended for intermediate-risk patients (Grade C1).
- Postoperative progesterone therapy is not recommended (Grade D).
- Postoperative radiotherapy is one of the options for reducing intra-pelvic recurrence (Grade C1).
- May be useful for predicting high-risk disease for which pelvic and para-aortic lymphadenectomy or omentectomy is appropriate (Grade C1).
- Not recommended for definite diagnosis of histological type, histological grade, and myometrial invasion (Grade C2).
- Omission of lymphadenectomy in patients with negative sentinel lymph node metastasis can be considered in the context of a clinical trial by a team proficient in the procedure and with strong assistance from a pathologist (Grade C1).
- Intraoperative peritoneal cytology is strongly recommended (Grade A).
- Laparoscopic surgery is recommended for cases with AEH or a low risk of recurrence in presumed stage I endometrial cancer (Grade B).
- Laparoscopic surgery is considered for cases with an intermediate or high recurrence risk in presumed stage I or II endometrial cancer (Grade C1).
- Laparoscopic surgery is not recommended for advanced endometrial cancer (Grade C2).

c) Post-treatment surveillance

- Standard intervals between routine follow-up appointments are as follows (Grade C1):
  - Every 1 to 4 months for the first 1 to 3 years after the first treatment
  - Every 6 months for the fourth and fifth years after the first treatment
  - Annually from the sixth year after the first treatment
- Pelvic examination should be performed to detect intra-pelvic recurrence (Grade A).
- Vaginal vault cytology can be used to detect vaginal stump recurrence (Grade C1).
- Measurement of cancer antigen (CA) 125 or CA 19-9 as serum tumor markers should be considered in post-treatment follow-up (Grade C1).
- Based on the risk of recurrence in each case, diagnostic imaging methods such as chest X-ray and CT are considered to be appropriate. 3. When recurrence is suspected clinically, diagnostic imaging methods such as CT, MRI and PET-CT are recommended for detection of recurrent lesions.
- Hormone replacement therapy after treatment can be considered after the benefits and risks are explained to the patient (Grade C1).

d) Treatment of advanced/recurrent EC

- Surgery is recommended for cases considered to be stage III (Grade B).
- Surgery is suggested whenever hysterectomy and cytoreduction are possible for cases considered to be stage IV (Grade C1).
- Neoadjuvant chemotherapy is recommended for a locally invasive tumor that is difficult to resect or for a distant metastasis that cannot be resected completely.
- Radiotherapy is recommended (Grade B).
- Surgical resection should also be considered (Grade C1).
- Surgical resection is suggested for an isolated recurrent lesion that can be resected completely (Grade C1).
- Resection should also be considered for cases with a few small lung metastases (Grade C1).
- **Chemotherapy (doxorubicin/cisplatin)** is recommended for **advanced cancer** (Grade B).

- **Paclitaxel/carboplatin** or **paclitaxel/doxorubicin/cisplatin** therapy are also considered for advanced cancer because of their efficacy and safety (Grade C1).
- Doxorubicin/cisplatin therapy, paclitaxel/carboplatin therapy or monotherapy are considered for recurrent cancer based on the condition of the patient and previous treatment (Grade C1).
- Radiation therapy is considered for advanced cancer that cannot be resected or after incomplete surgery for local control or as a palliative procedure (Grade C1).
- Radiation therapy is considered as a palliative option for recurrent cancer without a vaginal stump for local control (Grade C1).
- Progesterone therapy is considered for endometrioid carcinoma (G1) or advanced/ recurrent cancer that is positive for progesterone receptors (Grade C1).

e) Fertility-sparing therapy

- Based on endometrial cancer, total hysterectomy with bilateral salpingo-oophorectomy is recommended (Grade B).
- Pelvic, para-aortic lymphadenectomy (biopsy) and omentectomy are also suggested (Grade C1).
- When adjuvant chemotherapy is selected, regimens including ifosfamide, platinum-based drugs, and paclitaxel are suggested (Grade C1).
- Radiation therapy (whole-pelvis external-beam irradiation) is also suggested (Grade C1).
- If total hysterectomy and cytoreductive surgery are possible, surgical treatment is suggested for advanced uterine carcinosarcoma (Grade C1).
- Regimens including ifosfamide, platinum-based drugs, and paclitaxel are suggested as chemotherapy for advanced or recurrent disease (Grade C1).
- If an isolated recurrent lesion can be resected completely, surgical resection is suggested (Grade C1).
- Complete extraction including total hysterectomy with bilateral salpingo-oophorectomy is recommended (Grade B).
- Chemotherapy is suggested as adjuvant therapy (Grade C1).
- Total hysterectomy with bilateral salpingo-oophorectomy is recommended (Grade B).

- Pelvic and para-aortic lymphadenectomy (biopsy) or cytoreductive surgery is also suggested (Grade C1).
- For stage I low-grade ESS, adjuvant therapy is not recommended (Grade D).
- When adjuvant therapy is considered to be necessary for high-grade ESS or undifferentiated uterine sarcoma, chemotherapy is suggested (Grade C1).
- Surgical resection is suggested for a completely resectable recurrent lesion (Grade C1).
- Chemotherapy should also be considered (Grade C1).
- Hormonal therapy is suggested for patients with low-grade ESS (Grade C1).
- Radiation therapy should also be considered for the purpose of palliative care (Grade C1).

1.4.2 Society for Immunotherapy of Cancer (SITC)

The Society for Immunotherapy of Cancer (SITC) released in 2023 clinical practice guidelines on immunotherapy for the treatment of gynecological cancer. The key treatment recommendations relevant for endometrial cancer are outlined in the following sections:

a) Immunotherapy biomarkers for gynecological cancers

- For all patients with advanced or recurrent gynecologic cancer, MMR IHC should preferentially be performed as a first-line immunotherapy biomarker for dMMR (LE:1).
- MSI and NGS testing can be considered as second-line immunotherapy biomarker tests (LE:3).
- With the exception of cervical cancer (LE:2) (and possibly other HPV-related gynecologic cancers), PD-L1 IHC expression should not be used for clinical decision-making for patients with advanced or recurrent gynecologic cancers.
- For all patients with advanced or recurrent gynecologic cancers, NGS should be considered to assess for TMB-H eligibility for pembrolizumab treatment under the tissue-agnostic indication (LE:3).
- For all patients with gynecologic cancer, biomarker evaluation of recurrent lesions may be considered at the time of recurrence.
- **Biomarkers testing recommendations for patients with EC are: mismatch repair deficient (dMMR) immunohistochemistry (IHC) (preferred); May be considered: Next generation sequencing (NGS) for high tumor mutational burden (TMB-H) and high microsatellite instability (MSI-H).**

b) Immunotherapy for the treatment of endometrial cancer

- Tumor PD-L1 expression should not be used to guide immunotherapy treatment decisions in endometrial cancer (LE:2).
- For all patients with advanced or recurrent endometrial cancer, MMR IHC on tumor tissue should preferentially be performed as a first-line immunotherapy biomarker for dMMR (LE:1). MSI and NGS testing can be considered as second-line immunotherapy biomarker tests (LE:3).
- For **first-line treatment** of recurrent or metastatic endometrial cancer, **carboplatin plus paclitaxel with or without trastuzumab** (if HER2+ serous endometrial cancer) was the standard of care at the time of guideline publication (LE:2).
    - Anti-PD-1 ICIs in combination with carboplatin plus paclitaxel demonstrated statistically significant and clinically meaningful improvements in PFS over chemotherapy alone for the treatment of previously untreated stage III or IV or first recurrent (after prior neoadjuvant or adjuvant chemotherapy) endometrial cancer. The observed benefit was regardless of MMR status (LE:2), however, this combination was not FDA-approved at the time of guideline publication.
- For **second-line treatment of patients with pMMR/ MSS advanced or recurrent** endometrial cancer, **pembrolizumab plus lenvatinib** is recommended, as indicated.
    - For second-line treatment of patients with TMB-H/pMMR/MSS endometrial cancer (LE:2), pembrolizumab plus lenvatinib is the standard of care option (LE:2) however, anti-PD-1 monotherapy may also be an option (LE:3).
- For **patients with dMMR/MSI-H advanced or recurrent endometrial cancer** who have **disease progression following prior systemic therapy** in any setting and who are not candidates for curative surgery or radiation, **pembrolizumab monotherapy** is recommended (LE:3).
- For patients with **dMMR/MSI-H advanced or recurrent endometrial cancer** who have disease **progression following prior platinum-containing regimen** in any setting and who are not candidates for curative surgery or radiation, **dostarlimab monotherapy** is recommended (LE:3).
- For all patients with endometrial cancer, clinical trial enrollment should be encouraged, as feasible.
- Non-FDA-approved immunotherapy combination strategies should only be considered in the context of a clinical trial.

The recommended immunotherapy treatments for patients with endometrial cancer are illustrated in figure 12.

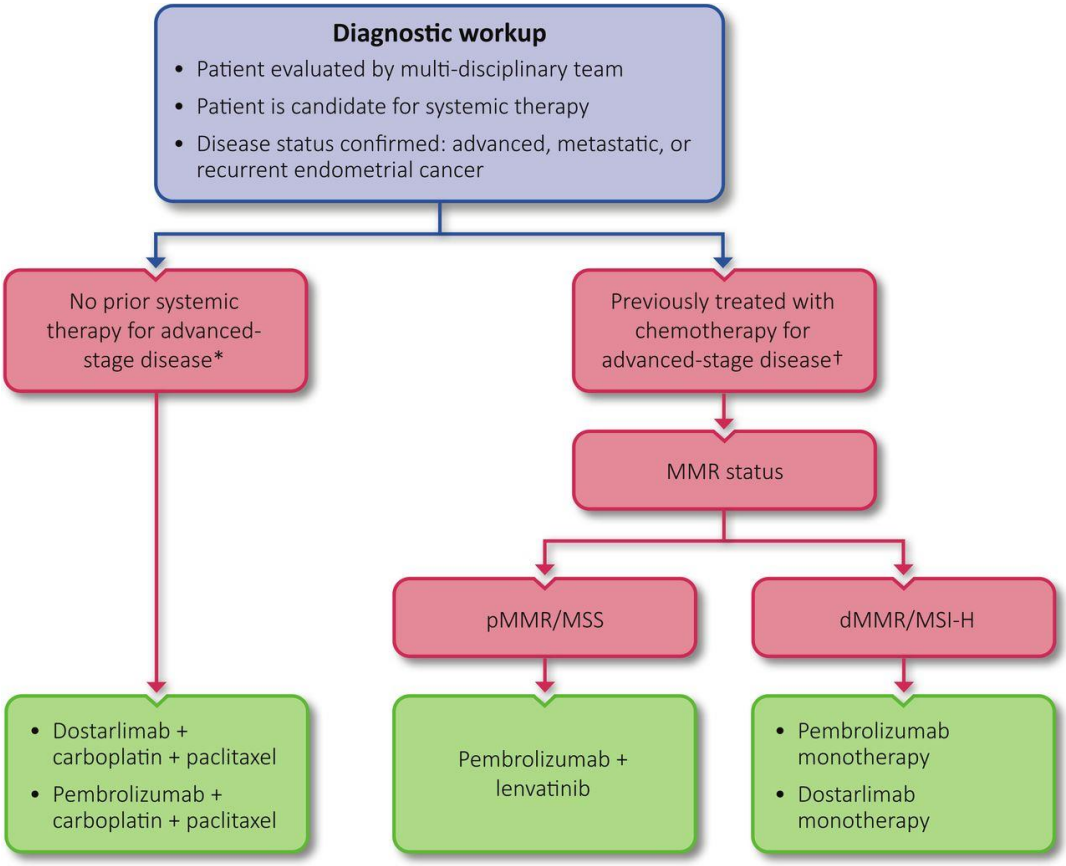


Figure 12. Advanced endometrial cancer diagnostic workup and treatment algorithm (SITC recommendations). Retrieved from Disis ML, Adams SF, Bajpai J, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer [published correction appears in J *Immunother Cancer*. 2023 Jun;11(6):1]. J Immunother Cancer. 2023;11(6):e006624. doi:10.1136/jitc-2022-006624

1.5 Systematic Reviews/Meta-analysis

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on endometrial management didn't yield any result more recent than the detailed previous guidelines. This is probably due to the fact that the treatment guidelines for endometrial cancer are constantly being updated with the many clinical trials and treatment alternatives emerging in the market.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Carboplatin

Table 17. Carboplatin Drug Information

Scientific Name Carboplatin[39]	
Trade Name(s) on Saudi Market	Carboplatin (Ebewe, Hospira), Cartinum
SFDA Classification	Prescription
SFDA approved Indication	Yes, Carboplatin Ebewe, 2001; Cartinum, 2019; Carboplatin Hospira, 2020
FDA approved / off label	Yes, 1989
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Carboplatin Ebewe: 2-355-01 (150mg); 3-355-01 (450mg) Carboplatin Hospira: 15-5287-20 (150mg); 16-5287-20 (450mg) Cartinum: 21-5223-19 (150mg); 22-5223-19 (450mg)
ATC Code	L01XA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	- Target AUC 6 on day 1 every 3 weeks (in combination with paclitaxel) for up to 7 cycles - Target AUC 5 on day 1 every 3 weeks (in combination with paclitaxel and dostarlimab) for 6 cycles

	- Target AUC 5 every 3 weeks (in combination with paclitaxel) for 6 to 9 cycles or until disease progression or unacceptable toxicity - Target AUC 2 on days 1, 8, and 15 every 28 days (in combination with paclitaxel) until disease progression or unacceptable toxicity - Target AUC 5 on day 1 every 3 weeks (in combination with paclitaxel and bevacizumab) for 6 to 8 cycles - Target AUC 5 every 3 weeks (in combination with paclitaxel and trastuzumab) for ~6 cycles, (for HER2+ uterine serous cancer)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for kidney dysfunction.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used as a single agent or in combination with paclitaxel (post chemoradiation) ± pembrolizumab or trastuzumab; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
ST (Step Therapy)	First and second-line treatment of newly diagnosed advanced or recurrent/metastatic endometrial cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol

Maximum Daily Dose Adults*	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Decreased serum Ca, K, Mg, gastrointestinal pain, nausea and vomiting, anemia, leukopenia, thrombocytopenia, increased liver enzymes, asthenia, pain, decreased creatinine clearance - Most serious: Ototoxicity, anemia, leukopenia, thrombocytopenia
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Carboplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	History of severe allergic reaction to carboplatin, cisplatin, other platinum-

	containing formulations, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding
Monitoring Requirements	CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, CrCl, LFTs; audiology evaluations (children <6 months of age); signs/symptoms of hypersensitivity reactions.
Precautions	- Bone marrow suppression - GI toxicity - Hepatic function abnormality - Hypersensitivity - Neurotoxicity - Ototoxicity - Renal toxicity - Vision loss
Black Box Warning	- Experienced physician - Bone marrow suppression - Vomiting - Hypersensitivity reactions
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for carboplatin in endometrial cancer. This is probably because carboplatin is a long-established standard of care in high-risk, advanced or recurrent EC. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Carboplatin

Carboplatin is recommended for the treatment of advanced newly diagnosed endometrial cancer as first-line adjuvant or primary therapy; preferred for advanced-stage disease or high-risk histologies in combination with paclitaxel ± pembrolizumab or trastuzumab. It is also the standard of care for the first and

second-line treatment of recurrent/metastatic endometrial cancer (preferred); used in combination with paclitaxel ± pembrolizumab or trastuzumab; or as a single agent. There is no data issued by HTA bodies regarding its use.

2.1.2 Cisplatin

Table 18. Cisplatin Drug Information

Scientific Name Cisplatin[40]	
Trade Name(s) on Saudi Market	Cisplatin (Ebewe, Hospira), Cipalin, Tinplat
SFDA Classification	Prescription
SFDA approved Indication	Yes, Cisplatin Ebewe, 2001; Cisplatin Jazeera Pharmaceutical Industries (JPI), 2018; Cisplatin Hospira, 2019; Tinplat, 2019
FDA approved / off label	Yes, 1978
EMEA approved / off label	Yes, 1996
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Cisplatin Ebewe: 409222579 (10mg); 0409222580 (50mg) Cipalin: 288-334-18 (10mg); 289-334-18 (25mg); 290-334-18 (50mg) Cisplatin Hospira: 4-5287-19 (50mg) Tinplat: 29-5223-19 (10mg); 30-5223-19 (50mg)
ATC Code	L01XA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Endometrial carcinoma, recurrent, metastatic, or high-risk**: 50 mg/m^2 on

	day 1 every 3 weeks (in combination with doxorubicin ± paclitaxel) for 7 cycles or until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥60 mL/mine: IV: No adjustment - CrCl 50 to <60 mL/min: IV: 75% of the dose - CrCl 40 to <50 mL/minute: IV: 50% of the dose - CrCl <40 mL/minute: Not recommended - Hemodialysis/PD: Poorly dialyzable due to rapid and high degree of protein binding: 50% of the dose after dialysis - CRRT/PIRRT: Use is not recommended - Nephrotoxicity during treatment: Patients that develop AKI (SCr >2 times baseline) may require discontinuation of therapy
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents; To be used with antiemetics, hyperhydration
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Total dose per cycle not to exceed 120 mg/m^2
ST (Step Therapy)	First-line treatment (primary or adjuvant therapy) of EC in combination with RT Second-line treatment of recurrent/metastatic EC in combination

	with doxorubicin ± paclitaxel or ifosfamide (for carcinosarcoma)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Total dose per cycle not to exceed 120 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Neurotoxicity, nausea and vomiting, nephrotoxicity, anemia, leukopenia, thrombocytopenia, increased liver enzymes, ototoxicity - Most serious: Neurotoxicity, anemia, leukopenia, thrombocytopenia, hearing loss
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Renal Impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks

Lactation	Cisplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	Severe hypersensitivity to cisplatin or any component of the formulation
Monitoring Requirements	Blood counts, serum creatinine, BUN, CrCl, and serum electrolytes Neurological examination, consider audiometric and vestibular testing Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hypersensitivity - Nephrotoxicity - Neurotoxicity - Ocular toxicity - Ototoxicity - Secondary malignancies - Tumor lysis syndrome
Black Box Warning	- Myelosuppression - Nausea and vomiting - Nephrotoxicity - Peripheral neuropathy
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for cisplatin in endometrial cancer. This is probably because cisplatin is more used as a later-line treatment for recurrent/metastatic disease. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Cisplatin

Cisplatin is a first-line agent used as a primary or adjuvant treatment for high-risk endometrial cancer in combination with RT. It is also a second-line agent used in

recurrent, metastatic, or high-risk endometrial cancer in combination with doxorubicin ± paclitaxel or ifosfamide (for carcinosarcoma). There is no data issued by HTA bodies regarding its use.

2.1.3 Ifosfamide

Table 19. Ifosfamide Drug Information

Scientific Name **Ifosfamide**[41]	
Trade Name(s) on Saudi Market	Holoxan
SFDA Classification	Prescription
SFDA approved Indication	Yes, Holoxan 1987
FDA approved / off label	Yes, 1988
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent (Nitrogen mustard)
SFDA Registration Number (New)	38-16-87 (Holoxan 500 mg) 39-16-87 (Holoxan 1g) 40-16-87 (Holoxan 2g)
ATC Code	L01AA06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Uterine carcinosarcoma**: *Adjuvant therapy for stage 1 to 4 disease:* 1,500 mg/m^2/day for 4 days (in combination with cisplatin and mesna) every 3 weeks for 3 cycles (Ref). *Persistent or refractory advanced disease:* 1,600 mg/m^2/day for 3 days (in combination with mesna, paclitaxel, and filgrastim) every 3 weeks for up to 8 cycles; reduce ifosfamide dose to 1,200

	mg/m^2/day for 3 days every 3 weeks in patients who received prior radiation
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥50 mL/min: No adjustment necessary - CrCl <50 mL/min: Use is not recommended - Hemodialysis: Use is not recommended Hepatic Impairment (Adult): - Bilirubin >3 mg/dL: Administer 25% of dose
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used as a single agent or in combination with paclitaxel or cisplatin; To be used with antiemetics; To be used with MESNA
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 3000 mg/m^2
ST (Step Therapy)	Second-line treatment of recurrent/metastatic endometrial cancer (carcinosarcoma histologies)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	3000 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Alopecia, nausea and vomiting, gross hematuria, hematuria, bone marrow depression, central nervous system toxicity (including neurotoxicity: aphasia, ataxia, cerebellar syndrome, coma, encephalopathy, extrapyramidal reaction, hallucination, motor

	dysfunction, muscle spasm, myoclonus, peripheral neuropathy, psychotic reaction, seizure, tremor) - Most serious: Encephalopathy, febrile neutropenia, infection
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, pediatrics
Pregnancy	Pregnancy Category D: Not used in pregnancy Fetal growth retardation and neonatal anemia have been reported with exposure to ifosfamide
Lactation	Ifosfamide is present in breast milk. Breastfeeding is not recommended during ifosfamide treatment
Contraindications	Known hypersensitivity to ifosfamide or any component of the formulation; urinary outflow obstruction
Monitoring Requirements	CBC with differential, urine output, urinalysis (for erythrocytes prior to each

	dose), liver function, and renal function tests Monitor for signs/symptoms of neurotoxicity, pulmonary toxicity, urotoxicity/hemorrhagic cystitis, and secondary malignancies
Precautions	- Bone marrow suppression - Cardiotoxicity - CNS Toxicity - Hemorrhagic cystitis - Hepatic effects - Hypersensitivity - Infection - Pulmonary Toxicity - Renal toxicity - Secondary malignancies - Wound healing - Radiation therapy: Use with caution
Black Box Warning	- Bone marrow suppression - CNS toxicity - Hemorrhagic cystitis - Nephrotoxicity
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for ifosfamide in endometrial cancer. This is probably because ifosfamide is only used as a later-line treatment option in patients with recurrent disease with specific histologies. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Ifosfamide

In endometrial cancer, ifosfamide is a second-line treatment of recurrent/metastatic endometrial cancer, specifically carcinosarcoma histologies, used as a single agent or in combination with paclitaxel or cisplatin. There is no data issued by HTA bodies regarding its use.

2.2 Antimicrotubular Agents

2.2.1 Docetaxel

Table 20. Docetaxel Drug Information

Scientific Name Docetaxel[42]	
Trade Name(s) on Saudi Market	Docetaxel Ebewe; Docetaxel SPC; Docadex; Taxotere; Docetaxel Accord; Tadoxel; Docetaxel Venus
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Taxane derivative
SFDA Registration Number (New)	Docetaxel Ebewe 10 mg/mL: 56-355-17 (80 mg); 55-355-17 (20 mg) Docetaxel SPC 20 mg/mL: 5-5171-18 (80mg) Docadex 20 mg/mL: 8-5251-20 (80mg); 2-5251-19 (20mg) Taxotere 20 mg/mL: 1-5079-20 (20mg); 2-5079-20 (80mg); 3-5079-20 (160mg) Docetaxel Accord 20 mg/mL: 2-5579-21 (20mg); 3-5579-21 (80mg); 4-5579-21 (160mg) Tadoxel 20 mg/mL: 0206210761 (20mg); 0206210762 (80mg) Docetaxel Venus 20 mg/mL : 2405233720 (20mg); 2405233721 (80mg)
ATC Code	L01CD
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	

Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*(off-label use)* 60 mg/m^2 every 3 weeks in combination with carboplatin; 70 mg mg/m^2 every 3 weeks as a single agent
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): - AST/ALT >2.5 to ≤5 times ULN and alkaline phosphatase ≤2.5 times ULN: Administer 80% of dose. - AST/ALT >1.5 to ≤5 times ULN and alkaline phosphatase >2.5 to ≤5 times ULN: Administer 80% of dose. - AST/ALT >5 times ULN and /or alkaline phosphatase >5 times ULN: Discontinue docetaxel.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	Can be used as a single agent or in combination with carboplatin; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Daily dose not to exceed 75 mg/m^2
ST (Step Therapy)	First (in patients not eligible for paclitaxel) and second-line treatment of recurrent/metastatic Endometrial Cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	75 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, dermatological reactions, nails diseases, fluid retention, diarrhea, nausea and vomiting, anemia,

	leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, central nervous system toxicity, asthenia, myalgia, fever, pulmonary disease - Most serious: Febrile neutropenia
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Dronedarone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if docetaxel is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last docetaxel dose.
Contraindications	History of severe hypersensitivity to docetaxel or any component of the formulation; severe hypersensitivity to

	other medications containing polysorbate 80; neutrophil count <1,500/mm^3.
Monitoring Requirements	- CBC with differential, LFTs (bilirubin, ALT, AST, alkaline phosphatase), renal function. - Pregnancy status - Monitor for hypersensitivity reactions - Monitor for signs/symptoms of neurosensory symptoms, GI toxicity, cutaneous reactions or severe skin toxicity, visual impairment, fluid retention, epiphora, canalicular stenosis, tumor lysis syndrome, and second primary malignancies. - Prompt comprehensive ophthalmic exam if vision impairment occurs.
Precautions	- Bone marrow suppression - Cutaneous reactions - Extravasation - Fluid retention - GI toxicity - Hypersensitivity - Neurosensory symptoms - Ocular adverse effects - Secondary malignancies - Tumor lysis syndrome - Weakness
Black Box Warning	- Increased mortality - Hepatic impairment - Neutropenia - Hypersensitivity - Fluid retention
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for docetaxel in endometrial cancer. This is probably because docetaxel is a later-line option mostly used in

patients not eligible for paclitaxel therapy. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Docetaxel

Docetaxel can be used for the first-line treatment of recurrent/metastatic endometrial cancer (in combination with carboplatin) in patients for whom paclitaxel is contra-indicated. I can also be used as a single agent for the second-line treatment of recurrent/metastatic endometrial cancer. There is no data issued by HTA bodies regarding its use.

2.2.2 Paclitaxel

Table 21. Paclitaxel Drug Information

Scientific Name Paclitaxel[43]	
Trade Name(s) on Saudi Market	Anzatax, Ebetaxel, Rotub
SFDA Classification	Prescription
SFDA approved Indication	Yes, Anzatax 1998; Ebetaxel 2006; Rotub 2018
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Taxane derivative
SFDA Registration Number (New)	Anzatax: 4-5669-22 (30 mg); 5-5669-22 (150 mg) Ebetaxel: 33-355-06 (300mg); 34-355-06 (150mg); 35-355-06 (100mg); 33-355-06 (30mg) Rotub: 1-5190-18 (30mg); 2-5190-18 (100mg); 3-5190-18 (150mg); 4-5190-18 (300mg)
ATC Code	L01CD01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents

Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	- 75 mg/m^2 (135 mg/m^2 in patients with a history of pelvic/spine irradiation) on day 1 every 3 weeks (in combination with carboplatin) for up to 7 cycles - 175 mg/m^2 on day 1 every 3 weeks (in combination with carboplatin and dostarlimab) for 6 cycles - 175 mg/m^2 on day 1 every 3 weeks (in combination with carboplatin) for 6 to 9 cycles or until disease progression or unacceptable toxicity - 80 mg/m^2 on days 1, 8, and 15 every 28 days (in combination with carboplatin) until disease progression or unacceptable toxicity - 175 mg/m^2 on day 1 every 3 weeks (in combination with carboplatin and trastuzumab) for ~6 cycles *(for HER2-positive uterine serous cancer)* - 80 mg/m^2 on days 1, 8, 15, and 22 every 28 days for at least 2 cycles and until disease progression or unacceptable toxicity - 175 mg/m^2 on day 1 every 3 weeks for 10 cycles
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): 3-hour infusion: - Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2 - Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m^2

	- Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m^2 - Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use
Prescribing edits*	AGE, MD, ST, PE, CU, QL
AGE (Age Edit)	Not used in pediatrics
CU (Concurrent Use)	To be used as a single agent or as adjuvant therapy in combination with chemotherapy (in combination with carboplatin post chemoradiation; in combination with carboplatin ± dostarlimab or trastuzumab – first-line setting) or (cisplatin/doxorubicin or ifosfamide; second-line setting) To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Daily dose not to exceed 250 mg/m^2
ST (Step Therapy)	First and second-line treatment of newly diagnosed advanced or recurrent/metastatic endometrial cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	250 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: ECG abnormality, edema, hypotension, alopecia, diarrhea, nausea and vomiting, stomatitis, anemia, hemorrhage, leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, injection-site reaction, asthenia

	peripheral neuropathy, arthralgia), myalgia, fever - Most serious: Bradycardia, cardiac arrhythmia, encephalopathy, tonic-clonic seizure, hemorrhage, leukopenia, neutropenia
Drug Interactions*	- Risk X: Abrocitinib, Atazanavir, Baricitinib, BCG Products, Brivudine, Bromperidol, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Amifostine, Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Obinutuzumab Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, Hepatic impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Paclitaxel is present in breast milk. Breastfeeding is not recommended during paclitaxel treatment
Contraindications	Hypersensitivity to paclitaxel, polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), or any component of the formulation

	Treatment of solid tumors in patients with baseline neutrophil counts <1,500/mm^3; treatment of Kaposi sarcoma in patients with baseline neutrophil counts <1,000/mm^3.
Monitoring Requirements	CBC with differential and platelet count (frequently), liver and kidney function Monitor for hypersensitivity reactions, vital signs (frequently during the first hour of infusion), and continuous cardiac monitoring (patients with conduction abnormalities). Monitor for signs/symptoms of peripheral neuropathy. Monitor infusion site during infusion.
Precautions	- Cardiovascular effects - Extravasation - Hepatic impairment
Black Box Warning	- Experienced physician - Hypersensitivity - Bone marrow suppression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for paclitaxel in endometrial cancer. This is probably because paclitaxel is a long-established standard of care in the advanced or recurrent setting of EC. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Paclitaxel

Paclitaxel is a first-line treatment option for newly-diagnosed advanced endometrial cancer, as first-line adjuvant or primary therapy in combination with carboplatin ± dostarlimab or trastuzumab. It is also a second-line treatment option in the recurrent/metastatic setting used as a single agent or in combination with cisplatin/doxorubicin or with ifosfamide (for carcinosarcoma). There is no data issued by HTA bodies regarding its use.

2.3 Hormonal Therapy

2.3.1 Levonorgestrel Intrauterine Device (IUD)

Table 22. Levonorgestrel Intrauterine Device Drug Information

Scientific Name Levonorgestrel IUD[44]	
Trade Name(s) on Saudi Market	Mirena intrauterine delivery system
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 1998
FDA approved/off label	Yes, 2000
EMEA approved/off label	Yes, not mentioned
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, not mentioned
Indication (ICD-10)	C54.1
Drug Class	Hormone
Drug Sub-Class	Progestin
SFDA Registration Number (New)	1310222732 (52 mg)
ATC Code	G03AC03
Pharmacological Class (ASHP)	68:12 – Contraceptives
Drug Information	
Dosage Form	Intrauterine delivery system
Route of Administration	Intrauterine
Dose (Adult) [DDD]*	**Endometrial hyperplasia, treatment (off-label use): 52 mg device:** Insert into the intrauterine cavity. IUDs that contain levonorgestrel 52 mg in a reservoir initially release ~20 mcg/day then progressively decrease to ~10 mcg/day after 5 years. Replace after 5 years; however, the optimal duration of treatment is not known
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A

MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Uterine limited endometrial carcinoma not suitable for primary surgery (or as part of a fertility-sparing approach)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Acne vulgaris, amenorrhea, abdominal pain, bacterial vaginosis, gynecological bleeding, ovarian cyst, pelvic pain, vaginal discharge, vaginal mycosis, vulvovaginitis, migraine, headache - Most serious: Ectopic pregnancy, uterine perforation, arterial thromboembolism, deep vein thrombosis, increased blood pressure, pulmonary embolism, malignant neoplasm of breast
Drug Interactions*	Risk X: Ulipristal Risk D: MetyraPONE Risk C: Antidiabetic Agents (diminished efficacy of antidiabetic agents; CYP3A4 Inducers (Strong): May diminish the therapeutic effect of Levonorgestrel (IUD); Chlorprothixene (enhanced toxicity)
Special Population	Smoking
Pregnancy	Pregnancy Category X
Lactation	Levonorgestrel is present in breast milk. In general, no adverse effects on the growth or development if the infant have been observed. Isolated cases of decreased milk production have been reported.

Contraindications	- Hypersensitivity to levonorgestrel or any component of the formulation - Pregnancy or suspected pregnancy - Postcoital contraception - Congenital or acquired uterine anomaly - Acute pelvic inflammatory disease or history of pelvic inflammatory disease - Postpartum endometritis or infected abortion within past 3 months - Untreated acute cervicitis or vaginitis (including bacterial vaginosis, known chlamydial or gonococcal cervical infection) or other lower genital tract infections until infection is controlled; - Conditions which increase susceptibility to pelvic infections - Unremoved IUD - Uterine bleeding of unknown etiology - Acute hepatic disease or hepatic tumors - Current or history of known or suspected breast cancer or other hormone-sensitive cancer
Monitoring Requirements	- Endometrial sampling every 3 to 6 months - Prior to insertion: Pregnancy status; bimanual examination and cervical inspection; weight; sexually transmitted infections screen. Evaluate any unexplained vaginal bleeding; exclude endometrial polyps or cancers. Complete medical and social history, which may determine conditions influencing an IUD use for contraception. - Following insertion: Transvaginal ultrasound to check placement.

	Assess changes in health status. Re-examine following insertion (4 to 6 weeks) and then yearly or more frequently if necessary. Pregnancy status. Monitor for significant changes in menstrual bleeding during prolonged use, Pap smear, BP, serum glucose in patients with diabetes. Monitor for signs of infection and of thromboembolism.
Precautions	- Bradycardia/syncope - Pelvic inflammatory disease - Depression - Gestational trophoblastic disease - Sepsis - Sexually transmitted infection - Tuberculosis - Smoking
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for levonorgestrel IUD in endometrial cancer.

Conclusion statement – Levonorgestrel intrauterine device

Levonorgestrel IUD is a hormonal therapy used for uterine limited endometrial carcinoma that is not suitable for primary surgery (or as part of a fertility-sparing approach). There are no HTA recommendations regarding its use in this setting.

2.3.2 Medroxyprogesterone Acetate

Table 23. Medroxyprogesterone Acetate Drug Information

Scientific Name Medroxyprogesterone acetate[45]	
Trade Name(s) on Saudi Market	Depo-Provera; Provera
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 1989
FDA approved/off label	Yes, 1959
EMEA approved/off label	Yes, not mentioned
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, not mentioned
Indication (ICD-10)	C54.1
Drug Class	Hormone
Drug Sub-Class	Progestin
SFDA Registration Number (New)	Depo-Provera: 28-44-89 (150 mg) Provera: 55-92-18 (5 mg)
ATC Code	L02AB02 (Depo-Provera) G03DA02 (Provera)
Pharmacological Class (ASHP)	68:12 – Contraceptives
Drug Information	
Dosage Form	Suspension for injection (Depo-Provera) Tablet (Provera)
Route of Administration	Intramuscular (Depo-Provera); Oral (Provera)
Dose (Adult) [DDD]*	**Endometrial carcinoma, recurrent or metastatic (adjunctive/palliative treatment):** IM: Initial: 400 to 1,000 mg/week. Oral: *Canadian manufacturer's labeling*: Usual dose: 200 to 400 mg daily. If improvement or disease stabilization occurs, 200 mg daily may be sufficient for maintenance. Discontinue use if no improvement within 2 to 3 months.
Adjustment	Hepatic Impairment (Adult):

	Medroxyprogesterone is extensively metabolized in the liver and elimination is significantly reduced in patients with advanced hepatic disease. Most products are **contraindicated** in patients with hepatic impairment. If needed for the palliative treatment metastatic EC, monitor closely; withhold or discontinue treatment if liver dysfunction develops and do not resume until hepatic function has returned to normal.
Prescribing edits*	AGE, MD, CU, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used as a single agent or in combination with tamoxifen
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose: IM 1000 mg/week PO: 400 mg/day
ST (Step Therapy)	Second-line treatment as a hormonal therapy for uterine limited inoperable disease not suitable for primary surgery (or as part of a fertility-sparing approach) and for recurrent or metastatic endometrial carcinoma.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	IM: 1000 mg/week; PO: 400 mg daily
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Amenorrhea, hot flashes, weight gain, abdominal pain, gynecological bleeding, headache, nervousness - Most serious: Decreased bone mineral density, acute myocardial infarction, deep vein thrombosis,

	pulmonary embolism, thrombophlebitis, varicose veins (post-marketing)
Drug Interactions*	Risk X: Encorafenib, Erdafitinib, Fexinidazole, Mobocertinib, Omaveloxolone, Pexidartinib, Taurursodiol, Tranexamic acid, Ulipristal Risk D: Aprepitant, Asparaginase, Asunaprevir, Atazanavir, Brigatinib, Carfilzomib, Cladribine, **CYP3A4 Inducers**, Efavirenz, Felbamate, Fosaprepitant, Griseofulvin, Ivosidenib, Ixazomib, MiFEPRIStone, Mycophenolate, Nirmatrelvir and Ritonavir, Octreotide, OXcarbazepine, Protease inhibitors, Tirzepatide, Topiramate
Special Population	N/A
Pregnancy	Pregnancy Category X
Lactation	Medroxyprogesterone acetate (MPA) is present in breast milk. Composition, quality, and quantity of breast milk are not affected; adverse developmental and behavioral effects have not been noted following exposure of infant to MPA while breastfeeding. The manufacturer does not recommend the use of MPA tablets in breastfeeding mothers; however, guidelines note that the injectable DMPA contraceptives can be initiated immediately postpartum in patients who are breastfeeding. The manufacturer recommends medroxyprogesterone 400 mg/mL be used with caution in patients who are breastfeeding.
Contraindications	Hypersensitivity to medroxyprogesterone or any component of the formulation; active thrombophlebitis; thromboembolic disorders (current or history of); cerebral

	vascular disease; undiagnosed vaginal bleeding; breast cancer (known, suspected, or history of); significant hepatic disease.
Monitoring Requirements	- Monitor blood glucose - Monitor for depression - Evaluate abnormal bleeding that persists or is severe - Consider evaluating bone mineral density in patients receiving long-term high medroxyprogesterone doses; breast cancer (in patients with a strong family history of breast cancer)
Precautions	- Adrenal suppression - Anaphylaxis/hypersensitivity reactions - Breast cancer - Ectopic pregnancy - Endometrial hyperplasia - Hypertriglyceridemia - Ovarian cancer - Retinal thrombosis - Asthma - Cardiovascular disease - Dementia - Depression - Diabetes - Diseases exacerbated by fluid retention - Epilepsy - Hepatic dysfunction - Hepatic hemangioma - Hypoparathyroidism - Migraine - Porphyria - Systemic lupus erythematosus - When used for endometrial carcinoma, the effects of long-term use on adrenal, hepatic, ovarian,

	pituitary, and uterine function is not known. Use for endometrial carcinoma may mask the onset of menopause
Black Box Warning	- Long-term use - Loss of bone mineral density
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for medroxyprogesterone acetate in endometrial cancer.

Conclusion statement – Medroxyprogesterone acetate

Medroxyprogesterone acetate is a second-line treatment used as a hormonal therapy for uterine limited disease not suitable for primary surgery (or as part of a fertility-sparing approach) and as adjunctive/palliative treatment for recurrent or metastatic endometrial carcinoma. There are no HTA recommendations regarding its use in this setting.

2.3.3 Megestrol Acetate

Table 24. Megestrol Acetate Drug Information

Scientific Name Megestrol Acetate[46]	
Trade Name(s) on Saudi Market	Megace
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 1983
FDA approved/off label	Yes, not mentioned
EMEA approved/off label	Yes, not mentioned
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, not mentioned
Indication (ICD-10)	C54.1
Drug Class	Hormone
Drug Sub-Class	Progestin
SFDA Registration Number (New)	2-134-83 (20 mg); 3-134-83 (40 mg)
ATC Code	G03AC05

Pharmacological Class (ASHP)	68:32 – Progestins
Drug Information	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Endometrial cancer, advanced:** Oral: 40 to 320 mg daily in divided doses for at least 2 months.
Adjustment	N/A Use with caution in renal impairment
Prescribing edits*	AGE, MD, CU, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used as a single agent or in combination with tamoxifen
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	800 mg per day
ST (Step Therapy)	Second-line treatment as a hormonal therapy for recurrent or metastatic endometrial carcinoma or for uterine limited disease not suitable for primary surgery (or as part of a fertility-sparing approach).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	800 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Skin rash, impotence, hypertension, flatulence - Most serious: Heart failure, venous thromboembolism (including pulmonary embolism, thrombophlebitis), Adrenocortical insufficiency
Drug Interactions*	Risk X: Dofetilide, Ulipristal
Special Population	N/A
Pregnancy	Pregnancy Category X

Lactation	Megestrol acetate is present in breast milk. The manufacturer recommends discontinuing breastfeeding while receiving megestrol for the treatment of cancer.
Contraindications	Hypersensitivity to megestrol or any component of the formulation; known or suspected pregnancy (suspension).
Monitoring Requirements	- Observe for signs of thromboembolic events; blood pressure, weight; serum glucose. - Evaluate pregnancy status prior to treatment in patients who may become pregnant.
Precautions	- Adrenal suppression - Bleeding irregularities - Cushing syndrome
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for megestrol acetate in endometrial cancer.

Conclusion statement – Megestrol acetate

Megestrol acetate is a second-line treatment used as a hormonal therapy for recurrent or metastatic endometrial carcinoma or for uterine limited disease not suitable for primary surgery (or as part of a fertility-sparing approach). There are no HTA recommendations regarding its use in this setting.

2.3.4 Tamoxifen

Table 25. Tamoxifen Drug Information

Scientific Name Tamoxifen[47]	
Trade Name(s) on Saudi Market	Nolvadex; Tamofen
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 1983
FDA approved/off label	Yes, 1977
EMEA approved/off label	Yes, not mentioned
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, not mentioned
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic Agent
Drug Sub-Class	Estrogen Receptor Antagonist; Selective Estrogen Receptor Modulator (SERM)
SFDA Registration Number (New)	Nolvadex: 1-5761-23 (10 mg; 30 tabs); 26-7-83 (10 mg; 250 tabs); 2-5761-23 (Nolvadex-D 20 mg) Tamofen: 3-205-91 (10 mg; 30 tabs); 4-205-91 (10 mg; 100 tabs)
ATC Code	L02BA01
Pharmacological Class (ASHP)	68:16.12 – Estrogen Agonists-Antagonists
Drug Information	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Endometrial carcinoma, recurrent, metastatic, or high-risk (endometrioid histologies only)** (off-label use): *Monotherapy:* Oral: 20 mg twice daily until disease progression or unacceptable toxicity. *Combination therapy:* Oral: 20 mg twice daily for 3 weeks (alternating with megestrol acetate every 3 weeks);

	continue alternating until disease progression or unacceptable toxicity)
Adjustment	N/A Chronic dialysis: No dosage adjustment necessary
Prescribing edits*	AGE, MD, CU, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used as a single agent or in combination with megestrol acetate (or medroxyprogesterone acetate)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose: 60 mg
ST (Step Therapy)	Endometrial carcinoma, recurrent, metastatic, or high-risk (endometrioid histologies only)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	60 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Flushing, hypertension, peripheral edema, vasodilation, skin changes, amenorrhea, fluid retention, hot flash, weight loss, nausea, vomiting, irregular menses, vaginal discharge, vaginal hemorrhage, lymphedema, depression, fatigue, mood changes, pain, arthralgia, arthritis, asthenia, pharyngitis - Most serious: Ischemic heart disease, venous thromboembolism, increased bilirubin, increase aspartate aminotransferase, cerebrovascular accident

Drug Interactions*	Risk X: Anastrozole, CYP3A4 Inducers (Strong), Letrozole, Ospemifene, Vitamin K Antagonists Risk D: CYP2D6 Inhibitors, Ribociclib
Special Population	CYP2D6 poor metabolizers
Pregnancy	Pregnancy Category D
Lactation	Tamoxifen is present in breast milk. Tamoxifen has been shown to inhibit early postpartum milk production; effects on established milk production is not known. Breastfeeding during tamoxifen therapy is **contraindicated** by some guidelines Breastfeeding is not recommended by the manufacturer during treatment and for 3 months following the last tamoxifen dose.
Contraindications	Known hypersensitivity (e.g., angioedema, serious skin reactions) to tamoxifen or any component of the formulation.
Monitoring Requirements	- CBC with platelets, serum calcium, liver function tests; triglycerides and cholesterol; INR and PT (in patients on vitamin K antagonists) - Pregnancy status - Monitor for and promptly evaluate abnormal vaginal bleeding, menstrual irregularities, changes in vaginal discharge, or pelvic pain/pressure; breast exam - Gynecologic exam, mammogram - Signs/symptoms of thromboembolism (eg, stroke, DVT [leg swelling, tenderness], or PE [shortness of breath]) - Ophthalmic exam - Bone mineral density (premenopausal patients). - Monitor adherence

Precautions	- Bone mineral density - Hyperlipidemia - Metastatic breast cancer - Selective serotonin reuptake inhibitors (concurrent use) - CYP2D6 poor metabolizers
Black Box Warning	- Long-term use - Loss of bone mineral density
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for tamoxifen in endometrial cancer.

Conclusion statement – Tamoxifen

Tamoxifen is a second-line treatment used for recurrent or metastatic endometrial carcinoma in the adjunctive, palliative, or high-risk setting (endometrioid histologies only). There are no HTA recommendations regarding its use in this setting.

2.4 Immune Checkpoint Inhibitors (ICIs)

2.4.1 Pembrolizumab

Table 26. Pembrolizumab Drug Information

Scientific Name Pembrolizumab[48]	
Trade Name(s) on Saudi Market	Keytruda
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes, 2014
EMEA approved / off label	Yes, 2015
MHRA approved / off label	Yes, date not available
PMDA approved / off label	Yes, 2016
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent, monoclonal antibody

Drug Sub-class	Immune Checkpoint Inhibitor (PD-1 Inhibitor)
SFDA Registration Number (New)	2501233168
ATC Code	L01XC
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	200 mg once every 3 weeks **or** 400 mg once every 6 weeks; continue until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose. - Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation*

	• Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. • Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently.
Prescribing edits*	MD, CU, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	Can be used as a single agent or in combination with chemotherapy (paclitaxel/carboplatin) To be used with lenvatinib in patient that are pMMR and/or are not MSI-H
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 400 mg
ST (Step Therapy)	First-line treatment of newly diagnosed or recurrent/metastatic endometrial cancer in combination with carboplatin/paclitaxel; preferred therapy except in patients with carcinosarcoma disease

	Second-line treatment of advanced endometrial carcinoma that is MSI-H or dMMR in patients with disease progression following prior systemic therapy Second-line treatment of advanced endometrial carcinoma that is NOT MSI-H or dMMR in patients with disease progression following prior systemic therapy in combination with lenvatinib
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	400 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash, vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis,

	pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis.
Drug Interactions*	- Risk X: Thalidomide (Enhanced toxicity of thalidomide). - Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib, Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis,

	rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of pembrolizumab in endometrial carcinoma treatment options.

Table 27. Pembrolizumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Pembrolizumab + Lenvatinib	HAS[25]	03/2022: **Favorable opinion for reimbursement** in the indication extension: **pembrolizumab, in combination with lenvatinib**, is indicated in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. - **Therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma. - **Moderate clinical added value** (CAV III)

		- Demonstration in a randomized, open-label phase 3 study of the superiority of pembrolizumab and lenvatinib combination compared to single-agent chemotherapy with doxorubicin or paclitaxel, particularly in terms of: ▪ Progression-free survival (PFS) (absolute increase of 3.4 months, HR=0.56 [CI95%: 0.47-0.66]): ▪ Overall survival (OS) (absolute increase of 6.9 months, HR=0.62 [CI95%: 0.51-0.75]) - Safety profile for the pembrolizumab and lenvatinib combination less favorable than that for single-agent chemotherapy, marked by additional toxicity with, in particular, more serious adverse events (53% versus 30%) - Absence of any formal conclusion that can be drawn based on the quality of life results
Pembrolizumab + Lenvatinib	NICE[27]	06/2023: Pembrolizumab plus lenvatinib is **recommended**, within its marketing authorization, for treating **advanced or recurrent endometrial cancer** in adults: · whose **cancer has progressed** on or after **platinum-based chemotherapy** and · who **cannot have curative surgery or radiotherapy**. - There is no standard second-line treatment for advanced or recurrent endometrial cancer. - Key evidence for pembrolizumab with lenvatinib comes from the KEYNOTE-775 trial: ▪ **Pembrolizumab plus lenvatinib improves OS and PFS compared with doxorubicin or paclitaxel monotherapy**. ▪ Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. - Pembrolizumab plus lenvatinib **meets NICE's criteria to be considered a life-extending treatment at the end of life**.

		- There is some uncertainty in the economic model about how long the effect of treatment lasts after people stop taking pembrolizumab at 2 years. - But the **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**. - The most plausible ICER is less than £50,000 per QALY gained
Pembrolizumab	CADTH[28,32]	04/2023: pERC recommends that pembrolizumab be **reimbursed** as monotherapy for the treatment of adult patients with **unresectable or metastatic MSI-H or dMMR endometrial cancer** whose tumors have **progressed following prior therapy** and who have **no satisfactory alternative treatment options**. - Single-arm, phase II, open-label, nonrandomized trial (KEYNOTE-158 [KN-158], N = 94). ▪ The median OS was 65.4 months (95% confidence interval [CI], 29.5 to not reported [NR]) and the OS rate of patients treated with pembrolizumab at 12 months was 70.0%. ▪ The median PFS was 13.1 months (95% CI, 4.3 months to 25.7 months) and the PFS rate at 12 months was 50.3%. - The cost-effectiveness of pembrolizumab relative to physician's choice of chemotherapy is unknown in patients with dMMR or MSI-H endometrial cancer owing to the lack of direct comparative clinical effectiveness data. - The committee considered an exploratory analysis conducted by CADTH that produced an ICER of $61,200 per QALY gained when compared with chemotherapy. - Based on this exploratory finding, a price reduction is needed for pembrolizumab to

		be cost-effective at a $50,000 per QALY willingness-to-pay threshold. 12/2022: pERC recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced endometrial carcinoma** that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are **not candidates for curative surgery or radiation**. - One multicenter, randomized, open-label phase III trial (KEYNOTE-775; N = 697 for patients with pMMR disease) demonstrated that treatment with pembrolizumab/lenvatinib resulted in added clinical benefit when compared with treatment of physicians' choice in that setting. - Pembrolizumab/lenvatinib was associated with statistically significant and clinically meaningful improvements in OS (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.56 to 0.84; P< 0.0001) and PFS (HR = 0.60; 95% CI, 0.50 to 0.72; P < 0.0001). - Pembrolizumab/lenvatinib was **unlikely to worsen HRQoL**. - Pembrolizumab/lenvatinib **is not considered cost-effective** when compared to physician's choice of chemotherapy. - Economic evidence suggests that even at a 100% price reduction in the cost of pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. - Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**.
Pembrolizumab	IQWIG[29,33]	07/2022: Adult patients with **advanced or recurrent endometrial cancer** whose disease has

		progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option: - *Patients for whom doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **indication of a considerable added benefit**; OS clearly prolonged - *Patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **added benefit not proven** 10/2022: Adult patients with **advanced or recurrent microsatellite instability high or mismatch repair deficient endometrial carcinoma**, who have **disease progression** on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation - **Added benefit not proven**
Pembrolizumab	PBAC[31,34]	03/2023: **Pembrolizumab plus lenvatinib** (combination therapy) is **recommended** for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following prior systemic therapy **regardless of biomarker status** - The claim of superior efficacy of pembrolizumab plus lenvatinib versus chemotherapy, based on the results of the comparative KN775 trial, was reasonable. - The PBAC noted that the superior efficacy was observed in the intention to treat population comprising both dMMR and pMMR patients, with a substantial OS gain observed (ITT HR: 0.62 (95% CI: 0.51, 0.75)), and a 6.9 month increase in median survival (18.3 versus 11.4 months). - The PBAC considered that an ICER of $75,000 to < $95,000/QALY or lower was reasonable for pembrolizumab plus

		lenvatinib in the all-comer population given the level of OS benefit observed in the KN775 trial, and the high clinical need in this patient population in which there have been no recent advances in therapy. 03/2023: Pembrolizumab monotherapy in the dMMR population **not recommended** in patients with deficient DNA mismatch repair (dMMR) endometrial cancer. - The PBAC considered that the clinical benefit of monotherapy, which was based on a relatively small single arm study, was **uncertain**. - The submission presented a naïve side-by-side comparison of point estimates of OS observed in KN158 versus the chemotherapy arm of the dMMR subgroup in KN775. The PBAC considered there was a **high risk of bias** with this analysis given the naïve nature of the comparison. - The submission **did not specifically assess the cost-effectiveness** of pembrolizumab monotherapy versus chemotherapy.

Conclusion Statement – Pembrolizumab

Pembrolizumab is used in the **first-line** setting of high-risk (adjuvant or primary treatment), advanced, or metastatic endometrial cancer in combination with carboplatin/paclitaxel; preferred regimen in patients with carcinosarcoma disease (preferred).

Pembrolizumab is also a **second-line** agent used for the management of advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) in patients with disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. Its used in this setting as a monotherapy is supported by CADTH, but not IQWIG and PBAC.

- Both IQWIG and PBAC **don't recommend** the use of pembrolizumab **monotherapy** in the **dMMR** population of endometrial cancer (added benefit not proven as per IQWIG). The PBAC considered that the clinical benefit of monotherapy, which was based on a relatively small single arm study, was **uncertain**, a **high risk of bias** a naïve side-by-side comparison of point estimates of OS observed in KN158 versus the chemotherapy arm of

the dMMR subgroup in KN775. The submission **did not specifically assess the cost-effectiveness** of pembrolizumab monotherapy versus chemotherapy[33,34].

- CADTH's pERC recommends that pembrolizumab be **reimbursed as monotherapy** for the treatment of adult patients with **unresectable or metastatic MSI-H or dMMR endometrial cancer** whose tumors have **progressed following prior therapy** and who have **no satisfactory alternative treatment options**, due to an improvement in OS and PFS versus chemotherapy. The ICER was $61,200 per QALY gained when compared with chemotherapy. Based on this exploratory finding, **a price reduction is needed** for pembrolizumab to be cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold[32].

Pembrolizumab is also used in the **second-line setting in combination with lenvatinib** in disease that is mismatch repair proficient (pMMR) or not MSI-H, in patients with endometrial cancer progressing after prior systemic therapy and are not candidates for curative surgery or radiation. Its use in this setting is supported by all the HTA bodies.

- HAS issued **favorable opinion for reimbursement** for **pembrolizumab, in combination with lenvatinib** in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. HAS states a **therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma and a **moderate clinical added value** (CAV III)[25].
- NICE guidelines **recommend** the use of pembrolizumab plus lenvatinib within its marketing authorization, for the treatment of **advanced or recurrent endometrial cancer** in patients whose **cancer has progressed** on or after **platinum-based chemotherapy** and who **cannot have curative surgery or radiotherapy**. The efficacy assessment was based on key evidence for the KEYNOTE-775 trial where pembrolizumab plus lenvatinib improved OS and PFS compared with doxorubicin or paclitaxel monotherapy. Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. The **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**, with the most plausible ICER being less than £50,000 per QALY gained[27].
- CADTH's pERC also recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced**

endometrial carcinoma that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are **not candidates for curative surgery or radiation**, due to an improvement in OS, PSF, without worsening HRQoL. However, pembrolizumab/lenvatinib i**s not considered cost-effective when compared to chemotherapy**. Economic evidence suggests that even at a 100% price reduction in the cost of pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**[28].

- IQWIG and PBAC both **support** the use of **pembrolizumab plus lenvatinib** (combination therapy) for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following prior systemic therapy **regardless of biomarker status** (**indication of a considerable added benefit**; OS clearly prolonged versus doxorubicin/paclitaxel)[29,31].

2.5 Topoisomerase Inhibitors

2.5.1 Doxorubicin

Table 28. Doxorubicin Drug Information

Scientific Name Doxorubicin[49]	
Trade Name(s) on Saudi Market	Doxorubicin (Ebewe, Accord), Adriablastina
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2004
FDA approved / off label	Yes, 1974
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent
Drug Sub-class	Anthracycline; Topoisomerase II inhibitor
SFDA Registration Number (New)	Doxorubicin Ebewe: 4-355-01 (10mg); 5-355-01 (50mg); 39-355-07 (100mg) Doxorubicin Accord:

	5-5223-18 (10mg); 6-5223-18 (50mg) Adriablastina: 6-5669-22 (10mg); 7-5669-22 (50mg)
ATC Code	L01DB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Endometrial carcinoma, advanced (off-label use):** 60 mg/m^2 on day 1 every 21 days for 8 cycles; maximum cumulative dose: 420 mg/m^2 (in combination with cisplatin) or 45 mg/m^2 on day 1 every 3 weeks (in combination with cisplatin and optional growth factor support) for up to 6 cycles or 60 mg/m^2 (as a single agent) once every 3 weeks until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl <10 mL/minute: No need for adjustment - Hemodialysis: Consider administering 75% of the original dose Hepatic Impairment (Adult): - Serum bilirubin 1.2 to 3 mg/dL: Administer 50% of dose. - Serum bilirubin 3.1 to 5 mg/dL: Administer 25% of dose. - Severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL): Use is contraindicated.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used as a single agent or concurrently with chemotherapy

	(cisplatin ± paclitaxel); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Cumulative lifetime limit: 400 mg/m^2
ST (Step Therapy)	Second-line treatment of recurrent, metastatic, or high-risk endometrial carcinoma
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Cumulative lifetime limit: 400 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Acute cardiotoxicity, malaise, alopecia, discoloration of sweat, pruritus, skin photosensitivity, skin rash, urticaria, amenorrhea, dehydration, hyperuricemia, abdominal pain, anorexia, diarrhea, discoloration of saliva, gastrointestinal ulcer, metastatic urothelial carcinomaositis, nausea, vomiting, urine discoloration, infertility, leukopenia, neutropenia, anemia, thrombocytopenia, weakness, discoloration of tears - Most serious: Acute cardiotoxicity (Atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles, nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia), Delayed cardiotoxicity (cardiac failure, decreased left ventricular ejection fraction, myocarditis, pericarditis)

Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, CYP2D6 Inhibitors/Inducers, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Lasmiditan, Nadofaragen, Natalizumab, Pacritinib, P-glycoprotein/ABCB1 Inducers/Inhibitors, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Sparsentan, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Ado-Trastuzumab Emtansine, COVID-19 Vaccine, Deferiprone, Denosumab, Erdafitinib, Influenza Virus Vaccines, Fam-Trastuzumab Deruxtecan, Leflunomide, Lenograstim, Lipegfilgrastim, Margetuximab, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Trastuzumab, Vaccines (Inactivated/Non-Replicating), Zidovudine
Special Population	Pediatrics, Radiation recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Doxorubicin and its metabolites are present in breast milk. The manufacturer does not recommend breastfeeding during doxorubicin therapy and for 10 days after the last doxorubicin dose.
Contraindications	Severe hypersensitivity to doxorubicin or any component of the formulation;

	recent myocardial infarction (within past 4 to 6 weeks), severe myocardial insufficiency; severe persistent drug-induced myelosuppression; severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL).
Monitoring Requirements	- Cumulative (lifetime) anthracycline/doxorubicin dose - CBC with differential and platelet count - LFTs (bilirubin, ALT/AST, alkaline phosphatase; renal function (creatinine), serum uric acid, and electrolytes (calcium, potassium, phosphate) - Assess cardiac function: ECG, left ventricular ejection fraction increase the frequency of assessments as the cumulative dose exceeds 300 mg/m^2) - Pregnancy status prior to use - Monitor hydration status and for signs/symptoms of tumor lysis syndrome and secondary malignancies - Monitor infusion site
Precautions	- Bone marrow suppression - Cardiomyopathy - Extravasation: Vesicant - Secondary malignancy - Tumor lysis syndrome - Hepatic impairment: - Special populations - Pediatric - Radiation recipients - Formulations (conventional vs liposomal)
Black Box Warning	- Cardiomyopathy - Extravasation - Secondary malignancy

	- Immunosupression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for doxorubicin in endometrial cancer. This is probably because doxorubicin is a later-line treatment in relapsed/metastatic disease. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Doxorubicin

Doxorubicin is a second-line agent used in recurrent, metastatic, or high-risk endometrial carcinoma as a single-agent or in combination with cisplatin (± paclitaxel). There is no data issued by HTA bodies regarding its use.

2.6 Tyrosine Kinase Inhibitors

2.6.1 Lenvatinib

Table 29. Lenvatinib Drug Information

Scientific Name Lenvatinib[50]	
Trade Name(s) on Saudi Market	Lenvima; Lenvatinib TBM
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2019
FDA approved/off label	Yes, 2019
EMEA approved/off label	Yes, 2020
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, 2021
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic Agent
Drug Sub-Class	Tropomyosin Receptor Kinase (TRK) Inhibitor
SFDA Registration Number (New)	Lenvima: 8-663-19 (4 mg); 9-663-19 (10 mg) Lenvatinib TBM: 3108234080 (4 mg); 1208222479 (10 mg)

ATC Code	L01XE07
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	**Endometrial carcinoma, advanced, mismatch repair proficient or not microsatellite instability-high: Oral:** 20 mg once daily (in combination with pembrolizumab), continue until disease progression or unacceptable toxicity
Adjustment	Renal impairment prior to treatment initiation: CrCl <30 mL/minute: 10 mg once daily. Renal toxicity during treatment: - Nephrotic syndrome: Permanently discontinue lenvatinib. - Proteinuria ≥2 g proteinuria/24 hours: Withhold lenvatinib; resume lenvatinib at a reduced dose when improved to <2 g proteinuria/24 hours. - Renal failure or impairment (grade 3 or 4): Withhold lenvatinib; if improves to ≤ grade 1 or baseline, depending on the severity and persistence, resume lenvatinib at a reduced dose or permanently discontinue therapy. Hepatic impairment prior to treatment initiation: Severe impairment (Child-Pugh class C): 10 mg once daily. Hepatic toxicity during treatment: Withhold lenvatinib; if improves to ≤ grade 1 or baseline, depending on the severity and persistence, resume lenvatinib at a reduced dose or permanently discontinue therapy.

	Permanently discontinue lenvatinib for hepatic failure.
Prescribing edits*	AGE, MD, CU, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used in combination with pembrolizumab
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 20 mg
ST (Step Therapy)	Second-line treatment of advanced endometrial carcinoma that is NOT MSI-H or dMMR in patients with disease progression following prior systemic therapy in combination with pembrolizumab.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	20 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Hypertension, peripheral edema, alopecia, palmar-plantar erythrodysesthesia, rash, hyponatremia hypothyroidism, increased gamma-glutamyl transferase, increased thyroid stimulating hormone level, abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, nausea, stomatitis, vomiting, xerostomia, proteinuria, hemorrhage, ascites, increased serum aspartate aminotransferase, dizziness, fatigue, headache, insomnia, mouth pain, voice disorder, arthralgia, myalgia, renal insufficiency, cough

	- Most serious: Arterial thromboembolism, cardiac failure, cardiomyopathy, hypotension, prolonged QT interval on ECG, pulmonary embolism, reduced ejection fraction, ventricular dysfunction, gastrointestinal perforation, Hepatic encephalopathy, hepatic failure, grade 3-4 anemia, leukopenia, thrombocytopenia, reversible posterior leukoencephalopathy syndrome
Drug Interactions*	Risk X: QT prolongation: Citalopram, Clarithromycin, Domperidone, Entrectinib, Fexinidazole, Flupentixol, Levoketoconazole, Moxifloxacin, Nilotinib, PAZOPanib, Pimozide, Piperaquine, Probucol, QT-prolonging Kinase Inhibitors , QUEtiapine, Ribociclib, Sertindole, Sparfloxacin, Thioridazine Risk D: QT-prolonging Agents
Special Population	Older adults
Pregnancy	Pregnancy Category D
Lactation	It is not known if lenvatinib is present in breast milk. The manufacturer recommends discontinuing breastfeeding during lenvatinib treatment and for 1 week after the last lenvatinib dose.
Contraindications	N/A
Monitoring Requirements	- Mismatch repair proficient status or not microsatellite instability-high status - LFTs - Serum calcium - Thyroid function (TSH levels) - Proteinuria (urine dipstick; if 2+ then obtain a 24-hour urine protein). - Pregnancy status

	- Monitor BP after 1 week, then every 2 weeks for 2 months, and at least monthly thereafter. - Dental exam - ECG in select patients (congenital long QT syndrome, heart failure, bradyarrhythmias, etc.)- - Monitor for clinical signs/symptoms of cardiac dysfunction, arterial thrombosis, reversible posterior leukoencephalopathy syndrome, fistula formation, GI perforation, bleeding/hemorrhagic events, diarrhea, dehydration, and wound healing complications
Precautions	- Cardiac effects (serious and fatal cardiac dysfunction; QT prolongation) - Fistula formulation/GI perforation - GI toxicity - Hemorrhage - Hepatotoxicity - Hypocalcaemia - Hypothyroidism - Osteonecrosis - Renal toxicity - Reversible posterior leukoencephalopathy syndrome - Thromboembolic events - Wound healing impairment - Older adults
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and

Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of lenvatinib in endometrial carcinoma treatment options.

Table 30. Lenvatinib HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Pembrolizumab + Lenvatinib	HAS[26]	03/2022: **Favorable opinion for reimbursement** in the indication extension: **pembrolizumab, in combination with lenvatinib**, is indicated in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. - **Therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma. - **Moderate clinical added value** (CAV III) - Demonstration in a randomized, open-label phase 3 study of the superiority of pembrolizumab and lenvatinib combination compared to single-agent chemotherapy with doxorubicin or paclitaxel, particularly in terms of: ▪ Progression-free survival (PFS) (absolute increase of 3.4 months, HR=0.56 [CI95%: 0.47-0.66]): ▪ Overall survival (OS) (absolute increase of 6.9 months, HR=0.62 [CI95%: 0.51-0.75]) - Safety profile for the pembrolizumab and lenvatinib combination less favorable than that for single-agent chemotherapy, marked by additional toxicity with, in particular, more serious adverse events (53% versus 30%) - Absence of any formal conclusion that can be drawn based on the quality of life results
Pembrolizumab + Lenvatinib	NICE[27]	06/2023: Pembrolizumab plus lenvatinib is **recommended**, within its marketing authorization, for treating **advanced or recurrent endometrial**

		cancer in adults: • whose **cancer has progressed** on or after **platinum-based chemotherapy** and • who **cannot have curative surgery or radiotherapy**. - There is no standard second-line treatment for advanced or recurrent endometrial cancer. - Key evidence for pembrolizumab with lenvatinib comes from the KEYNOTE-775 trial: ▪ **Pembrolizumab plus lenvatinib improves OS and PFS compared with doxorubicin or paclitaxel monotherapy**. ▪ Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. - Pembrolizumab plus lenvatinib **meets NICE's criteria to be considered a life-extending treatment at the end of life**. - There is some uncertainty in the economic model about how long the effect of treatment lasts after people stop taking pembrolizumab at 2 years. - But the **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**. - The most plausible ICER is less than £50,000 per QALY gained
Pembrolizumab + Lenvatinib	CADTH[28]	12/2022: pERC recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced endometrial carcinoma** that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are **not candidates for curative surgery or radiation**. - One multicenter, randomized, open-label phase III trial (KEYNOTE-775; N = 697 for patients with pMMR disease) demonstrated that treatment with pembrolizumab/lenvatinib resulted in added clinical benefit when compared with

		treatment of physicians' choice in that setting. - Pembrolizumab/lenvatinib was associated with statistically significant and clinically meaningful improvements in OS (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.56 to 0.84; P< 0.0001) and PFS (HR = 0.60; 95% CI, 0.50 to 0.72; P < 0.0001). - Pembrolizumab/lenvatinib was **unlikely to worsen HRQoL**. - Pembrolizumab/lenvatinib **is not considered cost-effective** when compared to physician's choice of chemotherapy. - Economic evidence suggests that even at a 100% price reduction in the cost of pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. - Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**.
Pembrolizumab + Lenvatinib	IQWIG[29]	07/2022: Adult patients with **advanced or recurrent endometrial cancer** whose disease has **progressed during or after prior platinum-based therapy** at any stage of the disease when surgery or radiation to cure the cancer is not an option: - *Patients for whom doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **indication of a considerable added benefit**; OS clearly prolonged - *Patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy* according to physician's choice: **added benefit not proven**
Pembrolizumab + Lenvatinib	PBAC[31]	03/2023: **Pembrolizumab plus lenvatinib** (combination therapy) is **recommended** for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following

		prior systemic therapy **regardless of biomarker status** - The claim of superior efficacy of pembrolizumab plus lenvatinib versus chemotherapy, based on the results of the comparative KN775 trial, was reasonable. - The PBAC noted that the superior efficacy was observed in the intention to treat population comprising both dMMR and pMMR patients, with a substantial OS gain observed (ITT HR: 0.62 (95% CI: 0.51, 0.75)), and a 6.9 month increase in median survival (18.3 versus 11.4 months). - The PBAC considered that an ICER of $75,000 to < $95,000/QALY or lower was reasonable for pembrolizumab plus lenvatinib in the all-comer population given the level of OS benefit observed in the KN775 trial, and the high clinical need in this patient population in which there have been no recent advances in therapy.

Conclusion statement - Lenvatinib

Lenvatinib is approved for the second-line treatment of advanced endometrial cancer (in combination with pembrolizumab) that is mismatch repair proficient (pMMR) or not microsatellite instability-high, in patients who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. Its use in this setting is supported by all the HTA bodies.

- HAS issued a **favorable opinion for reimbursement** for **lenvatinib, in combination with pembrolizumab** in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. HAS states a **therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma and a **moderate clinical added value** (CAV III)[26].
- NICE guidelines **recommend** the use of pembrolizumab plus lenvatinib within its marketing authorization, for the treatment of **advanced or recurrent endometrial cancer** in patients whose **cancer has progressed** on or after **platinum-based chemotherapy** and who **cannot have curative**

surgery or radiotherapy. The efficacy assessment was based on key evidence from the KEYNOTE-775 trial where pembrolizumab plus lenvatinib improved OS and PFS compared with doxorubicin or paclitaxel monotherapy. Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. The **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**, with the most plausible ICER being less than £50,000 per QALY gained[27].

- CADTH's pERC also recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced endometrial carcinoma** that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are **not candidates for curative surgery or radiation**, due to an improvement in OS, PSF, without worsening HRQoL. However, pembrolizumab/lenvatinib i**s not considered cost-effective when compared to chemotherapy**. Economic evidence suggests that even at a 100% price reduction in the cost of pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**[28].
- IQWIG and PBAC both support the use of **pembrolizumab plus lenvatinib** (combination therapy) for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following prior systemic therapy **regardless of biomarker status** (**indication of a considerable added benefit**; OS clearly prolonged versus doxorubicin/paclitaxel)[29,31].

2.7 Vascular Endothelial Growth Factor (VEGF) Inhibitors

2.7.1 Bevacizumab

Table 31. Bevacizumab Drug Information

Scientific Name Bevacizumab[51]	
Trade Name(s) on Saudi Market	Avastin; Zirabev; Mvasi
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered; data on brain tumors not available
FDA approved/off label	Yes, 2009
EMEA approved/off label	No (approval denied in 2014)

MHRA approved/off label	No
PMDA approved/off label	Yes (malignant glioma); June 2013
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	Avastin 100mg: 269-24-14 Avastin 400mg: 270-24-14 Zirabev 100mg: 2411200290 Zirabev 400mg: 2411200291 Mvasi 100mg: 2402210547 Mvasi 400mg: 2402210550
ATC Code	L01XC07
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	15 mg/kg every 3 weeks (as monotherapy) until disease progression or unacceptable toxicity
Dose (Pediatric)	N/A
Adjustment	Renal impairment prior to treatment: No dosage adjustment Renal impairment during treatment: - Nephrotic syndrome (proteinuria >3.5 g per 24 hours): discontinue bevacizumab and refer to a kidney specialist. - Proteinuria ≥2 to ≤3.5 g per 24 hours: Withhold bevacizumab and resume therapy if and when urine protein levels are <2 g per 24 hours. Hepatic impairment prior to or during treatment: No dosage adjustment
Prescribing Edits*	MD, ST, PE, QL
AGE (Age Edit)	N/A

CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose: 15 mg/kg
ST (Step Therapy)	Second and later-line treatment of recurrent/metastatic endometrial cancer in patients who have progressed on previous cytotoxic chemotherapy
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	15 mg/kg/day
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: increased ALTs, increased alkaline phosphatase, thrombocytopenia, leukopenia, hypoalbuminemia, hyponatremia, hypocalcemia, hyperglycemia, hypertension - Most serious: nephrotic syndrome
Drug Interactions*	Anthracyclines: enhanced cardiotoxicity (risk X) Cladribine, dipyrone, fexinidazole: enhanced myelosuppressive effect (risk X) Sunitinib: increased risk of microangiopathic hemolytic anemia (risk X)
Special Population	Patients ≥ 65 years of age have an increased incidence of arterial thrombotic events.
Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, bevacizumab may cause fetal harm if administered during pregnancy. Information from post-marketing reports following

	systemic exposure in pregnancy is limited.
Lactation	It is not known if bevacizumab is present in breast milk.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	Proteinuria/nephrotic syndrome Blood pressure Pregnancy status HBV screening prior to initiation (do not delay treatment for screening results)
Precautions	- GI perforation/fistula - Heart failure - Hemorrhage - Hypertension - Infusion reactions - Necrotizing fasciitis - Osteonecrosis of the jaw - Ocular adverse events - Posterior reversible encephalopathy syndrome - Proteinuria/nephrotic syndrome - Wound healing complications - Thromboembolism
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of endometrial cancer treatment options by the following agencies/institutes/authorities: Pharmaceutical Benefits Advisory Committee (PBAC).

Table 32. Bevacizumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Bevacizumab	PBAC[35]	07/2020: The PBAC recommended the listing of the biosimilar brand of bevacizumab, Zirabev for all of the indications for which the reference brand, Avastin, is currently PBS-listed, including **advanced FIGO Stage IIIB, IIIC or Stage IV epithelial ovarian**, fallopian tube or primary peritoneal **cancer** - The PBAC recommended listing Zirabev on a cost-minimization basis to the Avastin brand of bevacizumab

Conclusion Statement – Bevacizumab

Bevacizumab is recommended as a second or later-line treatment of endometrial cancer for recurrent or persistent disease in patients who have progressed on previous cytotoxic chemotherapy. It is approved for use by PBAC.

2.8 Anti-HER2 Agents

2.8.1 Trastuzumab

Table 33. Trastuzumab Drug Information

Scientific Name Trastuzumab[52]	
Trade Name(s) on Saudi Market	Herceptin; Ogivri; Herzuma; Canhera; Kanjinti ; Trazimera ; Hercepac
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2008 (used off-label in EC)
FDA approved/off label	Yes, 1998
EMEA approved/off label	Yes, 2000
MHRA approved/off label	Yes, not mentioned
PMDA approved/off label	Yes, 2008
Indication (ICD-10)	C54.1
Drug Class	Antineoplastic Agent
Drug Sub-Class	Monoclonal Antibody; Anti-HER2
SFDA Registration Number (New)	Herceptin IV: 266-24-08 (150 mg);

	Herceptin SC *(not used in EC)* 289-24-18 (600 mg) Ogivri: 1-5548-20 (420 mg) Herzuma: 325-334-20 (150 mg); 352-334-20 (440 mg) Canhera: 1-5366-19 (150 mg); 2-5366-20 (440 mg) Kanjinti: 2211200281 (420 mg); 2211200282 (150 mg) Trazimera: 2012200344 (150 mg); 1306210785 (440 mg) Hercepac: 2211222921 (150 mg)
ATC Code	L01XC03
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous; Subcutaneous (different formulation, not used in EC)
Dose (Adult) [DDD]*	**Endometrial cancer, uterine serous, advanced or recurrent, HER2+:** Initial: 8 mg/kg (cycle 1) followed by a maintenance dose of 6 mg/kg every 3 weeks (in combination with carboplatin and paclitaxel for ~6 cycles), followed by trastuzumab maintenance of 6 mg/kg every 3 weeks until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl 30 to 90 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling, although no clinically significant pharmacokinetic differences have been observed.

	- CrCl <30 mL/minute; End-Stage Renal Disease: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Hepatic Impairment (Adult): No dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	AGE, CU, MD, PA, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used concurrently with chemotherapy
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	Restricted for HER-2 positive tumors
QL (Quantity Limit)	Maximum daily dose: 8 mg/kg
ST (Step Therapy)	First and second-line treatment of newly diagnosed or recurrent/metastatic endometrial cancer in combination with carboplatin/paclitaxel in patient with HER2-positive tumors (preferred in uterine serous histologies)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	8 mg/kg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Decreased left ventricular ejection fraction, skin rash, abdominal pain, anorexia, diarrhea, nausea, vomiting, infection, chills, dizziness, headache, insomnia, pain, asthenia, back pain, cough, dyspnea, pharyngitis, infusion-related reactions - Most serious: Cardiac arrhythmia , cardiac failure

Drug Interactions*	- Risk D: Anthracyclines: Trastuzumab may enhance the cardiotoxic effect of Anthracyclines
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if trastuzumab is present in human milk. The 7-month wash out period for trastuzumab should be considered for decisions regarding breastfeeding after treatment is completed.
Contraindications	N/A
Monitoring Requirements	- Pregnancy status - Cardiovascular assessment prior to treatment initiation, including a history and physical examination. - Assess left ventricular ejection fraction (by ECG or MUGA scan) at baseline (immediately prior to trastuzumab initiation), every 3 months during trastuzumab therapy, every 4 weeks if trastuzumab is withheld for significant left ventricular cardiac dysfunction, and every 6 months for at least 2 years following completion of adjuvant trastuzumab therapy. - Monitor vital signs during infusion; monitor for hypersensitivity or infusion reaction; if a reaction occurs, monitor carefully until symptoms resolve completely. - Monitor for signs/symptoms of cardiac dysfunction or pulmonary toxicity.
Precautions	- **Cardiomyopathy** - Infusion reactions - Pulmonary toxicity - Renal toxicity
Black Box Warning	- Cardiomyopathy

	- Infusion reactions and pulmonary toxicity - Pregnancy
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for trastuzumab in endometrial cancer, probably because it's still used in an off-label setting.

Conclusion statement - Trastuzumab

Trastuzumab is used for the first-line management of high risk, advanced or recurrent, HER2-positive, endometrial cancer (preferably uterine serous histology) in combination with carboplatin/paclitaxel.

There are no HTA recommendations regarding its use in this setting.

Section 3.0 Key Recommendations Synthesis

Most patients with endometrial carcinoma have a favorable prognosis. Prognosis is determined primarily by disease stage, grade, histology, and molecular classification (if known)[1,5].

Treatment strategies for patients with endometrial cancer are outlined in the below sections[11-16]:

A. Primary Treatment

Most patients with endometrial cancer have stage I disease at presentation, and **surgery (with or without adjuvant therapy) is recommended for medically operable patients** (Recommendation Level A, Evidence Level II) [11-16]. As a general principle, endometrial carcinoma should be removed ***en bloc*** to optimize outcomes; intraperitoneal morcellation should be avoided[11-16]. Pure endometrioid cancer can be divided into **three categories** for defining treatment:

- **Disease limited to the uterus** – For EC staging in patients with disease apparently confined to the uterus (based on physical examination, with or without pelvic imaging) who are surgical candidates and in whom the procedure is expected to be able to be completed without conversion to laparotomy, both NCCN and European guidelines agree on a **minimally invasive surgical approach** (MIS; laparoscopy or robotic surgery), even in patients with high-risk endometrial carcinoma rather than laparotomy (Recommendation Level A, Evidence Level II) [11-16].
  - Conventional **total laparoscopic hysterectomy** with **BSO** is the preferred option for most patients, with use of robotic surgery if this makes MIS possible in patients who have a high risk of conversion to laparotomy (e.g., patients with obesity) [11-16].
  - Patients with apparent uterine-confined endometrial carcinoma are candidates for **SLN mapping**, which assesses the pelvic nodes bilaterally and may be less morbid than complete lymphadenectomy[11-16].
  - For *patients not eligible for primary surgery*, **external beam radiotherapy (EBRT) and/or brachytherapy is the preferred treatment approach** (Recommendation Level A, Evidence Level II); progestational agents can be an alternative in select patients[11-16].
- **Suspected or Gross Cervical Involvement** – For patients with clinically apparent extension of EC to the cervix, **cervical biopsy** or **pelvic MRI** should be performed if not done previously[11-16].
  - If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described, although a radical

hysterectomy may be performed when necessary to obtain negative margins.

- It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for patients suitable for primary surgery, **TH or radical hysterectomy** is recommended along with **BSO, cytology** (peritoneal lavage), and **evaluation of lymph nodes** if indicated (Recommendation Level A, Evidence Level II) [11-16].
- Alternatively, the patient may undergo **EBRT and brachytherapy** (Recommendation Level B, Evidence Level II) followed by **TH/BSO** and **surgical staging**[11-16].
- For *patients who are not suited for primary surgery*, **EBRT and brachytherapy** is an effective alternative; it may be administered **with or without platinum-based chemosensitization**, depending on the clinical situation and medical fitness of the patient (Recommendation Level A, Evidence Level II) [11-16].
    - **Cisplatin** is the preferred chemosensitizing agent (Recommendation Level A, Evidence Level II) [11-16].
    - If rendered operable, local treatment consisting of **surgery** should follow.
    - **Systemic therapy alone** is also a primary treatment option (category 2B), but should be followed by EBRT + brachytherapy if the patient remains inoperable[11-16].

- **Suspected Extrauterine Disease** – If extrauterine disease (endometrioid histologies) is suspected, **imaging studies** are recommended along with **CA-125 testing**. **Estrogen Receptor** (ER) testing is recommended in the setting of stage III or IV endometrioid tumors[11-16].
    - Patients with abdominal- or pelvic-confined disease require surgical intervention using **TH/BSO with surgical staging** and **surgical debulking** with the goal to have no measurable residual disease (Recommendation Level A, Evidence Level II); several studies support debulking[11-16].
    - Consider preoperative chemotherapy.
    - Patients with *unresectable extrauterine pelvic disease* (i.e., vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with **EBRT with (or without) brachytherapy with (or without) systemic therapy**, followed by re-evaluation of tailored surgery[11-16].

        - Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT.
    - For distant visceral metastasis (e.g., liver involvement), recommended options include systemic therapy with (or without) EBRT with (or without) TH/BSO and with (or without) stereotactic body RT (SBRT). Ablative radiation can be considered for 1 to 5 metastatic lesions if disease is otherwise controlled (Recommendation Level B, Evidence Level II) [11-16].

- **Fertility-Sparing Therapy**: Conservative management may be considered in highly selected patients with **grade 1, stage IA non-invasive endometrioid endometrial carcinoma** who wish to preserve their fertility[11-16].
    - **Continuous progestin-based therapy** is used in that setting and may include megestrol acetate, medroxyprogesterone, or an intrauterine device (IUD) containing levonorgestrel[11-16].
    - Patient-specific factors should be carefully considered, including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking.
    - TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs[11].

B. Adjuvant therapy

B.1 Disease Limited to the Uterus

Thorough **surgical staging** provides important information to assist in selection of adjuvant therapy for endometrial tumors.

- Patients with **stage I** endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (i.e., age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement).
    - **Observation** is preferred for patients with **stage IA, grade 1/2 disease**, but **treatment with adjuvant vaginal brachytherapy** is strongly suggested for patients **≥60 years** and/or with **LVSI** (Recommendation Level A, Evidence Level II) [11-16].
    - For **patients with stage IA, grade 3 tumors**, especially those who have been surgically staged, **vaginal brachytherapy** is the **preferred** option, or observation can be considered if no myometrial invasion is present (Recommendation Level A, Evidence Level II) [11-16].
    - If higher risk factors are present, i.e., age ≥70 years or LVSI, **EBRT** can be considered (Recommendation Level B, Evidence Level II) [11-16].

- For **patients with stage IB, grade 1–2 disease**, **vaginal brachytherapy is preferred** although observation can be considered if no adverse risk factors are present (Recommendation Level A, Evidence Level II) [11-16].
  - **EBRT** can be considered in grade 2 tumors if additional risk factors are present such as age ≥60 years and/or if LVSI is present.
  - For **stage IB, grade 3 disease with adverse risk factors**, **systemic therapy** in addition to **EBRT** and/or **vaginal brachytherapy** can be considered (Recommendation Level B, Evidence Level II) [11-16].
- For patients with an **invasive cervical component**, **adjuvant therapy** is to be considered if extrafascial hysterectomy is performed.
- Patients with **deeply invasive, grade 3, uterine-confined disease** (2009 FIGO stage IB, grade 3) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have a significant risk of distant metastases, and an optimal adjuvant therapy is still sought[11-16].
  - Adding **systemic therapy** to **adjuvant RT** may provide added therapeutic benefit (i.e., decrease in distant metastases) (Recommendation Level B, Evidence Level II) [11-16].

B.2 Advanced Stage/Extrauterine Disease

- Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field **RT alone or with chemotherapy** (radiation is targeted to sites of nodal disease) [11-16].
- However, **systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease** (Recommendation Level A, Evidence Level II) [11-16].
- International guidelines include **carboplatin/paclitaxel as the preferred systemic therapy** option in the **primary/adjuvant setting** for advanced-stage disease or high-risk histologies (Recommendation Level A, Evidence Level II) [11-16].
- Recently, the **pembrolizumab/carboplatin/paclitaxel** and **dostarlimab carboplatin/paclitaxel** triplet regimens are added as **preferred, primary therapy options for stage III or IV disease** based on the data from phase III NRG-GY018 and RUBY trials, respectively (Recommendation Level A, Evidence Level I) [11,16].
  - The **pembrolizumab/carboplatin/paclitaxel** regimen is recommended for **stage III or IVA with measurable disease or for stage IVB with or without measurable disease**. Since the NRG-

GY018 trial did not include patients with carcinosarcoma histology, it is not recommended for patients with carcinosarcoma disease[11,16].

- The **dostarlimab carboplatin/paclitaxel** option is recommended for patients with stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV disease regardless of the presence of measurable disease[11,16].

- For **stages III and IV disease**, **systemic therapy forms the mainstay of treatment** and can be combined with **EBRT with (or without) vaginal brachytherapy**. The combination of therapies depends on assessment of both locoregional and distant metastatic risk. Combination therapy can be considered for stages IIIB and IIIC disease (Recommendation Level A, Evidence Level II) [11-16].

C. High-Risk EC Histologies

- **Uterine serous carcinomas**, **clear cell carcinomas**, **carcinosarcomas**, and **undifferentiated/dedifferentiated carcinomas** are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation[11].
- Even patients with apparent early-stage disease may have distant metastases.
- Thus, **fertility-sparing therapy is not recommended** for these aggressive tumors.
- If done, SLN mapping should proceed with particular caution.
- Serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/dedifferentiated carcinomas are all considered high-risk histologies and **high grade by default**, although they are staged using the same FIGO/AJCC staging system as endometrial cancers.
- Patients may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding.
- **CA-125** and **MRI** or **chest/abdominal/pelvic CT** may be useful before surgery to assess if extrauterine disease is present; **PET** may also be useful (Recommendation Level A, Evidence Level II).

C.1 Patients suitable for primary surgery

- **Multimodality therapy** is typically recommended for these histologically aggressive tumors. Primary treatment includes **TH/BSO with surgical staging**, **peritoneal lavage** for cytology, **omental and**

peritoneal biopsies, and consideration of **maximal tumor debulking** for gross disease (Recommendation Level A, Evidence Level II)[11].

- **Minimally invasive surgery** is the preferred approach when technically feasible (Recommendation Level A, Evidence Level II)[11].
- For patients with *clear cell* or *serous carcinomas* with *no residual disease* in the hysterectomy specimen, **observation** is the recommended option.
    - For **stage IA disease** without myometrial invasion with negative peritoneal washings, options include **vaginal brachytherapy** with (or without) **systemic therapy** (Recommendation Level A, Evidence Level II; Recommendation Level B, Evidence Level II for systemic therapy) or **observation**. If the washings are positive, both systemic therapy and vaginal brachytherapy are recommended[11].
    - For patients with **invasive stage IA, IB, or II**, options include **systemic therapy** with (or without) **EBRT** with (or without) **vaginal brachytherapy**; or EBRT with (or without) vaginal brachytherapy (Recommendation Level A, Evidence Level II) [11].
    - For patients with clear cell or serous carcinoma at a more advanced stage (i.e., **stage III or IV**), or with undifferentiated/dedifferentiated histology, **systemic therapy** with (or without) **EBRT** with (or without) **vaginal brachytherapy** is recommended (Recommendation Level A, Evidence Level II) [11].
- For the patients with *carcinosarcoma* histology at stage IA, **systemic therapy** and **vaginal brachytherapy** are recommended with an option for **EBRT**, if it has high-grade epithelial components and is sarcoma dominant (>50% of sarcoma component in uterine tumor) (Recommendation Level A, Evidence Level II) [11].

C.2 Patients Not Suitable for Primary Surgery

- The primary treatment option is **EBRT** with (or without) **brachytherapy** with (or without) **systemic therapy** and then re-evaluation for surgery (Recommendation Level A, Evidence Level II)[11-16].
- Alternatively, **systemic therapy** could be given first, and then patients can be re-evaluated for surgery before giving RT based on the tumor response[11-16].
- For patients with carcinosarcoma histology with unresectable tumor that has metastasized, the panel recommends systemic therapy with (or without) EBRT or best supportive care[11-16].

D. Recurrent or Metastatic Disease

D.1 Disease Limited to the Uterus

For recurrences confined to the vagina or the pelvis alone, **second-line treatment** (typically with RT and/or surgery or systemic therapy) can be effective and selection depends on **prior therapy**.

- For patients with *no prior RT exposure* at the recurrence site, **EBRT** with (or without) **brachytherapy** and **systemic therapy**, or **surgery** with (or without) **intraoperative RT** (IORT) and **systemic therapy** are recommended options (Recommendation Level A, Evidence Level II) [11].
- For patients *previously treated with brachytherapy* only at the recurrence site, **surgery** with (or without) **IORT** is recommended (Recommendation Level A, Evidence Level II; Recommendation Level C, Evidence Level III for IORT) [11].
- For patients *previously treated with EBRT* at the recurrence site, recommended therapy for isolated relapse includes **surgery** with (or without) **IORT** (Recommendation Level A, Evidence Level II; Recommendation Level C, Evidence Level III for IORT) plus or minus **systemic therapy**[11].

D.2 Distant Metastasis

- For *resectable isolated metastases*, **surgical resection** and/or **EBRT**, or **ablative therapy** are to be considered (Recommendation Level A, Evidence Level II). **Ablative RT** can be considered for 1 to 5 metastatic lesions if the primary cancer has been controlled (Recommendation Level B, Evidence Level II) [11].
- Providers can also consider **systemic therapy** (Recommendation Level B, Evidence Level II) [11].
- Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Treatment options for disseminated metastases are **systemic therapy** with (or without) **palliative EBRT**. For persistent progression of disseminated metastases (Recommendation Level A, Evidence Level II), **best supportive care** is recommended[11-16].

D.3 Hormonal Therapy

- Hormonal therapy is typically used for **lower-grade endometrioid histologies**, preferably in patients with small tumor volume or an indolent growth pace[11-16].

- Hormonal agents for treating **metastatic disease** include **megestrol acetate with alternating tamoxifen**, **everolimus/letrozole** combination, **progestational agents** (such as medroxyprogesterone acetate and megestrol acetate), **aromatase inhibitors**, **tamoxifen** alone, or **fulvestrant** (Recommendation Level A, Evidence Level II) [11-15].
- No drug, dose, or schedule has been found to be superior.

D.4 Systemic Therapy

- The combination ca**rboplatin/paclitaxel for 6 cycles [with pembrolizumab (for up to 2 years**; except in patients with carcinosarcoma histology) or **dostarlimab (for up to 3 years) in patients with MSI-H/dMMR disease]** are the preferred first-line therapy options for metastatic or recurrent endometrial carcinoma, based on the results from the NRG-GY018 and RUBY trials (Recommendation Level A, Evidence Level I) [11-16].
- It is to note that the NCCN guidelines recommend the three drug combination with immunotherapy regardless of the MSI-I/dMMR status (based on the mentioned trials)[11], which can be considered.
- The **NRG-GY018**, randomized, phase III trial evaluated the benefits of **pembrolizumab/carboplatin/paclitaxel** regimen over the **carboplatin/paclitaxel regimen** in 816 patients with stage III or IVA endometrial carcinoma with measurable disease, or stage IVB or recurrent disease of any histologic subtype, except for carcinosarcoma[23].
  - The PFS was 74% versus 38% in the dMMR cohort for the triplet regimen versus the chemotherapy arm, respectively (HR, 0.30; 95% CI, 0.19–0.48; P < .001). In pMMR tumors, the median PFS was 13.1 months in pembrolizumab arm versus 8.7 months in the chemotherapy arm (HR, 0.54; 95% CI, 0.41–0.71; P < .001)[23].
- Another phase III, randomized trial **(RUBY)** showed benefits of **adding dostarlimab** to the **carboplatin/paclitaxel** regimen in 494 patients with stage III or IV or recurrent disease, including all histologies[24].
  - At 24 months, PFS was 36.1% versus 18.1% (HR, 0.64; 95% CI, 0.51–0.80; P < .001) and OS was 71.3% versus 56% (HR, 0.64; 95% CI, 0.46–0.87) in the dostarlimab-based arm versus the chemotherapy arm, respectively[24].
  - Significantly more benefits were observed in patient with dMMR/MSI-H tumors with PFS of 61.4% versus 15.7% (HR, 0.28; 95%

CI, 0.16–0.50; P < .001) in the triplet versus the doublet therapy arms, respectively[24].

- **Biomarker-Directed Therapies:**
  - **Pembrolizumab** is a recommended treatment option for patients with **recurrent endometrial cancer with MSI-H/dMMR disease** that has *progressed on or following prior treatment with a platinum-containing regimen* in any setting including neoadjuvant or adjuvant therapy (Recommendation Level A, Evidence Level II) [11-16].
  - **Dostarlimab** is recommended by international guidelines for the treatment of patients with **recurrent dMMR/MSI-H endometrial cancer** that has *progressed on or following prior treatment with a platinum-containing regimen* in any setting including neoadjuvant or adjuvant therapy (Recommendation Level A, Evidence Level II) [11-16].
  - **Nivolumab** and **avelumab** are included in the NCCN guidelines as biomarker-directed **subsequent therapy options for recurrent dMMR/MSI-H endometrial tumors** (Recommendation Level A, Evidence Level II)[11].
  - **Larotrectinib** or **entrectinib** are included in the NCCN guidelines for **NTRK gene fusion-positive** endometrial tumors as a subsequent therapy option (Recommendation Level B, Evidence Level II) [11].
- Other multiagent regimens such as **carboplatin/paclitaxel**, **carboplatin/docetaxel**, and **carboplatin/paclitaxel/bevacizumab** are alternative first-line therapy options for the recurrent disease setting (Recommendation Level A, Evidence Level II) [11-15].
- Other combination therapies such as **cisplatin/doxorubicin**, **cisplatin/doxorubicin/paclitaxel**, **ifosfamide/paclitaxel** (for carcinosarcoma), and **cisplatin/ifosfamide** (for carcinosarcoma) are recommended as **subsequent therapy options** (Recommendation Level A, Evidence Level II) [11-15].
- **Bevacizumab** can be considered as a single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy (Recommendation Level A, Evidence Level II) [11-15].
- If multiagent chemotherapy regimens are contraindicated, then **single-agent therapy** options for recurrent disease include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, temsirolimus, cabozantinib, and docetaxel (Recommendation Level A, Evidence Level II)[11].

- **Systemic Therapy Options for High-Risk Endometrial Histologies:**
  - The previously mentioned systemic therapy options can be used for all carcinoma histologies.
  - Among these, **carboplatin/paclitaxel is a preferred** option for patients with **carcinosarcoma** histology (Recommendation Level A, Evidence Level I) [11].
  - The triplet therapy regimen **carboplatin/paclitaxel/trastuzumab** is recommended by the NCCN guidelines as a preferred option for **HER2-positive uterine serous carcinoma** or **HER2-positive carcinosarcoma** as: 1) primary therapy for stage III/IV disease; or 2) a first-line option for recurrent disease (Recommendation Level A, Evidence Level II; Recommendation Level B, Evidence Level II for HER2-positive carcinosarcoma in both disease settings) [11].
  - In **subsequent therapy**, the NCCN Panel has included **ifosfamide**, **ifosfamide/paclitaxel**, and **ifosfamide/cisplatin** as options for **carcinosarcoma** treatment only (Recommendation Level A, Evidence Level II) [11].

E. HTA Recommendations

Recommendations were issued by different Health Technology Assessment (HTA) bodies on the use of the pembrolizumab, lenvatinib, bevacizumab, and dostarlimab (not SFDA registered) in endometrial cancer. The key recommendations are outlined below:

- The use of **pembrolizumab monotherapy** in the **second-line** setting of advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) in patients with disease progression following prior systemic therapy and are not candidates for curative surgery or radiation is supported by CADTH, but not IQWIG and PBAC.
  - CADTH's pERC recommends that pembrolizumab be **reimbursed as monotherapy** for the treatment of adult patients with **unresectable or metastatic MSI-H or dMMR endometrial cancer** whose tumors have **progressed following prior therapy** and who have **no satisfactory alternative treatment options**, due to an improvement in OS and PFS versus chemotherapy. The ICER was $61,200 per QALY gained when compared with chemotherapy. Based on this exploratory finding, **a price reduction is needed** for pembrolizumab to be cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold[32].
  - IQWIG states an "added benefit not proven".

- The PBAC considered that the clinical benefit of monotherapy, which was based on a relatively small single arm study, was **uncertain**, a **high risk of bias** a naïve side-by-side comparison of point estimates of OS observed in KN158 versus the chemotherapy arm of the dMMR subgroup in KN775. The submission **did not specifically assess the cost-effectiveness** of pembrolizumab monotherapy versus chemotherapy[33,34].

- The use of **pembrolizumab in combination with lenvatinib** in the **second-line setting** in disease that is mismatch repair proficient (pMMR) or not MSI-H, in patients with endometrial cancer progressing after prior systemic therapy and are not candidates for curative surgery or radiation is supported by all the HTA bodies.

  - HAS issued **favorable opinion for reimbursement** for **pembrolizumab, in combination with lenvatinib** in the treatment of adult patients with **advanced or recurrent endometrial carcinoma** who have **disease progression** on or following **prior treatment with a platinum-containing therapy** in any setting and **are not candidates for curative surgery or radiation**. HAS states a **therapeutic improvement** compared to single-agent chemotherapy with doxorubicin or paclitaxel in the second-line treatment of advanced endometrial carcinoma and a **moderate clinical added value** (CAV III)[25].

  - NICE guidelines **recommend** the use of pembrolizumab plus lenvatinib within its marketing authorization, for the treatment of **advanced or recurrent endometrial cancer** in patients whose **cancer has progressed** on or after **platinum-based chemotherapy** and who **cannot have curative surgery or radiotherapy**. The efficacy assessment was based on key evidence for the KEYNOTE-775 trial where pembrolizumab plus lenvatinib improved OS and PFS compared with doxorubicin or paclitaxel monotherapy. Pembrolizumab plus lenvatinib may be better in **dMMR disease than in pMMR disease** but there is not enough evidence to conclude this. The **cost-effectiveness estimates are within the range considered acceptable for an end of life treatment**, with the most plausible ICER being less than £50,000 per QALY gained[27].

  - CADTH's pERC also recommends that **pembrolizumab combined with lenvatinib** be **reimbursed** for the treatment of adult patients with **advanced endometrial carcinoma** that is **not MSI-H or dMMR**, who have **disease progression** following **prior platinum-based systemic therapy**, and are **not candidates for curative surgery or radiation**, due to an improvement in OS, PSF, without worsening HRQoL. However, pembrolizumab/lenvatinib i**s not considered cost-effective when compared to chemotherapy**. Economic evidence suggests that even at a 100% price reduction in the cost of

pembrolizumab, pembrolizumab/lenvatinib would not be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in the indicated population. Based on public list prices, **pembrolizumab/lenvatinib will cost the public drug plans $106,543,234 over 3 years**[28].

- IQWIG and PBAC both **support** the use of **pembrolizumab plus lenvatinib** (combination therapy) for the treatment of patients with **advanced endometrial cancer** who have **disease progression** following prior systemic therapy **regardless of biomarker status** (**indication of a considerable added benefit**; OS clearly prolonged versus doxorubicin/paclitaxel)[29,31].

- The PBAC **recommends** the listing of the biosimilar brand of bevacizumab, Zirabev for all of the indications for which the reference brand, Avastin, is currently PBS-listed, including advanced FIGO Stage IIIB, IIIC or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer on a **cost-minimization** basis[35].

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of endometrial cancer.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428. doi: 10.1016/S0140-6736(22)00323-3. PMID: 35397864.
2. American Cancer Society: Key Statistics for Endometrial Cancer. Available online: https://www.cancer.org/cancer/endometrial-cancer/about/key-statistics.html
3. Kitchener HC, Trimble EL; Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. *Int J Gynecol Cancer*. 2009;19(1):134-140. doi:10.1111/IGC.0b013e3181995f90
4. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ. Contemporary clinical management of endometrial cancer. *Obstet Gynecol Int*. 2013;2013:583891. doi:10.1155/2013/583891
5. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. *Int J Cancer*. 2010;127(11):2678-2684. doi:10.1002/ijc.25501
6. Kimura T, Kamiura S, Yamamoto T, Seino-Noda H, Ohira H, Saji F. Abnormal uterine bleeding and prognosis of endometrial cancer. *Int J Gynaecol Obstet*. 2004;85(2):145-150. doi:10.1016/j.ijgo.2003.12.001
7. Seebacher V, Schmid M, Polterauer S, et al. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. *BMC Cancer*. 2009;9:460. Published 2009 Dec 22. doi:10.1186/1471-2407-9-460
8. American Cancer Society: Detailed Guide: Endometrial Cancer: What are the Risk Factors for Endometrial Cancer? Atlanta, Ga: American Cancer Society, 2005.
9. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and Management of Endometrial Cancer. *Am Fam Physician*. 2016;93(6):468-474.
10. Török P, Krasznai Z, Molnár S, Lampé R, Jakab A. Preoperative assessment of endometrial cancer. *Transl Cancer Res*. 2020;9(12):7746-7758. doi:10.21037/tcr-20-2068
11. Abu-Rustum N, Yashar C, Arend R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023;21(2):181-209. doi:10.6004/jnccn.2023.0006

12. Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-877. doi:10.1016/j.annonc.2022.05.009
13. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39. doi:10.1136/ijgc-2020-002230
14. Morrison J, Balega J, Buckley L, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2022;270:50-89. doi:10.1016/j.ejogrb.2021.11.423
15. Yamagami W, Mikami M, Nagase S, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol. 2020;31(1):e18. doi:10.3802/jgo.2020.31.e18
16. Disis ML, Adams SF, Bajpai J, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer [published correction appears in J Immunother Cancer. 2023 Jun;11(6):1]. J Immunother Cancer. 2023;11(6):e006624. doi:10.1136/jitc-2022-006624
17. Brinton LA, Trabert B, Anderson GL, Falk RT, Felix AS, Fuhrman BJ, Gass ML, Kuller LH, Pfeiffer RM, Rohan TE, Strickler HD, Xu X, Wentzensen N. Serum Estrogens and Estrogen Metabolites and Endometrial Cancer Risk among Postmenopausal Women. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1081-9. doi: 10.1158/1055-9965.EPI-16-0225. Epub 2016 Apr 12. PMID: 27197275; PMCID: PMC4930692.
18. Restaino S, Paglietti C, Arcieri M, Biasioli A, Della Martina M, Mariuzzi L, Andreetta C, Titone F, Bogani G, Raimondo D, Perelli F, Buda A, Petrillo M, Greco P, Ercoli A, Fanfani F, Scambia G, Driul L, Vizzielli G, The Udine Hospital Gynecological-Oncological Tumor Board Group. Management of Patients Diagnosed with Endometrial Cancer: Comparison of Guidelines. Cancers (Basel). 2023 Feb 8;15(4):1091. doi: 10.3390/cancers15041091. PMID: 36831434; PMCID: PMC9954548.
19. Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet. 2023;162(2):383-394. doi:10.1002/ijgo.14923
20. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
21. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for

36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492

22. Turkistani AK, Abdullah L. Uterine Malignancy: Pathological Pattern and Changing Incidence in a Teaching Hospital in Jeddah, Saudi Arabia. Cureus. 2023;15(7):e42074. Published 2023 Jul 18. doi:10.7759/cureus.42074
23. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med. 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312.
24. Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388(23):2145-2158. doi:10.1056/NEJMoa2216334
25. Haute Autorite de Sante. (2022). Keytruda CT19659 [HAS CT19659]. https://www.has-sante.fr/upload/docs/application/pdf/2022-08/keytruda_300322_summary_ct19659.pdf.
26. Haute Autorite de Sante. (2022). Lenvima CT19557 [HAS CT19557]. https://www.has-sante.fr/upload/docs/application/pdf/2022-08/lenvima_300322_summary_ct19557.pdf.
27. National Institute for Health and Care Excellence. (2023). Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer [NICE Guideline TA904]. www.nice.org.uk/guidance/ta904.
28. Canada's drug and health technology agency. (2022). Keytruda and Lenvima CADTH Reimbursement Recommendation [CADTH PC0288-000]. https://www.cadth.ca/sites/default/files/DRR/2023/PC0280%20Keytruda%20-%20Final%20CADTH%20Recommendation.pdf
29. Institute for Quality and Efficiency in Health Care. (2022). Pembrolizumab (endometrial carcinoma) – Benefit assessment according to §35a Social Code Book V. [A22-76] URL: https://www.iqwig.de/download/a22-76_pembrolizumab_extract-of-dossier-assessment_v1-0.pdf
30. Institute for Quality and Efficiency in Health Care. (2022). Lenvatinib (endometrial carcinoma) – Benefit assessment according to §35a Social Code Book V. [A21-162] URL: https://www.iqwig.de/download/a21-162_lenvatinib_extract-of-dossier-assessment_v1-0.pdf
31. Pharmaceutical Benefits Advisory Committee. (2023). Public Summary Document (PSD) November 2023 PBAC Meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/pembrolizumab-ec-psd-03-2022-03-2023.pdf

32. Canada's drug and health technology agency. (2023). Keytruda CADTH Reimbursement Recommendation [CADTH PC0280-000]. https://www.cadth.ca/sites/default/files/DRR/2023/PC0280%20Keytruda%20-%20Final%20CADTH%20Recommendation.pdf
33. Institute for Quality and Efficiency in Health Care. (2022). Pembrolizumab (endometrial carcinoma) – Benefit assessment according to §35a Social Code Book V. [A22-76] URL: https://www.iqwig.de/download/a22-76_pembrolizumab_extract-of-dossier-assessment_v1-0.pdf
34. Pharmaceutical Benefits Advisory Committee. (2023). Public Summary Document (PSD) November 2023 PBAC Meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/pembrolizumab-ec-psd-03-2022-03-2023.pdf
35. Pharmaceutical Benefits Advisory Committee. (2020). Public Summary Document (PSD) November 2020 PBAC Meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-07/files/bevacizumab-psd-july-2020.pdf
36. National Institute for Health and Care Excellence. (2022). Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [NICE Guideline TA779]. www.nice.org.uk/guidance/ta779.
37. Canada's drug and health technology agency. (2022). Jemperli CADTH Reimbursement Recommendation [CADTH PC0263-000]. https://www.cadth.ca/sites/default/files/DRR/2022/PC0263%20Jemperli%20-%20CADTH%20Final%20Recommendation_JH_SC-meta.pdf
38. Institute for Quality and Efficiency in Health Care. (2021). Dostarlimab (endometrial carcinoma) – Benefit assessment according to §35a Social Code Book V. [A21-84] URL: https://www.iqwig.de/download/a21-139_dostarlimab_addendum-to-commission-a21-84_v1-0.pdf
39. Paraplatin (carboplatin) [package insert]. Princeton, NJ : Bristol-Myers Squibb Company; 2010.
40. Cispatin (cisplatin) [package insert]. Paramus, NJ: WG Critical Care, LLC; 07652; 2019.
41. Ifex (ifosfamide) [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2012.
42. Taxotere (docetaxel) [package insert]. Bridgewater, NJ 08807: Sanofi-Aventis U.S. LLC; 2020.

43. Taxol (paclitaxel) [package insert]. Princeton, NJ : Bristol-Myers Squibb Company; 2011.
44. Mirena (levonorgestrel intrauterine device) [package insert]. Whippany, NJ 07981. 10977: Bayer HealthCare Pharmaceuticals Inc.; 2022.
45. Medroxyprogesterone acetate (Medroxyprogesterone acetate) [package insert]. New York, NY 10017: Pfizer Inc.; 2007.
46. Megestrol acetate (megestrol acetate) [package insert]. Chestnut Ridge, N.Y. 10977: Par Pharmaceutical, Inc.; 2023.
47. Nolvadex (tamoxifen) [package insert]. Wilmington, Delaware 19850-5437: AstraZeneca Pharmaceuticals LP; 2021.
48. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ 08889: MSD International GmbH; 2020.
49. Doxorubicin hydrochloride injection (doxorubicin hydrochloride) [package insert]. New York, NY 10017: Pfizer Inc.; 2020.
50. Lenvima (lenvatinib) [package insert]. Woodcliff Lake, NJ 07677: Eisai Inc.; 2021.
51. Avastin (bevacizumab) [package insert]. South San Francisco, CA 94080-4990: Genentech, Inc.; 2011.
52. Herceptin (trastuzumab) [package insert]. South San Francisco, CA 94080-4990: Genentech, Inc.; 2010.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

1. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:

Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.

Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.

Gender Edit: Exemestane in Endometriosis should be used only by Females.

Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose

Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after: First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR

Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

2. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

3. What information are available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

4. Drug interactions

1. A: No known interaction
2. B: No action needed
3. C: Monitor therapy
4. D: Consider therapy modification
5. X: Avoid combination

6. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

7. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

1. **Level of Evidence Adopted:**

Grade of research[1]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Endometrial Cancer guideline search:

Query	Sort By	Filters	Search Details	Results
(((((Endometrial Neoplasms[Title/Abstract]) OR (Endometrial Neoplasms[MeSH Major Topic])) OR (endometrial cancer[MeSH Major Topic])) OR (endometrial carcinoma[Title/Abstract])) OR (endometrial carcinoma[MeSH Major Topic])) OR (endometrial cancer[Title/Abstract])		Guideline, in the last 5 years	("endometrial neoplasms"[Title/Abstract] OR "endometrial neoplasms"[MeSH Major Topic] OR "endometrial neoplasms"[MeSH Major Topic] OR "endometrial carcinoma"[Title/Abstract] OR "endometrial neoplasms"[MeSH Major Topic] OR "endometrial cancer"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	29

Appendix D. Treatment Algorithms

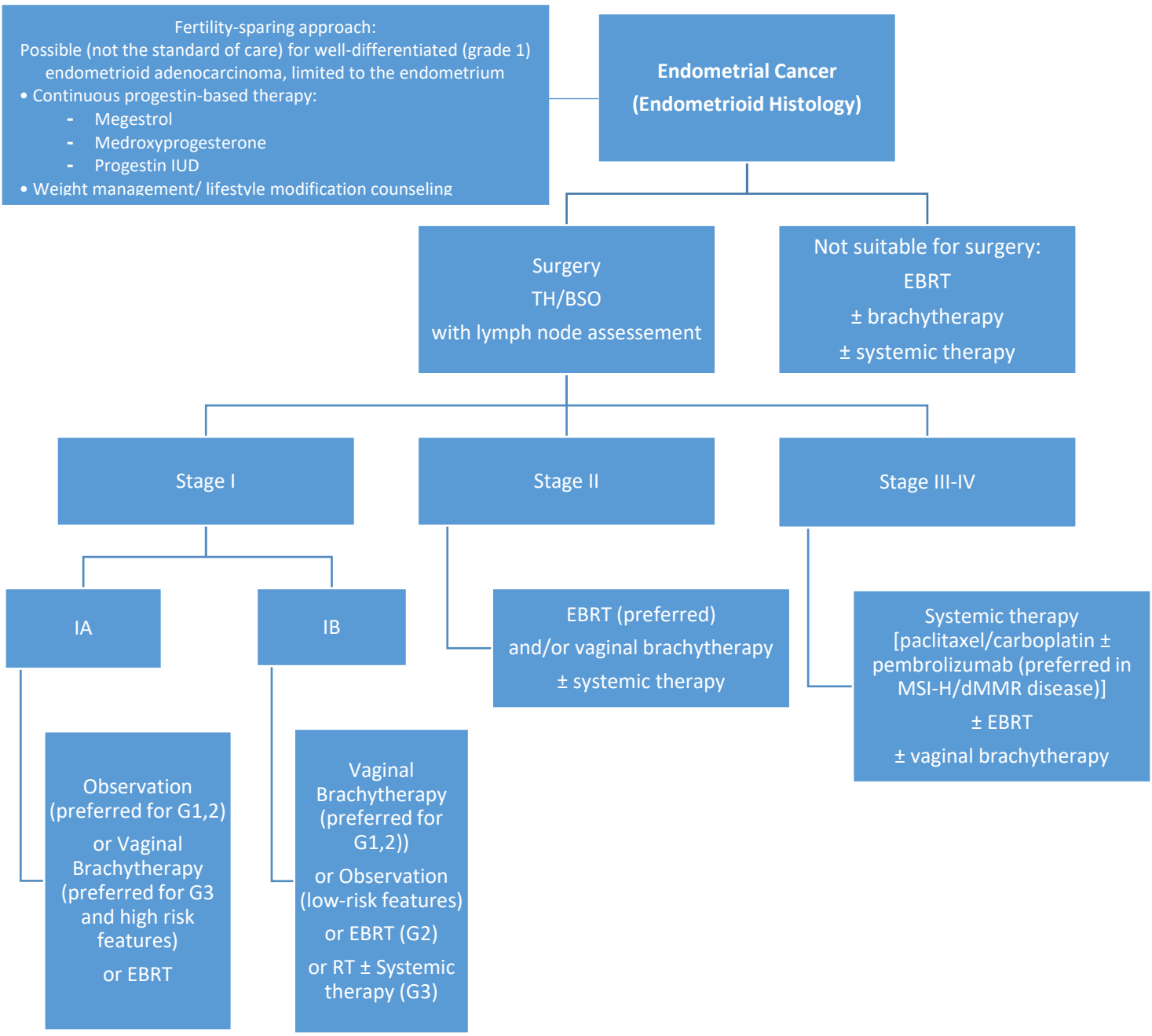


Figure 13. Management of Endometrial Cancer (Endometrioid Histology)

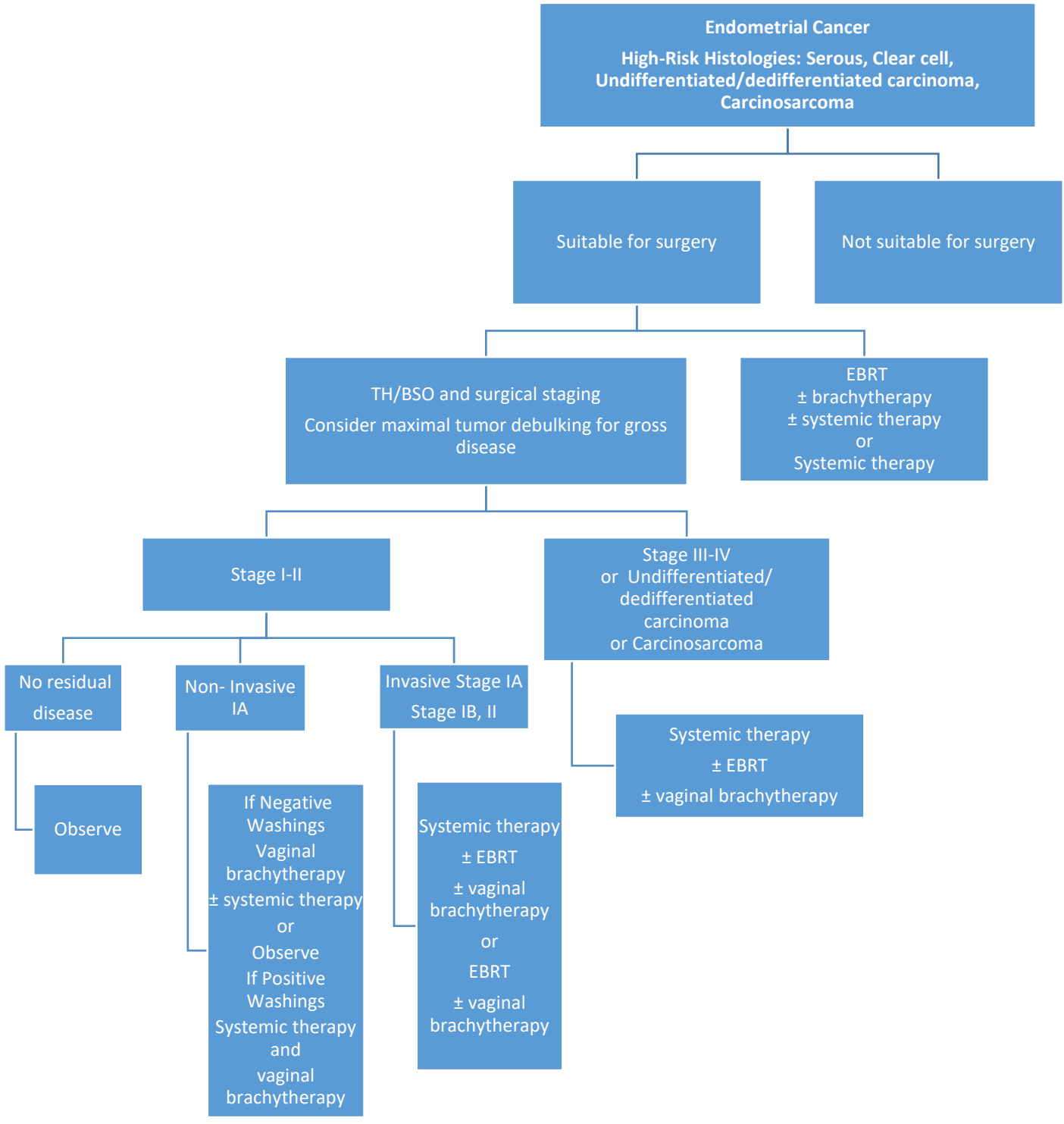


Figure 14. Management of Endometrial Cancer (High-Risk Histologies)

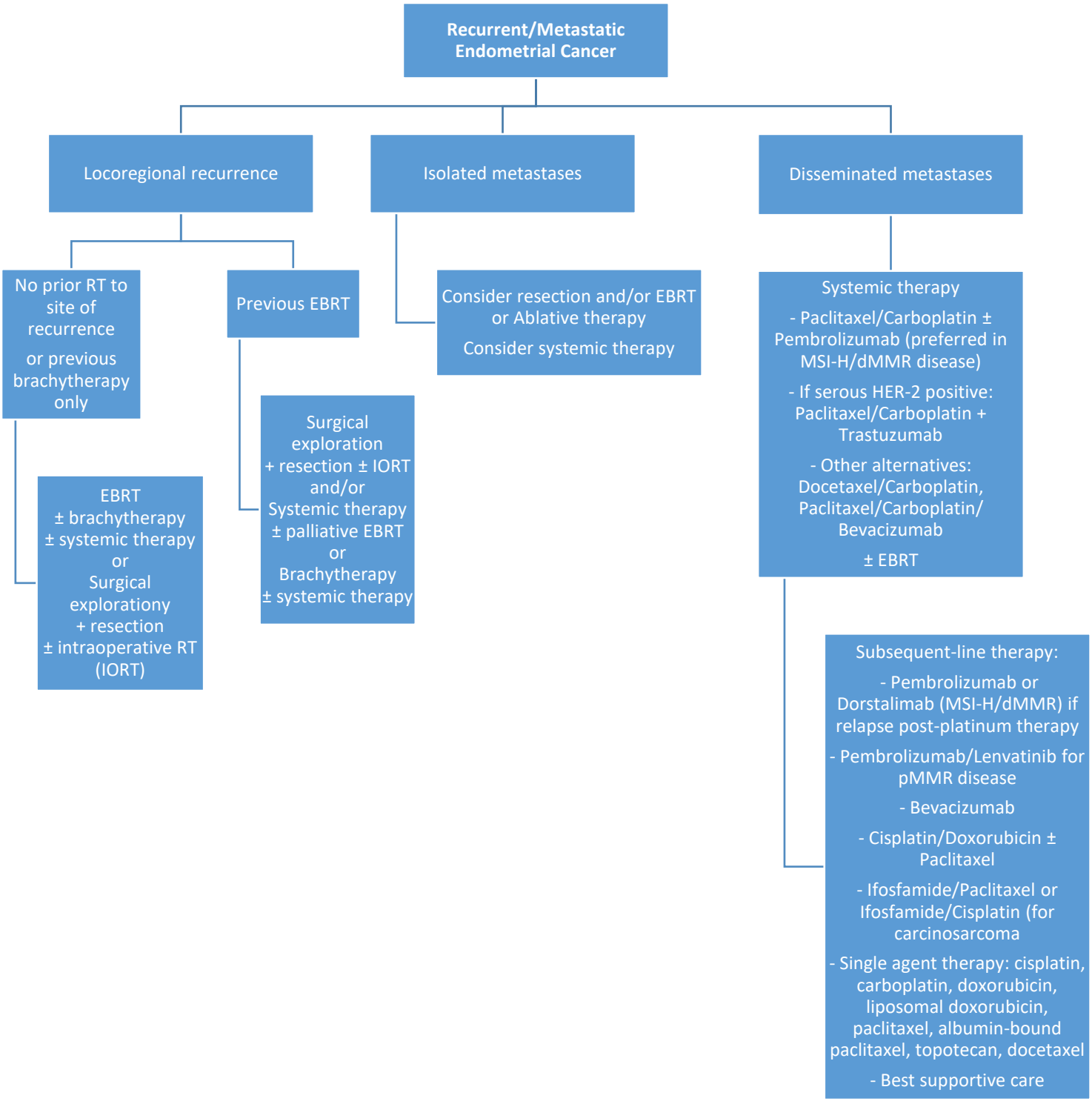


Figure 15. Management of Recurrent/Metastatic Endometrial Cancer