OVARIAN CANCER

CHI Formulary Development Project

مجلس الضمان الصحي
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Contents

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Abbreviations

AUC	Area Under the Curve
ASCO	American Society of Clinical Oncology
BSO	Bilateral Salpingo Oophorectomy
CA	Cancer Antigen
CADTH	Canadian Agency for Drugs and Technologies in Health
CCC	Clear Cell Carcinoma
CEA	Carcinoembryonic Antigen
CHI	Council of Health Insurance
CrCl	Creatinine Clearance
CT	Computed Tomography
dMMR	Mismatch Repair Deficient
EOC	Epithelial Ovarian Carcinoma
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
GI	Gastro-Intestinal
GFR	Glomerular Filtration Rate
HAS	Haute Autorite de Sante
HGSC	High Grade Serous Carcinoma
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HR	Hazard Ratio
HrQoL	Health-Related Quality of Life
HRD	Homologous recombination deficiency
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDF	Insurance Drug Formulary
IDS	Interval Debulking Surgery
IQWIG	Institute for Quality and Efficiency in Health Care
IP	Intraperitoneal
IV	Intravenous
JSGO	Japan Society of Gynecologic Oncology
KSA	Kingdom of Saudi Arabia
LCOC	Less Common Ovarian Tumors
LGSC	Low-grade serous carcinoma
MAPK	Mitogen-Activated Protein Kinase

MC	Mucinous Carcinoma
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability High
NACT	Neo-Adjuvant Chemotherapy
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PARPi	poly(ADP-ribose) polymerase inhibitor
PBAC	Pharmaceutical Benefits Advisory Committee
PFS	Progression-Free Survival
PD	Peritoneal Dialysis
PDS	Primary Debulking Surgery
PLD	Pegylated Doxorubicin
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
SFDA	Saudi Food and Drug Authority
TNM	Tumor, Node, Metastasis
TMBH	Tumor Mutational Burden High

Executive Summary

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's 5th most common cause of cancer death in females[1]. The average age at diagnosis of ovarian cancer in the United States is 63 years old[2]. The age at diagnosis is younger among patients with a hereditary ovarian cancer syndrome (breast cancer susceptibility [*BRCA*] gene mutations or Lynch syndrome). The lifetime risk of developing ovarian cancer is approximately 1%[1]. Five-year survival is about 49%, although survival is longer for select patients with early-stage disease and certain histological subtypes[1]. Approximately half of patients have distant disease at presentation. In 2020, ovarian cancer accounted for an estimated 314,000 new cancer cases and 207,000 deaths worldwide[3].

Ovarian neoplasms consist of several histopathologic entities, with **epithelial ovarian cancer (EOC)** accounting for most malignant ovarian neoplasms (about 90%). Subtypes include high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinoma. The remainder arise from other ovarian cell types (germ cell tumors, sex cord-stromal tumors)[4].

Clinical presentation – The clinical presentation of EOC may be acute (e.g., pleural effusion, bowel obstruction), sub-acute (e.g., pelvic and abdominal symptoms), or in some cases, found incidentally during examination, imaging, or surgery for another indication (e.g., adnexal mass, occult fallopian tube carcinoma after salpingectomy)[5].

Diagnostic evaluation – Evaluation of patients with features suggestive of EOC is typically a multi-phase process and includes[6]:

- An initial evaluation, including physical examination, imaging (typically pelvic ultrasound), and laboratory studies to determine whether an adnexal mass and/or serum biomarker are present.
- Subsequent evaluation, including further imaging (e.g., CT or MRI) and possible fluid or tissue sampling to exclude metastatic disease, an extraovarian (or extratubal) primary cancer, or a synchronous endometrial cancer.
- Surgical evaluation for removal of the intact specimen, histologic diagnosis, and staging.
- Complete blood count, chemistry profile with liver function tests, CA-125 or other tumor markers as clinically indicated; Evaluation of performance status and nutritional status; Obtaining family history.

Diagnosis – EOC is a histologic diagnosis. For most patients, tissue is obtained during surgical removal of an ovary or fallopian tube. Less commonly, the diagnosis is based on tissue or fluid obtained via image-guided biopsy (e.g., omental or pleural biopsy), paracentesis, or thoracentesis[5].

- Image-guided biopsy of the ovary is **not** recommended.
- The differential diagnosis typically depends on the presence or absence of an adnexal mass and/or peritoneal carcinomatosis. If an adnexal mass is present, the differential diagnosis includes both benign and malignant conditions.
- All patients with a diagnosis of EOC, irrespective of their family history, should have testing for hereditary cancer syndromes (e.g., *BRCA1* or *BRCA2,* Lynch syndrome).

Prognosis – Major prognostic factors associated with improved outcomes among patients with resected EOC include younger age, low volume of residual disease, good performance status, and serous histology.

Treatment

A. Primary Treatment

These recommendations are primarily based on data from patients with the most common subtypes—**high-grade serous and grade 2 and 3 endometrioid carcinoma**; treatment for less common ovarian cancers will be discussed separately in section C.

Primary treatment for presumed ovarian, fallopian tube, or primary peritoneal cancer usually consists of appropriate **surgical staging** and **debulking surgery**, followed in most (but not all) patients by **systemic chemotherapy**[6–10].

- Ovarian cancer is staged according to the joint 2017 **International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Node, Metastasis (TNM)** classification system[6–10].
- An open laparotomy is recommended for most patients, but minimally invasive techniques may be appropriate in certain circumstances.
- For some patients with early-stage disease, surgery alone (followed by observation) may be sufficient as primary treatment.
- For certain histologic subtypes, adjuvant therapy with hormonal agents are options that may be considered.
- Neo-adjuvant chemotherapy (NACT) with interval debulking surgery (IDS) should be considered in patients with advanced-stage ovarian cancer who are not good candidates for upfront primary debulking surgery (PDS) due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced[6–10].

A.1. Surgery

- For most patients presenting with suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, initial surgery should include a **hysterectomy** (if uterus present) and bilateral salpingo-oophorectomy **(BSO)** with comprehensive staging and debulking as indicated[6–10].
- This is the recommended approach for stage IA–IV if optimal cytoreduction appears feasible, the patient is a surgical candidate, and fertility is not a concern.
- For patients with early-stage disease who wish to preserve fertility, less extensive surgery may be an option.
- **NACT with IDS** should be considered for patients with advanced-stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced[6–10].
- Patients treated with NACT and IDS should also receive **postoperative adjuvant chemotherapy**[6–10].

A.2. Management after Primary Surgery

- Most patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer should receive **adjuvant systemic chemotherapy** after primary surgery[6–10].
- Postoperative **observation** is an option for select patients with **stage I disease**, depending on cancer histologic type and substage (i.e., grade 2 endometrioid, Stage IA-IB). This approach is only possible in patients who have had resection of all disease and complete surgical staging to rule out the possibility of clinically occult disease that would result in upstaging[6–10].
- Several options are possible for postoperative treatment (within 6 weeks) in patients with advanced epithelial cancers: platinum-based intravenous (IV) chemotherapy, platinum-based intravenous/intraperitoneal (IV/IP) chemotherapy, and platinum-based IP chemotherapy plus bevacizumab[6–10].
- The recommended options for platinum-based IV chemotherapy to treat stage II–IV epithelial disease are: **paclitaxel (175 mg/m²)/carboplatin [Area Under the curve (AUC) 5-6] (every 3 weeks)** (preferred), **paclitaxel (60 mg/m²)/carboplatin (AUC 2) (weekly)**, **dose-dense paclitaxel (80 mg/m²) Days 1, 8, and 15 + carboplatin AUC 5–6 Day 1 (every 3 weeks)**, **carboplatin/liposomal doxorubicin**, **docetaxel/carboplatin** (Recommendation Level A, Evidence Level II)[6–10].
- Based on results from GOG-0218 and ICON7, the international guidelines include **bevacizumab-containing regimens** as options for first-line chemotherapy following cytoreductive surgery

(**carboplatin/paclitaxel/bevacizumab**, followed by **bevacizumab maintenance**) for patient with **Stage II and higher disease**[6–10].

- **Intravenous/Intraperitoneal (IV/IP) chemotherapy** is a treatment option for patients with **optimally debulked (<1 cm residual) stage III disease** (Recommendation Level A, Evidence Level II)[6–10].
    - The NCCN guidelines note that patients with optimally debulked stage II disease may also receive IP chemotherapy, as the panel has decided that many of the regimens tested in stage III–IV should also be offered to patients with stage II disease[5].
    - The IV/IP protocol consists of **Paclitaxel 135 mg/m² as a continuous infusion over 3 or 24 hours on Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m² IP Day 8** (Recommendation Level A, Evidence Level II)[6–10].
- Adjuvant therapy options for **patients >70 years and those with comorbidities** include carboplatin AUC 5 (single agent), paclitaxel (135 mg/m²)/carboplatin (AUC 5) every 3 weeks, paclitaxel (60 mg/m²)/carboplatin (AUC 2) weekly (Recommendation Level A, Evidence Level II)[6–10].

A.3. Neoadjuvant Chemotherapy

- For advanced-stage epithelial ovarian cancer, including fallopian tube and primary peritoneal cancers, the best outcomes have been observed in patients whose primary treatment included **complete resection of all visible disease** and **combination chemotherapy**[6–10].
- For most patients presenting with suspected advanced-stage malignant ovarian, fallopian tube, or primary peritoneal cancer, initial surgery should include a hysterectomy and BSO with comprehensive staging and debulking as indicated.
- PDS is the recommended approach for advanced-stage disease if the patient is a surgical candidate, optimal cytoreduction (residual disease <1 cm [R1] and preferably removal of macroscopic disease [R0]) appears feasible, and fertility is not a concern.
- **NACT with IDS** should be considered for patients with **advanced-stage disease who are not good candidates for PDS** due to advanced age, frailty, poor performance status, comorbidities, or disease that is unlikely to be optimally cytoreduced[6–10].
- Neoadjuvant therapy should be considered for patients with **bulky disease** that is unlikely to be optimally cytoreduced by up-front surgery.
- A wide variety of platinum-based regimens have been used in clinical trials testing NACT plus IDS and postoperative chemotherapy: **paclitaxel (175 mg/m²)/carboplatin (AUC 5-6) (every 3 weeks)** (preferred), **paclitaxel (60 mg/m²)/carboplatin (AUC 2) (weekly)**, **dose-dense paclitaxel (80 mg/m²)**

Days 1, 8, and 15 + carboplatin AUC 5–6 Day 1 (every 3 weeks), **carboplatin/liposomal doxorubicin**, **docetaxel/carboplatin** (Recommendation Level A, Evidence Level II)[6–10].

- After 3 to 4 cycles of NACT, patients should be evaluated to determine the likelihood of optimal cytoreduction[6–10].
    - For patients whose disease responded to NACT and are likely to have optimal cytoreduction, IDS with completion hysterectomy/BSO and cytoreduction should be performed.
    - Those with stable disease after 3 to 4 cycles of NACT can consider IDS (with completion hysterectomy/BSO, and cytoreduction), but also should consider either 1) switching to treatment for persistent/recurrent disease; or 2) treatment with additional cycles of NACT (to a total of ≥6 cycles), then re-evaluating to determine whether to perform IDS (with completion hysterectomy/BSO, and cytoreduction) or switch to therapy for persistent/recurrent disease; The option to continue on beyond 6 cycles is usually reserved for those who are tolerating therapy and have signs that a response may be achieved, such as those whose CA-125 is continuing to fall.
    - Patients who experience disease progression during NACT should switch to therapy for persistent/recurrent disease[6].
- Regardless of the number of cycles of NACT received, IDS should always be followed by **adjuvant chemotherapy**. For all patients who undergo NACT plus IDS, a minimum of **6 cycles** of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS. Patients with stable disease who are tolerating therapy may continue past 6 cycles[6–10].

A.4. Hyperthermic Intraperitoneal Chemotherapy at the Time of IDS

- Hyperthermic intraperitoneal chemotherapy (HIPEC) is a technique in which chemotherapy is delivered in a heated solution perfused throughout the peritoneal space.
- HIPEC is a treatment option to consider at the time of IDS in patients with stage III disease treated with NACT for patients who have response or stable disease after NACT (3 cycles preferred, but 4–6 allowed)[6].
- All patients treated with NACT and IDS (± HIPEC) should receive postoperative chemotherapy.
- The HIPEC chemotherapy agent is **cisplatin, 100 mg/m²** (Recommendation Level A, Evidence Level II)[6].

A.5. Maintenance Options After First-Line Chemotherapy

- For patients who have completed primary surgery and systemic therapy, the recommended options for the treatment of patients who have completed primary therapy include:

- **Stage I disease**: observation (Recommendation Level A, Evidence Level II)[6–10].
- **Stage II-IV disease**:

- *BRCA 1/2 mutated*[6–10]*:*
  - Observation (Recommendation Level A, Evidence Level II)
  - **Olaparib** (Recommendation Level A, Evidence Level I)
  - **Bevacizumab + Olaparib** (Recommendation Level A, Evidence Level I; in patients who received bevacizumab with chemotherapy)
  - **Niraparib** (Recommendation Level A, Evidence Level I)
  - **Rucaparib** (Recommendation Level A, Evidence Level II)
- *BRCA status wild-type or unknown*[6–10]*:*
  - Observation (Recommendation Level A, Evidence Level II)
  - Bevacizumab + Olaparib for patients with genomic instability (Recommendation Level A, Evidence Level II)
  - Niraparib (Recommendation Level A, Evidence Level II)
  - Rucaparib (Recommendation Level A, Evidence Level I)

Certain patients with **newly diagnosed stage II–IV disease** (high-grade serous, grade 2/3 endometrioid, or BRCA1/2-mutated clear cell carcinoma or carcinosarcoma) may benefit from **maintenance therapy with PARP inhibitors** (PARPi) if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. Data are limited for use of maintenance PARPi post primary treatment in patients with stage II disease and for those with less common ovarian tumors (LCOC)[6].

Certain patients with **recurrent disease** may benefit from maintenance therapy with PARPi after recurrence therapy, if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARPi[6].

B. Recurrent Disease

- **Platinum-based combination chemotherapy** is recommended (Recommendation Level A, Evidence Level I) for a total of **6 cycles** for **platinum-sensitive recurrence**[6–10].
- For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred **single agent** is **carboplatin** or **cisplatin** (Recommendation Level A, Evidence Level II)[6–10].
- **Preferred combinations** for **platinum-sensitive recurrent disease** include: carboplatin/paclitaxel (Recommendation Level A, Evidence Level I), carboplatin/liposomal doxorubicin (Recommendation Level A, Evidence Level I), carboplatin/weekly paclitaxel (Recommendation Level A, Evidence Level II), carboplatin/albumin-bound paclitaxel (for taxane hypersensitivity)

(Recommendation Level A, Evidence Level II), carboplatin/docetaxel (Recommendation Level A, Evidence Level II), carboplatin/gemcitabine (which has been shown to improve PFS) (Recommendation Level A, Evidence Level II), cisplatin/gemcitabine (Recommendation Level A, Evidence Level II), or carboplatin/gemcitabine/bevacizumab (Recommendation Level A, Evidence Level II)[6–10].

- For **platinum-resistant disease**, **non-platinum–based agents** or regimens are preferred (i.e., docetaxel, oral etoposide, gemcitabine, weekly paclitaxel with or without pazopanib, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel/bevacizumab, topotecan with or without bevacizumab) (Recommendation Level A, Evidence Level II); sequential therapy using single agents is typically used[6–10].
- **Other potentially active agents** include capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), pemetrexed, and vinorelbine (Recommendation Level A, Evidence Level II)[6–10].
- **Immunotherapy drugs** including pembrolizumab and dorstarlimab are mentioned in the NCCN guidelines as treatment options for patients with recurrent disease with MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥ 10 mutations/megabase (platinum sensitive or resistant) (Recommendation Level A, Evidence Level II)[6,11].
- **Targeted therapy options** are also mentioned for recurrent disease (platinum sensitive or resistant) (Recommendation Level A, Evidence Level II)[6]:
    - Dabrafenib + trametinib (for BRAF V600E-positive tumors)
    - Entrectinib or larotrectinib (for NTRK gene fusion-positive tumors
    - Selpercatinib (for RET gene fusion-positive tumors)

C. Less Common Ovarian Cancers

C.1 Clear Cell Carcinoma

- Clear cell carcinomas are considered high-grade tumors. Most clear cell carcinomas are negative for WT1 and estrogen receptors.
- Primary treatment for these patients includes completion **surgery** with comprehensive **staging** followed by **postoperative therapy**[6–10]. Fertility-sparing surgery is not recommended for stage IA to C clear cell carcinomas. Lymphadenectomy has been shown to improve survival.
- For patients with *stage IA to IC disease*, recommended postoperative treatment is the **standard IV taxane-carboplatin regimens** (with paclitaxel or docetaxel) used for high-grade serous ovarian cancer[6–10].

- For patients with *stage II to IV* clear cell carcinoma, postoperative treatment is **standard regimens used for epithelial ovarian cancer** (e.g., IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin).
- Patients with advanced clear cell carcinoma have a poor prognosis.
- Data suggests that **6 or 3 cycles** of postoperative chemotherapy are equivalent for patients with clear cell carcinoma[6–10].

C.2 Mucinous Carcinoma

- Mucinous tumors are unusual because they may be very large cystic masses that may fill the abdomen and pelvis; this presentation often suggests mucinous histology.
- Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year DFS is about 80% to 90%.
- Primary treatment for these patients includes completion **surgery** with comprehensive **staging** followed by **postoperative therapy** or **observation**[6–10].
- An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors.
- The additional workup includes a **gastro-intestinal (GI) tract evaluation and carcinoembryonic antigen (CEA) level** for patients with mucinous histology to determine whether patients have either occult GI primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries[6].
- Postoperative **observation** and **monitoring** are recommended for patients with **stage IA or IB** mucinous tumors because most of these tumors are benign or borderline.
- For patients with **stage IC mucinous carcinomas**, postoperative options include: 1) **observation**; 2) **IV carboplatin with either paclitaxel or docetaxel**; 3) **5-FU/leucovorin/oxaliplatin** (GI regimen); or 4) **capecitabine/oxaliplatin** (GI regimen) (Recommendation Level A, Evidence Level II)[6–10].
- Some clinicians find the GI regimens appropriate because mucinous carcinomas of the ovary are similar to GI tumors[6].
- For patients with **stages II to IV mucinous carcinomas**, postoperative options include: 1) **chemotherapy** using the regimens for **epithelial ovarian cancer** (e.g., **IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin**); 2) **5-FU/leucovorin/oxaliplatin** (GI regimen); or 3) **capecitabine/oxaliplatin** (GI regimen) (Recommendation Level A, Evidence Level II)[6].

- Recommendations for **recurrence** therapy for mucinous carcinomas include: 1) **5-FU/leucovorin/oxaliplatin with or without bevacizumab** (Recommendation Level B, Evidence Level II for bevacizumab); or 2) **capecitabine/oxaliplatin** (Recommendation Level A, Evidence Level II)[6].

C.3 Low-Grade Serous Carcinoma (LGSC)

- Low-grade serous carcinoma is a subtype of serous carcinoma that is considered pathologically distinct from the more commonly diagnosed high-grade serous carcinoma and represents less than 5% of epithelial ovarian cancers.
- Activating mutations in the mitogen-activated protein kinase (MAPK) pathway are frequently identified in low-grade, but not high-grade, serous carcinomas.
- Primary treatment for low-grade serous carcinomas is comprised of completion **surgery** with comprehensive **staging**, followed by **adjuvant therapy** or **observation**[6–10].
- Low-grade serous carcinomas often **respond poorly to chemotherapy** compared with high-grade serous carcinomas; therefore, neoadjuvant chemotherapy is less favored for patients with low-grade serous carcinoma[6].
- Postoperative observation is an option for patients with stage IA and IB disease (Recommendation Level A, Evidence Level II) and for those with stage IC disease (Recommendation Level B, Evidence Level II)[6].
- Several adjuvant systemic therapy options, including **paclitaxel/platinum-containing regimens**, are recommended for patients with stage IC or stage II–IV disease, although there are limited data on systemic therapy regimens in patients with low-grade serous carcinoma in general[6].
- Patients with low-grade serous carcinomas may also benefit from **maintenance hormone therapy** following adjuvant chemotherapy, with **letrozole, anastrozole, exemestane, or leuprolide acetate** (Recommendation Level B, Evidence Level II)[6].
- **Adjuvant hormone therapy** is mentioned in the NCCN guidelines as a potential substitute for adjuvant chemotherapy for these patients. However, as there are no supporting prospective data, this is a category 2B recommended option in the guidelines[6].
- Unfortunately, patients with low-grade serous carcinoma, particularly those with advanced stage disease, may experience disease relapse.
    - Secondary cytoreduction can be considered for patients with a long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction.

- Systemic therapy is another option for this patient population; however, the guidelines emphasize that there is no standard sequencing of drugs for recurrent disease.
- Importantly, recent studies have suggested that **MEK inhibitors** have activity in recurrent low-grade serous carcinoma. The NCCN panel recommends trametinib as a category 2A option for patients with recurrent low-grade serous carcinoma[6].
- In June 2022, the U.S. Food and Drug Administration granted accelerated approval to selective **BRAF inhibitor dabrafenib** in combination with trametinib for the treatment of adult and pediatric patients (6 years and older) with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options[6].

Post-treatment evaluation and surveillance – Following the completion of treatment, a post-treatment evaluation is performed with a history, physical (including pelvic) exam, and cancer antigen (CA) 125. Imaging such as CT of the chest, abdomen, and pelvis may be utilized as needed, especially in those with a non-informative CA 125 marker. Following the documentation of a response, patients are monitored serially with physical examination and tumor marker studies. Recurrence can be detected either serologically using tumor markers (e.g., CA 125) and/or by the development of clinical or radiologic signs of progression. For women who have completed initial chemotherapy, we recommend retreatment based on signs and/or symptoms of relapsed EOC, not based on a rising CA 125 alone[6–10].

With a median age at diagnosis of 51 years, ovarian cancer ranked **7th in incidence among Saudi females**, and accounted for 3% of all newly diagnosed cases reported in 2013[12]. In 2020, 444 new cases of ovarian cancer were diagnosed in Saudi Arabia, raking **19th most common cancer**, and accounting for 1.6% of all new cancer cases[3]. Ovarian cancer was correlated with **281 deaths in KSA in 2020**, with a **5-year prevalence of 1357 cases (9.24 cases per 100,000)**[8].

This report compiles all clinical and economic evidence related to ovarian cancer according to the relevant sources. The ultimate objective of issuing ovarian 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 ovarian 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-analyses.

The management of ovarian cancer involves a **multidisciplinary approach** and greatly differs based on the stage of the disease. There are currently **multiple treatment regimen options for the management of ovarian cancers on the global market**. KSA has access to most of them; two of the PARP inhibitors,

niraparib and rucaparib, the immunotherapy agent dorstarlimab, and the MEK inhibitor trametinib, are not yet registered by the Saudi Food and Drug Authority (SFDA). Section 2 provides a full description of each with final statements on the placement of 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 management of ovarian cancer. Section 3 lists the key recommendations synthesis for ovarian cancer treatment.

Major recommendations for suggested drug therapies are summarized in the table below[6–10]:

Table 1. Treatment Options for the Management of Ovarian Cancer

Management of Ovarian Cancer				
Medication/ Protocol	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
Paclitaxel	First and second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer (preferred)	**1st, 2nd**	A	II
Carboplatin	First and second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer (preferred)	**1st, 2nd**	A	II
5-FU	First-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer used for mucinous carcinoma (stage IC) histology (preferred)	**1st**	A	II
Oxaliplatin	First-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer [preferred for mucinous carcinoma (stage IC)] Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	A	II
Capecitabine	First-line treatment of epithelial ovarian/fallopian tube/primary	**1st, 2nd**	A	II

	peritoneal cancer used for mucinous carcinoma (stage IC) histology (preferred) Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer			
Liposomal Doxorubicin	First and second-line (preferred for platinum resistant disease) treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	A	II
Docetaxel	First and second-line (preferred for platinum resistant disease) treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	A	II
Bevacizumab	First (preferred for Stage II–IV Disease) and second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	A	II
Ifosfamide	First-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer [used only in carcinosarma] Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	A	II

Aromatase Inhibitors (Anastrozole, Letrozole, Exemestane)	First-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer [used in Low-grade serous (stage IC)/Grade I endometrioid (stage IC)] (preferred) Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	B	II
Other hormone therapy (Leuprolide acetate, Tamoxifen, Fulvestrant)	First-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer [used in Low-grade serous (stage IC)/Grade I endometrioid (stage IC)] Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**1st, 2nd**	B	II
Gemcitabine	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer (preferred)	**2nd**	A	II
Irinotecan	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II
Melphalan	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II

Pemetrexed	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II
Topotecan	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer (preferred for platinum resistant disease)	**2nd**	A	II
Albumin-bound paclitaxel	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II
Vinorelbine	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II
Cyclophosphamide (oral, IV)	Second-line treatment of platinum resistant epithelial ovarian/fallopian tube/primary peritoneal cancer (oral: preferred)	**2nd**	A	II
Etoposide (oral)	Second-line treatment of platinum resistant epithelial ovarian/fallopian tube/primary peritoneal cancer (preferred)	**2nd**	A	II
Sorafenib	Second-line treatment of platinum resistant epithelial ovarian/fallopian tube/primary peritoneal cancer (platinum resistant)	**2nd**	B	II

PARP Inhibitors (Niraparib, Olaparib, Rucaparib)	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	C	III
Pazopannib	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	B	II
Megestrol acetate	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer	**2nd**	A	II
Pembrolizumab	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer in patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/Mb	**2nd**	A	II
Dabrafenib + Trametinib	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer in patients with BRAF V600E-positive tumors	**2nd**	A	II
Trametinib	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer in patients with low grade serous carcinoma	**2nd**	A	II
Entrectinib Larotrectinib	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer in patients with NTRK gene fusion positive tumors	**2nd**	A	II

Selpercatinib	Second-line treatment of epithelial ovarian/fallopian tube/primary peritoneal cancer in patients with RET gene fusion-positive tumors	**2nd**	A	II

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in ovarian 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 (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

HTA recommendations were found for olaparib and bevacizumab in ovarian cancer (cf. section 2).

All HTA organisms **support the reimbursement of olaparib** for the **maintenance** treatment of patients with **newly diagnosed**, **advanced (FIGO stages 3 and 4), BRCA-mutated**, high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are **in response (complete or partial) to first-line platinum-based chemotherapy**.

- Patients must have received at least **four cycles** of their most recent platinum-based chemotherapy. Maintenance therapy with olaparib should begin **within eight weeks** of the last dose of platinum-based chemotherapy.
- There is a **net clinical benefit** of olaparib maintenance treatment compared with placebo, based on a statistically significant improvement in PFS, no detrimental effect on quality of life, and a manageable toxicity profile.
- HAS, NICE, and IQWIG support both the use of **olaparib monotherapy** and the **combination of olaparib plus bevacizumab** in this maintenance indication.
- CADTH mentions that a condition for olaparib reimbursement is that **cost-effectiveness should be improved to an acceptable level** through a **reduction in price**. They note that given the high level of uncertainty in the magnitude of long-term overall survival benefit, olaparib is not cost-effective compared with best supportive care.
- CADTH also supports the use of olaparib monotherapy in the maintenance setting of **relapsed BRCA-mutated** high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have completed **at least two previous lines of platinum-based chemotherapy** and are in radiologic response (complete or partial response) to their most recent platinum-based chemotherapy regimen.

However, it is important to note that 2022 saw a wave of FDA regulatory approval removals for PARP inhibitors in the treatment of some patients with ovarian cancer, including *BRCA*-mutated and homologous recombination deficiency (HRD)-positive disease. These removals were prompted by long-term overall survival (OS) data analyses. The ARIEL4 and SOLO3 trials – investigating single-agent PARPi therapy for relapsed *BRCA*-mutated ovarian cancer – both met their

primary endpoints of progression-free survival (PFS). Post-marketing, long-term follow-up of overall survival (OS), requested by the US FDA, revealed hazard ratio (HR) point estimates in favor of comparator treatment for some patients. Voluntary removal of FDA regulatory approval for rucaparib and olaparib in the treatment of **heavily pre-treated *BRCA*-mutated ovarian cancer**, was followed by removals for niraparib in **heavily pre-treated HRD-positive ovarian cancer** and, further, for niraparib and rucaparib as maintenance therapy in patients with non-*BRCA*-mutated, recurrent platinum-sensitive disease[13].

Bevacizumab has received mixed reviews from HAS, NICE, and CADTH in the ovarian cancer indication:

- **HAS recommends the reimbursement** of bevacizumab **in addition to paclitaxel/carboplatin** in the **first line setting of advanced ovarian cancer**, citing however a **modest improvement in PFS without impacting OS**, a minor clinical benefit, and an addition of **adverse events** such as hypertension and gastrointestinal perforations compared to paclitaxel/carboplatin.
- **NICE** on the other hand **doesn't recommend the use of bevacizumab in this setting**, citing that the overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218 because of the uncertainty related to the extent to which patients received bevacizumab after progression. The committee, however, noted that there was an apparent differential response, with little benefit shown in the stage III population with optimally debulked cancer. NICE gave a range of ICERs from £128,000 to £161,000 per QALY gained.
- **NICE** also **doesn't support the reimbursement** of bevacizumab in combination with gemcitabine and carboplatin for the **first recurrence of platinum-sensitive advanced ovarian cancer** (including fallopian tube and primary peritoneal cancer).
- A recent CADTH review of published studies data concluded that **it was not clear** from the studies whether **bevacizumab plus chemotherapy does or does not improve overall survival** compared to chemotherapy alone (or with placebo) for recurrent platinum-sensitive ovarian cancer.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

The Saudi Clinical Management Guidelines for Invasive Epithelial Ovarian Cancer were published in 2018 by the National Cancer Center (NCC) at the Saudi Health Council (SHC)[12].

Tumors were categorized according to the 2014 International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Nodes, Metastasis (TNM) classification system.

A summary of the guidelines is detailed below.

1. Initial presentation:
    a. Perform history and clinical examination including pelvic assessment.
    b. Full blood count, liver, and renal function tests.
    c. CA-125 or other tumor markers as clinically indicated.
    d. Ultrasound of abdomen and pelvis.
    e. Calculate risk of malignancy index[12].
2. Initial oncology assessment if highly suspicious or confirmed diagnosis.
    a. CT scan of the chest, abdomen, and pelvis.
    b. Review of outside pathology and imaging.
    c. BRCA mutation test if available[12].
3. Treatment
    a. Surgery
        i. Should be performed by gynecologic oncologist.
        ii. Early-stage ovarian cancer (stage I)
            1. Staging surgery (laparotomy, laparoscopic or robotic) with the following: unilateral salpingo-oopherectomy or total hysterectomy and bilateral saplingo-oopherectomy (depending on the fertility desire), pelvic, right and left washings for cytology, infracolic omentectomy, multiple peritoneal biopsies (right and left paracolic gutters, anterior and posterior cul-de-sac, mesentery of large and small bowel, right and left diaphragm (this could be replaced by diaphragmatic scrapping), pelvic and para-aortic lymph node

sampling, +/- appendectomy and consider biopsy of any suspicious lesion in the contralateral ovary.

2. Consider unilateral salpingo-oopherectomy (fertility-sparing surgery) with comprehensive staging for stage IA or IC (grade 1+/- grade 2) with unilateral involvement and favorable histology if patient desires fertility.

iii. Advanced stage ovarian cancer (stage II- IV)

1. Perform optimal debulking / cytoreductive surgery with removal of all visible disease (EL-1).
2. Cytoreductive surgery & HIPEC can be considered if available (EL-2).
3. Consider interval debulking after chemotherapy for patients with bulky stage IIIC/IV who are poor surgical candidates due to location and volume of disease or medical comorbidities (EL-1).
4. Poor surgical candidate includes diffuse and/or deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving the stomach and/or large parts of the small or large bowel, infiltration of the duodenum and/or parts of the pancreas (not limited to the pancreatic tail), involvement of the large vessels of the hepatoduodenal ligament, celiac trunk or behind the porta hepatis, bulky high lymph nodes above renal vessels or involvement of the liver parenchyma.

b. Chemotherapy

i. Early-stage ovarian cancer (stage I)

1. Observation for stage IA or IB (grade 1) is recommended.
2. Adjuvant chemotherapy can be considered for stage IA or IB (grade 2), observation is an acceptable alternative.
3. Adjuvant chemotherapy is recommended for stage I grade 3, clear cell by histology, or stage IC to IV.
4. Intravenous paclitaxel 175mg/m2 plus carboplatin AUC 5 or 6 every 3 weeks for 3-6 cycles is recommended (preferably 6 cycles for serous cancer) (EL-1).

ii. Advanced stage ovarian cancer (stage II- IV)

1. For women who undergo optimal cytoreductive surgery, we recommend IV paclitaxel/carboplatin Q3W for 6 cycles (EL-1).

2. Intraperitoneal chemotherapy can be considered for women with optimally debulked stage III ovarian cancer (EL-1).
3. For women who had suboptimal cytoreductive surgery, weekly IV dose dense chemotherapy can be considered as carboplatin AUC 5 or 6 on day 1 plus paclitaxel 80 mg/m2 on days 1, 8 and 15 of 21 days cycle, particularly if histological subtype is not clear cell or mucinous. However, for patients who refuse weekly treatment or those with clear cell or mucinous carcinoma, we suggest IV paclitaxel/carboplatin every 3 weeks (EL-1).
4. Paclitaxel/carboplatin with bevacizumab can be considered for suboptimal debulked stage III and stage IV (EL-1).
5. For elderly patients and/or those with comorbidities, we consider single agent carboplatin or weekly carboplatin AUC 2 plus weekly paclitaxel 60mg/m2 (EL-1).
6. Docetaxel may be substituted for paclitaxel if there is significant neuropathy (EL-1).
7. Liposomal doxorubicin/carboplatin can be considered as an alternative for patients who develop allergy to taxane (EL-1)[12].

4. Follow-up:

   Evaluation includes history and physical examination including pelvic exam, CA-125 or other tumor markers if initially elevated:

   a. Every 3 months for 2 years then every 6 months for 3 years and thereafter annually.
   b. Imaging as clinically indicated (development of new symptoms, signs, or raised tumor markers)[12].

5. Relapse:

   a. Biochemical relapse: observation is recommended for rising CA 12-5 with no evidence of clinical relapse (EL-1).
   b. Platinum-sensitive relapse
      i. Patients who respond to initial platinum-based therapy and have relapse ≥ 6 months after completing chemotherapy.
      ii. Secondary cytoreductive surgery is to be considered if optimal debulking is feasible and the patient is fit (EL-2).

iii. Platinum-based combination therapy is recommended. Acceptable regimens include liposomal doxorubicin /carboplatin, paclitaxel/carboplatin, or gemcitabine/carboplatin (EL-1).

iv. Other regimens that may be considered include paclitaxel/carboplatin, or gemcitabine/carboplatin with bevacizumab (EL-1).

v. For patients with BRCA mutation, a poly-ADP ribose polymerase (PARP) inhibitor is recommended as maintenance therapy (EL-1).

c. Platinum-resistant relapse

i. Patients who don't respond to initial platinum-based therapy or relapse < 6 months after completing chemotherapy.

ii. Single agent chemotherapy rather than combination therapy is recommended.

iii. Acceptable regimens include weekly paclitaxel, liposomal doxorubicin, gemcitabine, oral etoposide, topotecan and docetaxel (EL-1).

iv. Bevacizumab in combination with paclitaxel, liposomal doxorubicin or topotecan is recommended in patients meeting the following criteria: if there is no history of bowel obstruction or evidence of malignant bowel involvement, no prior treatment with bevacizumab, and no more than 2 prior lines of chemotherapy (EL-1).

v. PARP inhibitors are recommended for patients with BRCA mutation who have progressed on multiple prior lines of treatment and not received prior PARP inhibitors (EL-2).

vi. Endocrine therapy can be a reasonable option for patients with disease progression but with little or no symptoms (Tamoxifen or Aromatase inhibitors) (EL-2).

vii. Palliative radiation therapy can be considered to alleviate symptoms in patients with recurrent disease.

viii. Best supportive care is recommended for patients who failed multiple lines of therapy or with poor performance status[12].

1.2 North American Guidelines

Multiple organizations have published guidelines for the management of central nervous system cancers, most notably the National Comprehensive Cancer Network (NCCN) in 2023, and the American Society of Clinical Oncology (ASCO) in 2020. Recommendations from these guidelines are detailed in the following section.

1.2.1 National Comprehensive Cancer Network (NCCN) Version 2.2023

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of ovarian cancer in June 2023, including fallopian tube cancer and primary peritoneal cancer[6]. These recommendations are summarized in the section below.

Table 2. Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

Clinical Stage	Fertility	Primary treatment
IA	Desired	Unilateral salpingo-oophorectomy (USO) + comprehensive surgical staging
IB	Desired	Bilateral salpingo-oophorectomy (BSO) + comprehensive surgical staging
IA-IV	Not desired	Hysterectomy/BSO + comprehensive staging and debulking as needed
Poor surgical candidate	N/A	Neoadjuvant Therapy
Low likelihood of optimal cytoreduction		

Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation, and germline and somatic testing (if not previously done)[6].

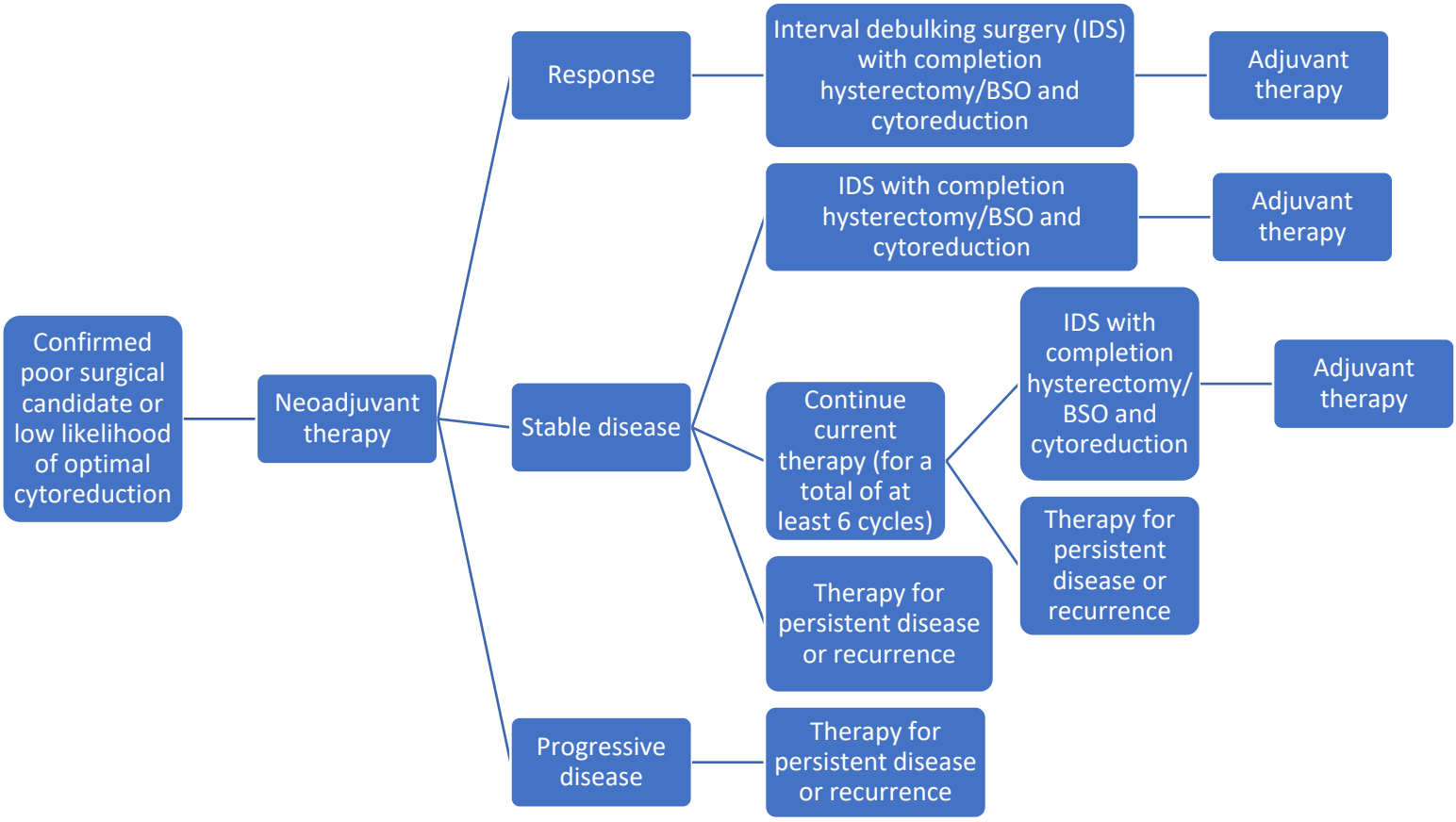

Figure 1. *Primary treatment for primary peritoneal cancer in poor surgical candidates or patients with low likelihood of optimal cytoreduction*

Adjuvant platinum-based chemotherapy is optional for stages IA and IB, and is recommended for stages IC, II, III, and IV[6].

Prior to the initiation of any therapy:

- All patients with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for primary cytoreductive surgery (PCS).
- Patients of childbearing potential who desire fertility-sparing procedures should be referred to an appropriate fertility specialist.
- Goals of systemic therapy should be discussed.

Table 3. Primary Systemic Therapy Regimens for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Primary Therapy for Stage I Disease		
High-grade serous; Endometrioid (grade 2/3); Clear cell carcinoma; Carcinosarcoma		
• Paclitaxel/carboplatin q3weeks	• Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	• Docetaxel/oxaliplatin /bevacizumab + maintenance bevacizumab (for stage IB/IC) For carcinosarcoma: • Carboplatin/ ifosfamide • Cisplatin/ifosfamide • Paclitaxel/ifosfamide (category 2B)
Mucinous carcinoma (stage IC)		
• 5-FU/leucovorin/ oxaliplatin • Capecitabine/ oxaliplatin • Paclitaxel/carboplatin q3weeks	• Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	• Docetaxel/ oxaliplatin/ bevacizumab + maintenance bevacizumab (category 2B)
Low-grade serous (stage IC)/Grade I endometrioid (stage IC)		
• Paclitaxel/carboplatin q3weeks ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B) • Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)	• Carboplatin/liposomal doxorubicin ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B) • Docetaxel/carboplatin ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B) • Hormone therapy (leuprolide acetate, fulvestrant) (category 2B)	• Docetaxel/ oxaliplatin/ bevacizumab + maintenance bevacizumab (category 2B)
Primary Therapy for Stage II–IV Disease		

High-grade serous; Endometrioid (grade 2/3); Clear cell carcinoma; Carcinosarcoma		
• Paclitaxel/carboplatin q3weeks • Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab	• Paclitaxel weekly/carboplatin weekly • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks • Docetaxel/ carboplatin/ bevacizumab + maintenance bevacizumab	• Docetaxel/ oxaliplatin/ bevacizumab + maintenance bevacizumab • IP/IV paclitaxel/cisplatin (for optimally debulked stage II–III disease) For carcinosarcoma: • Carboplatin/ ifosfamide • Cisplatin/ifosfamide • Paclitaxel/ ifosfamide (category 2B)
Mucinous carcinoma		
• 5-FU/leucovorin/ oxaliplatin ± bevacizumab (category 2B for bevacizumab) • Capecitabine/ oxaliplatin ± bevacizumab (category 2B for bevacizumab) • Paclitaxel/carboplatin q3weeks • Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab	• Paclitaxel weekly/carboplatin weekly • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks • Docetaxel/ carboplatin/ bevacizumab + maintenance bevacizumab	• Docetaxel/ oxaliplatin/ bevacizumab + maintenance bevacizumab
Low-grade serous/Grade I endometrioid		
• Paclitaxel/carboplatin q3weeks ± maintenance letrozole (category 2B) or other	• Paclitaxel weekly/carboplatin weekly • Docetaxel/carboplatin ± maintenance	• Docetaxel/ oxaliplatin/ bevacizumab + maintenance

hormonal therapy (category 2B) • Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab • Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)	letrozole (category 2B) or other hormonal therapy (category 2B) • Carboplatin/liposomal doxorubicin ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B) • Paclitaxel weekly/carboplatin q3weeks • Docetaxel/ carboplatin/ bevacizumab + maintenance bevacizumab • Hormone therapy (leuprolide acetate, fulvestrant) (category 2B)	bevacizumab (category 2B)

Table 4. Recommended Dosing Regimens for Primary Systemic Therapy

Primary Systemic Therapy Recommended Dosing	
Paclitaxel/ carboplatin every 3 weeks	Paclitaxel 175 mg/m2 IV followed by carboplatin AUC 5-6 IV on day 1 Repeat every 21 days for 3-6 cycles
IV/IP Paclitaxel/cisplatin	Paclitaxel 135 mg/m2 IV continuous infusion on day 1; cisplatin 75-100 mg/m2 IP on day after IV paclitaxel; paclitaxel 60 mg/m2 IP on day 8 Repeat every 21 days for 6 cycles
Paclitaxel weekly/ carboplatin every 3 weeks	Dose-dense paclitaxel 80 mg/m2 IV on days 1, 8, and 15 followed by carboplatin AUC 5-6 IV on day 1 Repeat every 21 days for 6 cycles
Paclitaxel weekly/ carboplatin weekly	Paclitaxel 60 mg/m2 IV followed by carboplatin AUC 2 IV Days 1, 8, and 15; repeat every 21 days for 6 cycles (18 weeks)
Docetaxel/ oxaliplatin/ bevacizumab +	Docetaxel 75 mg/m2 IV followed by oxaliplatin 85 mg/m2 IV, and bevacizumab 15 mg/kg IV Repeat every 21 days for 6 cycles

maintenance bevacizumab	Continue bevacizumab 15mg/kg IV every 21 days to complete one year of therapy
Docetaxel/ carboplatin	Docetaxel 60-75 mg/m2 IV followed by carboplatin AUC 5-6 IV on day 1 Repeat every 21 days x 3-6 cycles
Carboplatin/ liposomal doxorubicin	Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m2 IV Repeat every 28 days for 3-6 cycles
Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab (ICON-7)	Paclitaxel 175 mg/m2 IV followed by carboplatin AUC 5-6 IV, and bevacizumab 7.5 mg/kg IV on day 1 Repeat every 21 days for 5-6 cycles Continue bevacizumab for up to 12 additional cycles
Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab (GOG-218)	Paclitaxel 175 mg/m2 IV followed by carboplatin AUC 6 IV on day 1 Repeat every 21 days for 6 cycles Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 22 cycles
Docetaxel/ carboplatin/ bevacizumab + maintenance bevacizumab (GOG-218)	Docetaxel 75 mg/m2 IV followed by carboplatin AUC 6 IV on day 1 Repeat every 21 days for 6 cycles Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 22 cycles
Individuals Over the Age of 70 Years and/or Those with Comorbidities	
Paclitaxel 135/ carboplatin	Paclitaxel 135 mg/m2 IV followed by carboplatin AUC 5 IV on day 1 Repeat every 21 days for 3-6 cycles
Paclitaxel weekly/ carboplatin weekly	Paclitaxel 60 mg/m2 IV followed by carboplatin AUC 2 IV Days 1, 8, and 15; repeat every 21 days for 6 cycles (18 weeks)

Table 5. Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer – Platinum-Sensitive Disease

Recurrence Therapy for Platinum-Sensitive Disease (alphabetical order)		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**

▪ Carboplatin/ gemcitabine ± bevacizumab ▪ Carboplatin/ liposomal doxorubicin ± bevacizumab ▪ Carboplatin/ paclitaxel ± bevacizumab ▪ Cisplatin/ gemcitabine <u>Targeted therapy (single agent)</u>: ▪ Bevacizumab	▪ Carboplatin ▪ Carboplatin/ docetaxel ▪ Carboplatin/ paclitaxel (weekly) ▪ Capecitabine ▪ Cisplatin ▪ Cyclophosphamide ▪ Doxorubicin ▪ Ifosfamide ▪ Irinotecan ▪ Melphalan ▪ Oxaliplatin ▪ Paclitaxel ▪ Paclitaxel, albumin bound ▪ Pemetrexed ▪ Vinorelbine <u>Targeted therapy</u>: ▪ Niraparib/ bevacizumab (category 2B) ▪ Niraparib (category 3) ▪ Olaparib (category 3) ▪ Pazoparib (category 2B) ▪ Rucaparib (category 3) <u>Hormone therapy</u>: ▪ Aromatase inhibitors (anastrozole, exemestane, letrozole) ▪ Leuprolide acetate ▪ Megestrol acetate ▪ Tamoxifen	For mucinous carcinoma: ▪ 5-FU/leucovorin/ oxaliplatin ± bevacizumab (category 2B for bevacizumab) ▪ Capecitabine/ oxaliplatin ± bevacizumab (category 2B for bevacizumab) For age > 70: ▪ Carboplatin/paclitaxel For confirmed taxane hypersensitivity: ▪ Carboplatin/ paclitaxel, albumin bound For clear cell carcinoma: ▪ Irinotecan/ cisplatin <u>Hormone therapy</u>: ▪ Fulvestrant (for low-grade serous carcinoma) <u>Immunotherapy</u>: ▪ Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors) ▪ Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/ megabase)

Less Common Ovarian Tumors (LCOC)

1. Carcinosarcoma (malignant mixed Müllerian tumor (MMMT))

The preferred adjuvant treatment is paclitaxel + carboplatin every 3 weeks, or other systemic therapies detailed in table 5, depending on the disease stage[6].

2. Clear cell carcinoma of the ovary

In stages IA, IB, and IC1, observation or platinum-based therapy are the preferred options. In stages IC2 and IC3, platinum-based chemotherapy as detailed for stage I disease in table 5 is the preferred option. As for stages II to IV, systemic therapy options detailed in table 5 are recommended[6].

3. Mucinous carcinoma of the ovary

For stages IA and IB, treatment is not recommended, and observation is preferred. For stage IC, observation or systemic therapy are both options, while for stages II to IV, systemic therapy is recommended. Regimens used are detailed in table 5[6].

4. Grade 1 endometrioid carcinoma

For stages IA and IB, treatment is not recommended, and observation is preferred. For stage IC, observation, systemic therapy, or hormonal therapy are options, while for stages II to IV, systemic therapy (chemotherapy or hormonal therapy) is recommended. Regimens used are detailed in table 5[6].

5. Low-grade serous carcinoma

For stages IA and IB, treatment is not recommended, and observation is preferred. For stage IC, observation, systemic therapy, or hormonal therapy are options, while for stages II to IV, systemic therapy (chemotherapy or hormonal therapy) is recommended. Regimens used are detailed in table 5[6].

Treatment options for recurrent disease include clinical trials, trametinib, binimetinib, dabrafenib + trametinib (for BRAF V600E-positive tumors), or not previously used hormonal or chemotherapy[6].

6. Ovarian borderline epithelial tumors (low malignant potential (LMP)

If prior complete resection or no residual disease remains, observation is recommended. If residual disease is suspected after the first procedure, consider completion surgery (contralateral USO, hysterectomy) and resection of residual disease, or fertility-sparing surgery if fertility is desired[6].

7. Malignant sex cord-stromal tumors

Observation is recommended for patients with stage I low risk disease. In the case of stage I high risk (e.g., ruptured stage IC or poorly differentiated stage I) or in intermediate risk (e.g., heterologous elements) tumors, either observation or platinum-based chemotherapy can be considered (category 2B). In the case of stage II-IV disease, platinum-based chemotherapy is recommended (category 2B), or radiation therapy for limited disease (category 2B)[6].

Systemic therapy options are detailed in table 8[6].

8. Malignant germ cell tumors

Observation is recommended for a diagnosis of stage I dysgerminoma or stage I, grade 1 immature teratoma. In the case of any stage embryonal tumor, or any stage endodermal sinus tumor (yolk sac tumor), or stage II–IV dysgerminoma, or stage I, grade 2 or 3, or stage II–IV immature teratoma, or any stage nongestational choriocarcinoma, chemotherapy is recommended[6].

Table 6. Systemic Therapy Options for Malignant Germ Cell/Sex Cord-Stromal Tumors

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Primary Therapy	▪ BEP (bleomycin, etoposide, cisplatin) ➢ Bleomycin 30 units IV per week + etoposide 100 mg/m2 IV daily on days 1-5 + cisplatin 20 mg/m2 IV daily on days 1-5 ➢ Repeat every 21 days for 3 cycles for good risk (category 2B), or 4 cycles for poor risk.	▪ None	▪ Etoposide/ carboplatin (for select patients with stage IB–III resected dysgerminoma for whom minimizing toxicity is critical) ➢ Carboplatin 400 mg/m2 IV on day 1 + etoposide 120 mg/m2 IV on days 1, 2, and 3 every 28 days for 3 cycles.
Recurrence Therapy	Potentially curative: ▪ High-dose chemotherapy (varies among institutions) ▪ TIP (paclitaxel, ifosfamide, cisplatin)	Palliative only: ▪ Etoposide/ cisplatin (EP), if not previously used ▪ Docetaxel ▪ Docetaxel/ carboplatin ▪ Etoposide (oral)	▪ None

		▪ Etoposide/ ifosfamide/ cisplatin (VIP) ▪ Gemcitabine/ paclitaxel/ oxaliplatin ▪ Gemcitabine/ oxaliplatin ▪ Paclitaxel ▪ Paclitaxel/ carboplatin ▪ Paclitaxel/ gemcitabine ▪ Paclitaxel /ifosfamide ▪ Pembrolizumab (if microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) or tumor mutational burden-high (TMB-H)) ▪ VeIP (vinblastine, ifosfamide, cisplatin) ▪ VAC (vincristine, dactinomycin, cyclophosphamide) ▪ Supportive care	

Surgery

1. General considerations

An open laparotomy including a vertical midline abdominal incision should be used in most patients with a suspected malignant ovarian/ fallopian tube/primary peritoneal neoplasm in whom a surgical staging procedure, a primary debulking procedure, an interval debulking procedure, or secondary cytoreduction is planned.

For select patients, a minimally invasive surgical approach may be employed by an experienced surgeon to manage early-stage disease. Laparoscopy may be useful to evaluate whether optimal cytoreduction can be achieved in patients with newly diagnosed advanced stage or recurrent disease.

Minimally invasive techniques can be used for select patients for interval debulking procedures. Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure.

Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous tumors, or malignant sex cord-stromal tumors) who wish to preserve fertility[6].

2. Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to an Ovary or to the Pelvis (apparent stage IA–IIA)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal. For selected patients desiring to preserve fertility, USO or BSO with uterine preservation may be considered. Uterine preservation allows for potential future assisted reproductive approaches[6].

3. Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen (stage ≥ IIB)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease < 1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.

Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.

Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal (IP) therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery[6].

4. Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer

Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum.

IDS, including completion hysterectomy and BSO with staging, should be performed after 3–4 cycles of neoadjuvant chemotherapy for patients with a response to chemotherapy or stable disease.

Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease. Sodium thiosulfate may be administered at the start of perfusion, followed by a continuous infusion, to allow for renal protection during HIPEC.

All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied.

An omentectomy should be performed.

Suspicious and/or enlarged nodes should be resected, if possible. Removal of lymph nodes noted to have potential metastasis at the time of initial diagnosis should be considered, even if not currently suspicious or enlarged.

Procedures that may be considered for optimal surgical debulking include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/ or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy[6].

5. Secondary cytoreduction

A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who develop a recurrence more than 6 months since completion of initial chemotherapy, have a good performance status, have no ascites, and have an isolated focus or limited foci of disease amenable to complete resection. In addition to preoperative imaging, laparoscopy may be used to determine if complete resection can be achieved. Secondary cytoreduction can be performed with either open or minimally invasive approaches[6].

Maintenance therapy

Certain patients with **newly diagnosed stage II–IV disease** (high-grade serous, grade 2/3 endometrioid, or BRCA1/2-mutated clear cell carcinoma or carcinosarcoma) may benefit from maintenance therapy with **PARP inhibitors** (PARPi) if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. Data are limited for use of maintenance PARPi post primary treatment in patients with stage II disease and for those with LCOC[6].

Certain patients with **recurrent disease** may benefit from maintenance therapy with PARPi after recurrence therapy, if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARPi[6].

Table 7. PARP Inhibitors for Ovarian Cancer (NCCN Guidelines)

Regimen	Setting	Dose/Administration	Duration
Olaparib + bevacizumab	Maintenance post primary chemotherapy + bevacizumab	Olaparib 300 mg orally twice daily Bevacizumab 15 mg/kg IV every 21 days	Olaparib: until disease progression or unacceptable toxicity or up to 2 years Bevacizumab: until disease progression or unacceptable toxicity or up to 15 months
Niraparib monotherapy	Maintenance post primary chemotherapy	300 mg PO once daily (or 200 mg once daily for patients with a baseline body weight of < 77 kg, and/or a platelet count of < 150,000/mm^3)	Until disease progression or unacceptable toxicity or up to 36 months
	Maintenance post recurrence chemotherapy	300 mg PO once daily (or 200 mg once daily for patients with a baseline body weight of < 77 kg, and/or a platelet count of < 150,000/mm^3; after 2 to 3 months, in the absence of hematologic toxicity, may consider escalation to 300 mg once daily)	Until disease progression or unacceptable toxicity
Olaparib monotherapy	Maintenance post primary chemotherapy	300 mg orally twice daily	Until disease progression or complete remission (no evidence of disease) at 2 years or unacceptable toxicity
	Maintenance post recurrence chemotherapy	300 mg orally twice daily	Until disease progression or unacceptable toxicity

Rucaparib monotherapy	Maintenance post primary chemotherapy	600 mg orally twice daily	Until disease progression or unacceptable toxicity or up to 24 months
	Maintenance post recurrence chemotherapy	600 mg orally twice daily	Until disease progression or unacceptable toxicity

Recurrence

Table 8. Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer – Platinum-Resistant Disease

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Cytotoxic therapy: ▪ Cyclophosphamide (oral)/ bevacizumab ▪ Docetaxel ▪ Etoposide, oral ▪ Gemcitabine ▪ Liposomal doxorubicin ▪ Liposomal doxorubicin/ bevacizumab ▪ Paclitaxel (weekly) ▪ Paclitaxel (weekly)/ bevacizumab ▪ Topotecan ▪ Topotecan/ bevacizumab Targeted therapy (single agents): ▪ Bevacizumab ▪ Mirvetuximab soravtansine-gynx (for FRα-expressing tumors)	Cytotoxic therapy: ▪ Capecitabine ▪ Carboplatin ▪ Carboplatin/ docetaxel ▪ Carboplatin/ paclitaxel (weekly) ▪ Carboplatin/ gemcitabine ± bevacizumab ▪ Carboplatin/ liposomal doxorubicin ± bevacizumab ▪ Cisplatin ▪ Cyclophosphamide ▪ Doxorubicin ▪ Gemcitabine/ bevacizumab ▪ Gemcitabine/ cisplatin ▪ Ifosfamide ▪ Irinotecan	For age > 70: ▪ Carboplatin/paclitaxel For confirmed taxane hypersensitivity: ▪ Carboplatin/ paclitaxel, albumin bound Hormone therapy: ▪ Fulvestrant (for low-grade serous carcinoma) Immunotherapy: ▪ Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors) ▪ Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/ megabase) Targeted therapy: ▪ Dabrafenib + trametinib (for BRAF

	▪ Ixabepilone/ bevacizumab ▪ Melphalan ▪ Oxaliplatin ▪ Paclitaxel ▪ Paclitaxel, albumin bound ▪ Pemetrexed ▪ Sorafenib/topotecan ▪ Vinorelbine Targeted therapy: ▪ Niraparib (category 3) ▪ Olaparib (category 3) ▪ Pazoparib (category 2B) ▪ Rucaparib (category 3) Hormone therapy: ▪ Aromatase inhibitors (anastrozole, exemestane, letrozole) ▪ Leuprolide acetate ▪ Megestrol acetate ▪ Tamoxifen	V600E-positive tumors) ▪ Entrectinib or larotrectinib (for NTRK gene fusion positive tumors) ▪ Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors) (category 2B) ▪ Selpercatinib (for RET gene fusion-positive tumors) For low-grade serous carcinoma: ▪ Trametinib ▪ Binimetinib (category 2B)

1.2.2 American Society of Clinical Oncology (2020)

In 2020, the American Society of Clinical Oncology (ASCO) published clinical guidelines to provide recommendations on the use of poly(ADP-ribose) polymerase inhibitors (PARPis) for management of epithelial ovarian, tubal, or primary peritoneal cancer (EOC). The guideline pertains to patients who are PARPi naïve. The main recommendations are summarized in table 9[7].

Table 9. PARP Inhibitors in the Management of Ovarian Cancer (ASCO Guideline)

Repeating PARPi	
Repeating PARPi therapy in the treatment of EOC is not recommended at this time. Consideration should be made as to the best time in the life cycle of an individual patient's EOC in which to use PARPi; clinical trial participation is encouraged	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong

Newly Diagnosed Ovarian Cancer	
PARPis are not recommended for use in initial treatment of early stage (stage I-II) EOC because there is insufficient evidence to support use in this population	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong
Women with newly diagnosed stage III-IV EOC that is in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy with olaparib (for those with germline or somatic pathogenic or likely pathogenic variants in BRCA1 or BRCA2 genes) or niraparib (all women) in high-grade serous (HGS) or endometrioid ovarian cancer. PARPi maintenance therapy should consist of olaparib (300 mg orally every 12 hours for 2 years) or niraparib (200- 300 mg orally daily for 3 years). Longer duration could be considered in selected individuals.	Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong
The addition of olaparib to bevacizumab maintenance may be offered to patients who have stage III-IV HGS or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in BRCA1 or BRCA2 genes and/or genomic instability, and who have had a partial or complete response to chemotherapy plus bevacizumab combination	Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong
Inclusion of the PARPi veliparib with combination chemotherapy followed by veliparib maintenance therapy cannot be recommended at this time. There are no data that this approach is superior, equal, or less toxic than a switch maintenance	Type: evidence based; benefit/harms ratio unknown; Evidence quality: intermediate; Strength of recommendation: strong
Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment	
PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of BRCA mutation status; treatment is continued until progression of disease or toxicity	Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong

despite dose reductions and best supportive care. Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily.	
Treatment with a PARPi should be offered to patients with recurrent EOC who have not already received a PARPi and have a germline or somatic pathogenic or likely pathogenic variants in BRCA1 or BRCA2 genes. Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily.	Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong
Treatment with a PARPi monotherapy should be offered to patients with recurrent EOC who have not already received a PARPi and whose tumor demonstrates genomic instability, and has not recurred within 6 months of platinum-based therapy.	Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong
PARPis are not recommended for treatment of BRCA wild-type or platinum-resistant recurrent EOC.	Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong
PARPis in Combination	
PARPi are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Clinical trial participation is encouraged.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong
Management of Adverse Events	
Anemia: • Patients requiring a blood transfusion for symptom relief and/or hemoglobin level < 8 g/dL should be monitored. PARPi dose should be reduced with evidence of repeated anemia to avoid multiple transfusions. • Patients with progressive anemia may be offered growth factor per ASCO guidelines and physician and patient comfort.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate

Neutropenia: • Growth factor is not indicated for use in patients receiving daily PARPi. • Neutropenia (grade 4 lasting at least 5-7 days or associated with fever) should result in dose hold until recovery of infection and granulocyte count, followed by dose reduction. Growth factor support may be used in this setting to support patient safety during the drug hold.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate
Platelets: • Thrombocytopenia is most common with niraparib. Niraparib dosing guidelines should be used to lower starting dose (200 mg) based on weight and platelet count. • Discontinue PARPi for persistent thrombocytopenia or significant bleeding despite dose reduction.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate
Persistent cytopenia: Evaluation for treatment-related myelodysplastic syndrome/acute myeloid leukemia should be initiated in patients with persistent cytopenia that occurs despite drug hold.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate
Nausea: • Many patients will have tachyphylaxis of nausea symptoms over the first cycle of therapy. • Persistent nausea requiring daily antiemetic intervention, causing a reduction in performance status, and/or resulting in > 5% weight loss should result in dose reduction.	Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate

1.3 European Guidelines

1.3.1 European Society for Medical Oncology (ESMO)

The European Society for Medical Oncology (ESMO) published three clinical guidelines for the management of ovarian cancer. The first, published jointly with the European Society of Gynaecologial Oncology (ESGO) in 2019, covers pathology and molecular biology, early and advanced stages, borderline tumors, and recurrent disease[9]. The second, published in 2020, covers predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. The third, more recent clinical guidelines (August 2023), covers the diagnosis, treatment, and follow-up of newly diagnosed and relapsed epithelial ovarian cancer[8].

1.3.1.1 ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-up of Newly Diagnosed and Relapsed Epithelial Ovarian Cancer (2023)

a) Diagnosis and Pathology/Molecular Biology

The diagnosis and pathology recommendations for epithelial ovarian cancer (EOC) according to the ESMO guidelines are shown in table 10[8].

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

Recommendations	Strength
Diagnosis and pathology	
▪ If EOC is suspected, diagnostic work-up should include serum CA-125 measurement, pelvic US by an expert examiner and CT scan of the thorax, abdomen, and pelvis.	III,A
▪ Pathological diagnosis should be made according to the 2020 WHO classification by an expert gynecological pathologist.	IV,A
▪ All patients with high-grade ovarian cancer should be tested for germline and/or somatic BRCA1/2-muts at diagnosis.	I,A
▪ Testing for HRD is recommended in advanced high-grade cancers.	I,A

b) Staging and Risk assessment

The staging and risk assessment recommendations for epithelial ovarian cancer according to the ESMO guidelines are shown in table 11[8].

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

Recommendations	Strength
Staging and Risk Assessment	
▪ The revised 2014 FIGO staging system for EOC should be used [I, A].	I,A

c) Management of early epithelial ovarian cancer (FIGO STAGE I-II)

The treatment recommendations for patients with early epithelial ovarian cancer according to the ESMO guidelines are shown in table 12[8].

Table 12. Treatment Recommendations for Patients with Early Epithelial Ovarian Cancer (ESMO Guidelines)

Recommendations	Strength
Management of Early EOC (Figo Stage I-II)	
▪ Surgical staging is recommended in presumed early-stage ovarian cancer for classification and recommendation of optimal systemic therapy.	III,A
▪ Adjuvant chemotherapy in early-stage ovarian cancer is generally recommended for FIGO stage I-IIB (see exceptions below) [II, A], either paclitaxel/carboplatin [I, B] or carboplatin (six cycles) alone [I, A].	II,A I,B I,A
▪ For patients receiving paclitaxel/carboplatin, a minimum of three cycles are recommended except for high grade serous carcinoma (HGSC)/high-grade EC or any stage IC-II regardless of histotype, for which six cycles are suggested.	II,B
▪ The benefit of adjuvant chemotherapy is uncertain and can be considered as optional for: o LGSC stage IB-IC o Clear Cell Carcinoma (CCC) stage IA-IC1 o Low-grade EC stage IB-IC o Expansile Mucinous Carcinoma (MC) stage IC o Infiltrative MC stage IA	III,C
▪ Adjuvant chemotherapy is not recommended in completely staged patients with LGSC stage IA, low-grade EC stage IA or expansile MC stage IA-IB.	II,E

A proposed algorithm for the management of early epithelial ovarian cancer is shown in figure 2[8].

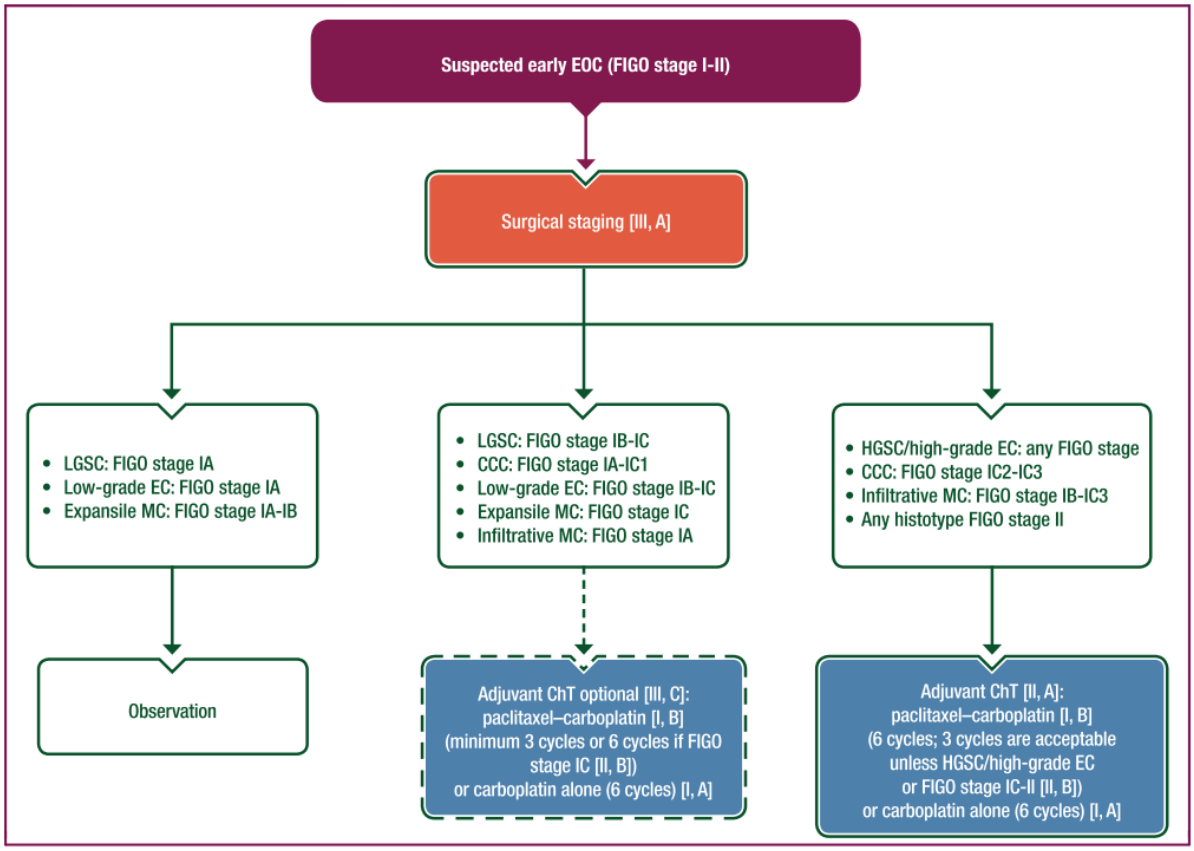

Figure 2. *Management of early epithelial ovarian cancer (FIGO stage I-III).*

Retrieved from González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011.

d) Management of advanced epithelial ovarian cancer (FIGO STAGE III-IV)

The advanced disease treatment recommendations for patients with epithelial ovarian cancer according to the ESMO guidelines are shown in table 13[8].

Table 13. Treatment Recommendations for Patients with Advanced Epithelial Ovarian Cancer (ESMO Guidelines)

Recommendations	Strength
Management of Advanced EOC (Figo Stage III-IV)	
▪ Patients with advanced EOC should be evaluated for primary cytoreductive surgery by a specialized team, with the aim of achieving complete cytoreduction (absence of all visible residual disease).	III,A
▪ When complete cytoreductive surgery is feasible, primary cytoreductive surgery is recommended; otherwise, obtaining	III,A

adequate biopsy tissue for histology and molecular testing is recommended.	
▪ When complete cytoreductive surgery is not feasible, neoadjuvant chemotherapy for three cycles followed by interval cytoreductive surgery and three cycles of paclitaxel/carboplatin are recommended.	I,A
▪ Bevacizumab in the neoadjuvant setting, before interval cytoreductive surgery, can be considered.	II,B
▪ When interval cytoreductive surgery is not possible, and in the absence of overt disease progression, three additional cycles of paclitaxel/carboplatin alone or with bevacizumab are recommended.	I,A II,B
▪ Systemic therapy decisions should be informed by BRCA1/2-mut (germline and/or somatic) and homologous recombination deficiency status testing carried out at primary diagnosis.	I,A
▪ Paclitaxel (175 mg/m^2/carboplatin (AUC 5-6) every 3 weeks for six cycles is the standard first-line chemotherapy in advanced ovarian cancer.	I,A
▪ The schedule of weekly chemotherapy with paclitaxel (60 mg/m^2)/carboplatin (AUC 2) can be considered as an alternative in frail patients.	I,B
▪ Bevacizumab improves PFS in patients with stage III-IV ovarian cancer and should be considered in addition to paclitaxel/carboplatin.	I,A
▪ Given the controversy about IP chemotherapy [I, E] and HIPEC [II, D], they are not considered a standard of care in first-line treatment.	I,E II,D
▪ Maintenance treatment with PARPis, with or without bevacizumab, is recommended for patients with BRCA1/2-mutated or BRCA1/2-wt/HRD-positive tumors with no evidence of disease at the end of chemotherapy or a complete or partial response to platinum/paclitaxel first-line chemotherapy. o For BRCA1/2-mutated: olaparib for 2 years [ESMOMCBS v1.1 score: 4; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A], niraparib for 3 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A] or olaparib/bevacizumab for 2 years [ESMOMCBS v1.1 score: 3; ESCAT score: I-A]. o For BRCA1/2-wt/HRD-positive: niraparib for 3 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A] or olaparib/bevacizumab for 2 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A).	-
▪ Maintenance treatment with either bevacizumab [I, A] or niraparib for 3 years [I, B; ESMO-MCBS v1.1 score: 3] can be	I,A

recommended for HRD-negative tumors, with the latter following complete or partial response to platinum-paclitaxel first-line chemotherapy. The choice of treatment should be based on disease and clinical characteristics of the patient.	I,B
▪ Maintenance with anti-estrogen therapy after first-line platinum-based chemotherapy can be considered in low-grade serous carcinoma.	IV,B

A proposed algorithm for the treatment recommendations for advanced epithelial ovarian cancer is shown in Figure 3[8].

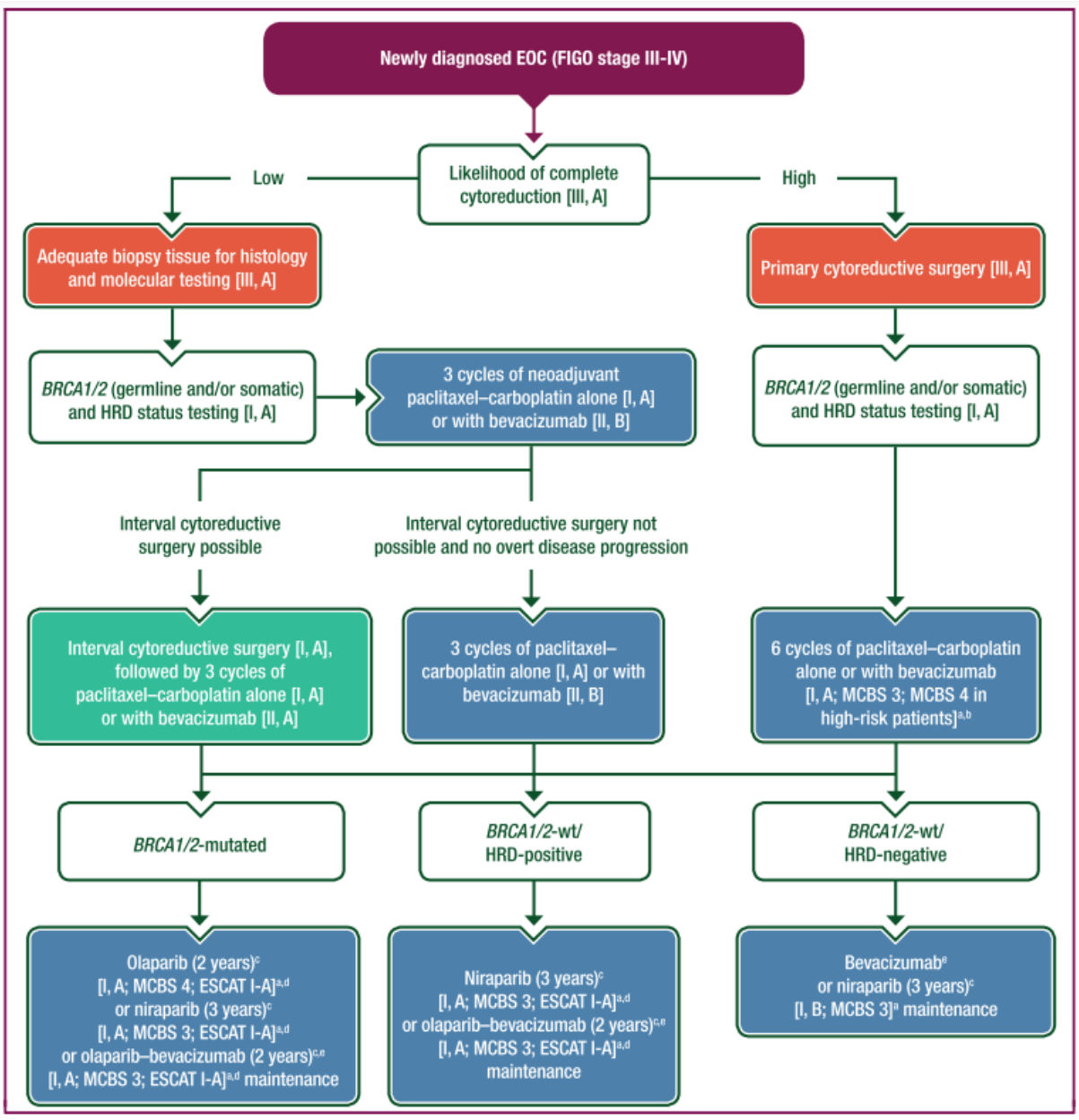

Figure 3. *Management of advanced epithelial ovarian cancer (FIGO stage III-IV).*

Retrieved from González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011.

e) Management of recurrent epithelial ovarian cancer

The recurrent disease treatment recommendations for patients with epithelial ovarian cancer according to the ESMO guidelines are shown in table 14[8].

Table 14. Treatment Recommendations for Patients with Recurrent Epithelial Ovarian Cancer (ESMO Guidelines)

Recommendations	Strength
Management of Recurrent EOC	
▪ The following should be assessed when selecting treatment for patients with recurrent disease: o Histotype o BRCA1/2-mut status o Number of prior lines of treatment o Exposure and response to prior treatment o Treatment-free interval from last platinum o Possibility of achieving a complete secondary surgical cytoreduction o Residual chemotherapy toxicity o The patient's general condition and preferences	I-III,A
▪ Patients with first relapse of ovarian cancer after > 6 months of last platinum administration should be evaluated by a gynecological oncology center experienced in surgery for ovarian cancer to identify potential candidates for surgical cytoreduction.	I,A
▪ Patients who have previously responded to platinum without early symptomatic relapse should be treated with either a platinum-based doublet (PLD, gemcitabine or paclitaxel) with bevacizumab [I, A; carboplatine gemcitabineebevacizumab ESMO-MCBS v1.1 score: 3] or a platinum-based doublet followed by maintenance with PARPi therapy if a response is achieved and the patient has not been previously exposed to PARPis [I, A; olaparib for BRCA1/2-mutated: ESMO-MCBS v1.1 score: 2; niraparib regardless of BRCA1/2-mut status: ESMO-MCBS v1.1 score: 3; rucaparib regardless of BRCA1/2-mut status: ESMO-MCBS v1.1 score: 3].	I,A
▪ For patients requiring rapid response, the combination of a platinum-based doublet (PLD, gemcitabine or paclitaxel) with bevacizumab is preferred.	V,A

▪ Bevacizumab should be continued until disease progression (symptomatic) or the next line of treatment is started, as continuation of bevacizumab beyond progression has not been evaluated in the recurrent setting.	I,A
▪ PARPis should be continued until disease progression or the next line of treatment is started [I, A], as the benefit of continuing treatment beyond progression has not been demonstrated conclusively to date [III, B].	I,A III,B
▪ Platinum rechallenge following treatment with a non-platinum regimen (monotherapy or combination) could be considered if the tumor did not progress during prior platinum therapy.	III,B
▪ Patients with relapsed EOC for whom platinum is not an option should be defined by: o Proven resistance (progression during platinum) o Expected resistance (early symptomatic progression post-platinum, response to rechallenge unlikely) o Platinum intolerance o Patient choice o QoL issues	II-IV,A
▪ For patients not candidates to receive platinum, integrating palliative care early in the treatment pathway is strongly recommended.	I,A
▪ Single-agent non-platinum options that can be recommended include weekly paclitaxel, pegylated doxorubicin (PLD), topotecan and gemcitabine.	I,B
▪ In patients with platinum intolerance who have relapsed >6 months from previous platinum, trabectedine/PLD may be recommended.	II,C
▪ Bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab.	I,A
▪ Hormonal therapy is recommended for relapsed low-grade serous carcinoma.	II,A
▪ For patients with recurrent low-grade serous carcinoma, treatment with the MEK inhibitor trametinib should be considered after prior platinum-based chemotherapy and hormone therapy (not EMA approved).	I,A

A proposed algorithm for the treatment recommendations for recurrent epithelial ovarian cancer is shown in figure 4[8].

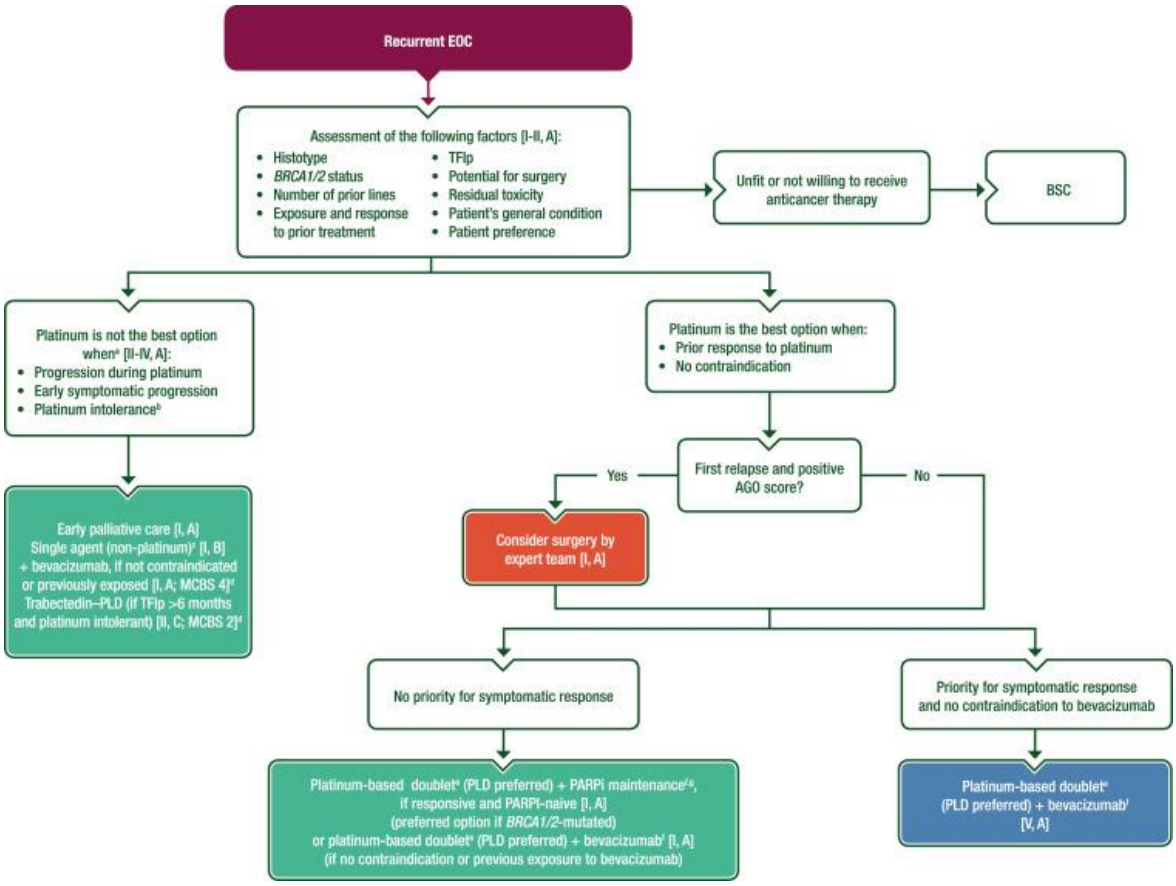

Figure 4. *Management of recurrent epithelial ovarian cancer.*

Retrieved from González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011.

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

The follow-up, long-term implications, and survivorship recommendations for patients with epithelial ovarian cancer according to the ESMO guidelines are shown in table 15[8].

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

Recommendations	Strength
Follow-up, Long-Term Implications, and Survivorship	
▪ Surveillance of ovarian cancer patients can include CA125 determination, physical examination, and CT scan evaluation.	IV,B
▪ BRCA1/2-mut carriers can be considered for follow-up beyond 5 years.	III,B

▪ Long-term BRCA1/2-mut survivors should be referred to high-risk breast cancer clinics for follow-up.	I,A

1.3.1.2 ESMO Recommendations on Predictive Biomarker Testing for Homologous Recombination Deficiency and PARP Inhibitor Benefit in Ovarian Cancer (2020)

a) Pathological considerations

The pathological considerations for ovarian cancer according to the ESMO guidelines are shown in Table 16[9].

Table 16. Pathological Considerations for Ovarian Cancer (ESMO Guidelines)

Recommendations	Strength
Pathological considerations	
▪ Pathological evaluation of the tumor tissue specimens used for assessment of somatic molecular alterations is essential. It is recommended that a pathologist with experience in gynecological pathology should be a member of the team and responsible for confirming diagnosis, assessing sample adequacy, selection of tumor area, and quantification of tumor cells, inflammatory cells and necrosis. An integrated pathology-molecular report is highly recommended.	(Level of agreement ¼ 100%; total agreement)

b) HRD gene test

The recommendations for HRD gene tests according to the ESMO guidelines are shown in Table 17[9].

Table 17. HRD Gene Tests (ESMO Guidelines)

Recommendations	Strength
HRD gene tests	
▪ BRCA mutation tests [germline (LOE I), tumour (incorporating germline and somatic) (LOE I) and somatic (LOE I/ II)] exhibit good clinical validity by consistently identifying the subgroup of ovarian cancer patients who derive the greatest magnitude of benefit from PARPi therapy. ▪ There is currently an insufficient quantity of evidence to determine the clinical validity of individual or panels of non-BRCA HRR genes for predicting a PARPi response and further prospectively collected data is required (LOE II). ▪ There is currently insufficient evidence to determine the clinical validity of BRCA1 or RAD51C promoter methylation to	(Level of agreement ¼ 100%; total agreement)

predict PARPi benefit, partly due to concerns regarding the analytic validity of previous studies.	

c) Genomic Signatures and Scars

The recommendations for genomic signatures and scars according to the ESMO guidelines are shown in table 18[9].

Table 18. Genomic Signatures and Scars (ESMO guidelines)

Recommendations	Strength
Genomic Signatures and Scars	
▪ HRD tests that incorporate scores of allelic imbalance (GIS or LOH) identify a subgroup of BRCA wild-type, platinum sensitive cancers that derive a greater magnitude of benefit from PARPi therapy in some settings (LOE I). ▪ There is currently insufficient evidence to ascertain the clinical validity of whole genome sequencing based mutational signatures for predicting PARPi benefit in HGSC. ▪ Pre-clinical evidence suggests that whole genome sequencing based mutational signature tests may compare favorably to existing genomic scar assays in terms of identifying cancers with HRD; their clinical validity in terms of PARPi benefit should be ascertained in archived clinical trial specimens and/or prospective clinical trial specimens.	(Level of agreement ¼ 100%; total agreement)

d) Functional Assays

The recommendations for the use of functional assays of HRD according to the ESMO guidelines are shown in table 19[9].

Table 19. Functional Assays (ESMO guidelines)

Recommendations	Strength
Functional Assays	
▪ There is currently insufficient evidence to ascertain the clinical validity of functional assays in predicting response to PARPi therapies, but these pre-clinical assays provide promise for ascertaining real-time estimates of HRD and their development should be a priority. The potential for using functional assays alongside HRR gene tests and genomic tests should be investigated.	(Level of agreement ¼ 100%; total agreement)

e) Clinical Utility of Available HRD Tests

The recommendations on the clinical utility of HRD tests according to the ESMO guidelines are shown in table 20[9].

Table 20. Clinical Utility of HRD Tests (ESMO guidelines)

Recommendations	Strength
Clinical Utility of HRD Tests	
▪ In the first-line maintenance setting, germline and somatic BRCA mutation testing is routinely recommended to identify HGSC patients who should receive a PARPi. ▪ In the first-line maintenance setting, it is reasonable to use a validated scar based HRD test to establish the magnitude of benefit conferred by PARPi use in BRCA wild-type high grade serous carcinoma. ▪ In the first-line maintenance setting, it is reasonable to use a validated scar based HRD test to identify the subgroup of BRCA wild-type patients who are least likely to benefit from PARPi therapy. (Level of agreement ¼ 100%; total agreement) In the platinum-sensitive relapse maintenance setting, it is reasonable to use BRCA mutation testing and validated scar based HRD tests to predict the likely magnitude of PARPi benefit for consideration of risks and benefits of maintenance therapy.	(Level of agreement ¼ 100%; total agreement)

1.4 International Guidelines

1.4.1 Japan Society of Gynecologic Oncology (2021)

The Japan Society of Gynecologic Oncology (JSGO) released in 2021 clinical practice guidelines for treatment of ovarian cancer[10].

The algorithm for the initial treatment of patients with ovarian cancer, fallopian tube cancer, and primary peritoneal cancer according to the JSGO guidelines is illustrated in figure 5[10].

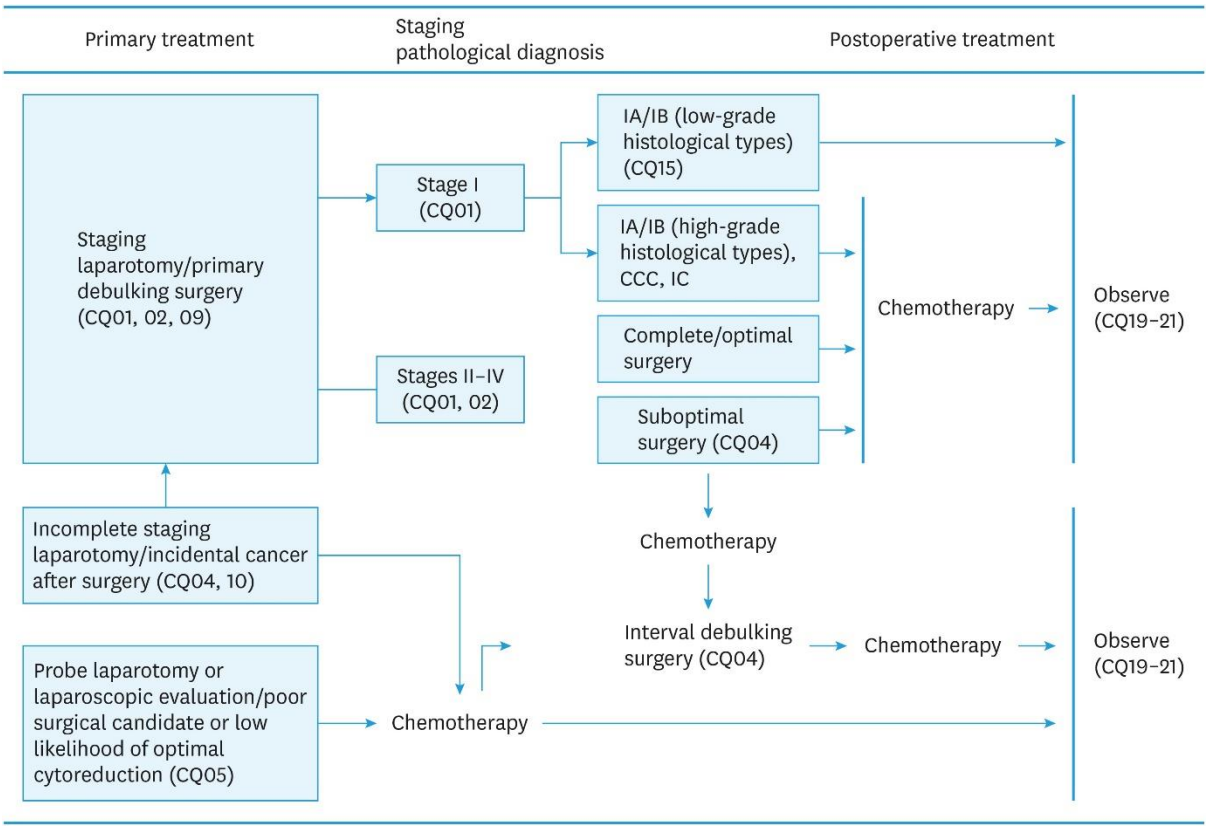

Figure 5. *Initial treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (JSGO guidelines).*

Retrieved from Tokunaga H, Mikami M, Nagase S, et al. The 2020 Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer. *J Gynecol Oncol*. 2021;32(2):e49. doi:10.3802/jgo.2021.32.e49.

The algorithm for the treatment of patients with recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer according to the JSGO guidelines is illustrated in figure 6[10].

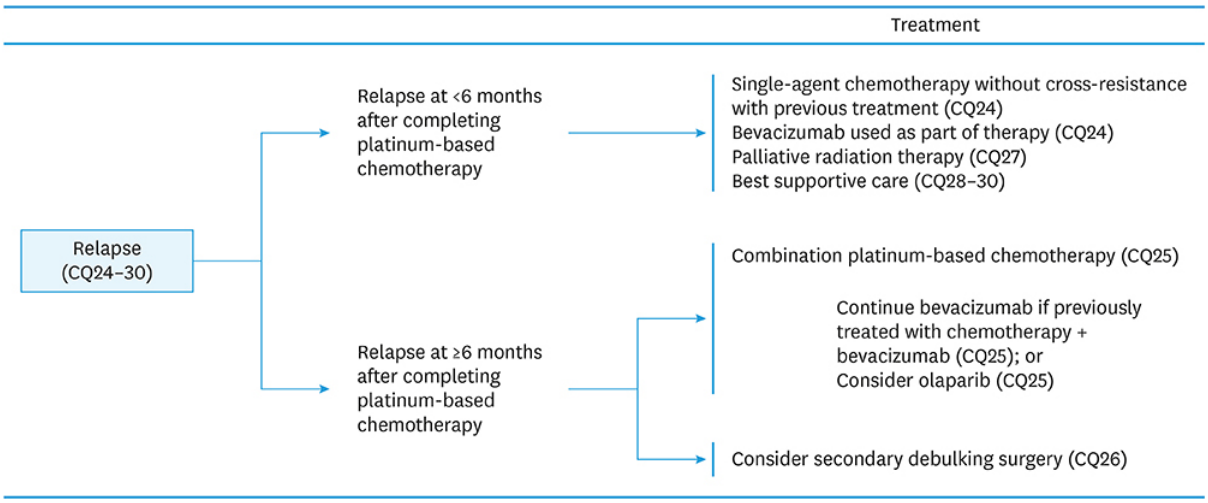

Figure 6. *Treatment for recurrent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (JSGO guidelines).*

Retrieved from Tokunaga H, Mikami M, Nagase S, et al. The 2020 Japan Society of Gynecologic Oncology guidelines for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer. *J Gynecol Oncol*. 2021;32(2):e49. doi:10.3802/jgo.2021.32.e49.

a) Epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer

- For patients with stage I–IIA ovarian cancer, what staging laparotomy is recommended?
  - Pelvic/para-aortic lymph node dissection (biopsy) is recommended in addition to bilateral salpingo-oophorectomy (BSO) + total hysterectomy + omentectomy (OMT) + peritoneal cytology + biopsies from sites in the abdominal cavity. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - When sampling from the abdominal cavity, specimens are suggested to be acquired from the surface of the pouch of Douglas, abdominal wall, diaphragm, bowel, and mesentery, in addition to the suspected lesions. Grade 2 (↑); level of evidence: C; consensus: 100%[10]
- For patients thought to have stage IIB or higher ovarian cancer, is primary debulking surgery (PDS) recommended as the initial treatment?
  - Maximal debulking surgery is recommended to achieve complete resection (i.e., no gross residual tumor). Grade 1 (↑↑); level of evidence: A; consensus: 100%
  - The procedures are recommended to be performed in a JSGO-designated training facility or an institute with a full-time JSGO-certified gynecologic oncologist where multidisciplinary treatment can be implemented in cooperation with surgeons, urologists, oncologists, etc. Grade 1 (↑↑); level of evidence: C; consensus: 94%[10]

- For patients thought to have stage IIB or higher ovarian cancer, is pelvic or para-aortic lymphadenectomy recommended as a primary surgery?
  - Pelvic or para-aortic lymph node dissection is suggested to be not performed if no lymph node metastasis is clinically detected on imaging or by intraoperative palpation and visual inspection. Grade 2 (↓); level of evidence: B; consensus: 95%
  - When lymph node metastasis is clinically detected on diagnostic imaging or by intraoperative palpation and visual inspection, pelvic or para-aortic lymph node dissection or removal of swollen lymph nodes is recommended if complete resection can be achieved. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- For patients with residual disease after PDS, is interval debulking surgery (IDS) recommended?
  - IDS is suggested. Grade 2 (↑); level of evidence: C; consensus: 95%[10]
- For patients with advanced-stage ovarian cancer, are neoadjuvant chemotherapy (NAC) and IDS recommended, as compared to PDS?
  - NAC + IDS is recommended for advanced-stage ovarian cancer when optimal surgery is expected to be difficult or impossible to achieve. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- CQ 06: For patients who desires that their fertility will be preserved, is fertility-sparing surgery recommended?
  - In addition to unilateral salpingo-oophorectomy (USO) (affected side) + OMT + peritoneal cytology, intraperitoneal examination is recommended to be performed as a basic surgical procedure for fertility preservation. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - Biopsy of the contralateral ovary, biopsy (dissection) of pelvic or para-aortic lymph nodes, and biopsy from sites in the abdominal cavity are suggested as staging laparotomy, depending on the case. Grade 2 (↑); level of evidence: C; consensus: 100%
  - Fertility-sparing treatment is recommended for stage IA non-clear cell carcinoma (CCC) with low histological grade. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - Fertility-sparing treatment is suggested for non-CCC patients (stage IC1 confined to one side of the ovary and low histological grade) or patients with CCC (stage IA). Grade 2 (↑); level of evidence: C; consensus: 100%
  - Adjuvant chemotherapy is recommended in the same manner as when standard surgical procedures are performed. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]

- For patients with ovarian cancer, is laparoscopic surgery instead of laparotomy recommended?
  - Laparoscopic surgery is suggested to be not performed at the moment. Grade 2 (↓); level of evidence: C; consensus: 100%[10]
- For patients thought to have peritoneal dissemination, is diagnostic laparoscopy recommended?
  - Diagnostic laparoscopy is suggested for the purpose of predicting complete surgery, staging, or collecting tissues. Grade 2 (↑); level of evidence: B; consensus: 100%[10]
- Is intraoperative pathology consultation recommended to determine operative procedures?
  - Intraoperative pathology consultation is recommended in order to determine the surgical procedures when the malignancy of a lesion is difficult to judge based on preoperative and/or intraoperative findings. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- For patients with incidental ovarian cancer after surgery, what treatment is recommended?
  - Staging laparotomy is recommended. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - IDS after chemotherapy is recommended for patients with advanced-stage ovarian cancer, in whom optimal surgery is difficult or impossible to achieve. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- For chemotherapy-naïve patients, what is the recommended regimen?
  - Conventional paclitaxel plus carboplatin (TC) therapy is recommended. Grade 1 (↑↑); level of evidence: A; consensus: 100%
  - Dose-dense TC therapy is suggested. Grade 2 (↑); level of evidence: B; consensus: 38%* *Rate for grade 1. The grade of recommendation for the second one was initially proposed as grade 1 because dose-dense TC therapy was superior to conventional TC therapy in the JGOG 3016 trial with respect to overall survival among Japanese patients. However, the ICON8 trial denied the superiority of dose-dense TC therapy, and committee consensus did not reach 75% (i.e., agreement criteria). Thus, the grade of recommendation was judged to be grade 2 (final consensus: 89%).
  - A combination of TC and bevacizumab followed by bevacizumab maintenance therapy is recommended for patients with stage III/IV disease. Grade 1 (↑↑); level of evidence: B; consensus: 89%**

    **There existed an opinion that the grade of recommendation should be scored as grade 2 instead, considering the adverse effects of bevacizumab and PARP inhibitors in BRCA variant carriers. In these

guidelines, we defined “variant” as pathogenic or likely a pathogenic variant[10].

- For patients with complete remission (CR) after chemotherapy following primary surgery, is maintenance therapy recommended?
  - Maintenance therapy is suggested to be not administered. Grade 1 (↓↓); level of evidence: B; consensus: 100%
  - Maintenance therapy with bevacizumab is recommended for patients with stage III/IV disease after CR is achieved by first-line chemotherapy with bevacizumab. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - Olaparib is recommended for patients with stage III/IV disease who carry BRCA1/2 variants after CR is achieved by first-line chemotherapy. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- For patients with persistent disease after first-line chemotherapy following primary surgery, is further treatment recommended?
  - Bevacizumab is recommended except for patients exhibiting disease progression after first-line chemotherapy with bevacizumab.
  - Grade 1 (↑↑); level of evidence: B; consensus: 95%
  - Olaparib is recommended for patients with BRCA1/2 variants when first-line chemotherapy results in partial response. Grade 1 (↑↑); level of evidence: B; consensus: 100%
  - For patients who fail to respond to first-line chemotherapy and those exhibiting tumor progression, another treatment (i.e., second-line chemotherapy or radiation therapy), participation in clinical trials, or best supportive care is suggested. Grade 2 (↑); level of evidence: C; consensus: 95%[10]
- For patients in whom TC therapy is considered inappropriate, what regimen is recommended?
  - Docetaxel plus carboplatin or pegylated liposomal doxorubicin plus carboplatin is recommended. Grade 1 (↑↑); level of evidence: B; consensus: 95%
  - For patients in whom docetaxel plus carboplatin or pegylated liposomal doxorubicin plus carboplatin is difficult to administer, weekly TC is suggested. Grade 2 (↑); level of evidence: C; consensus: 100%
  - For patients in whom combination chemotherapy is inappropriate to be provided, carboplatin monotherapy is suggested. Grade 2 (↑); level of evidence: C; consensus: 100%[10]
- For patients with stage I ovarian cancer, is the omission of postoperative chemotherapy recommended?

- Omission of adjuvant chemotherapy is suggested for non-CCC patients with low grade and stage IA or IB, as defined by staging laparotomy. Grade 2 (↑); level of evidence: B; consensus: 94%[10]

- Is it recommended to choose a different chemotherapy regimen depending on the histological* type of ovarian cancer?
  - It is suggested that chemotherapy regimen should not be altered based on histology. Grade 2 (↓); level of evidence: B; consensus: 84% *There is no evidence of a regimen that has superiority over TC therapy as a treatment for clear cell carcinomas and mucinous carcinomas, which are more likely to resist platinum-based chemotherapy than high-grade serous carcinomas and endometrioid carcinomas[10].
- For patients with advanced-stage ovarian cancer, is intraperitoneal chemotherapy recommended as first-line chemotherapy?
  - Intraperitoneal chemotherapy is suggested to be administered in an appropriate facility with provision of adequate informed consent concerning risks and benefits. Grade 2 (↑); level of evidence: B; consensus: 94%
  - Hyperthermic intraperitoneal chemotherapy is suggested to be provided in a clinical trial. Grade 2 (↑); level of evidence: B; consensus: 94%[10]
- When hypersensitivity reaction (HSR) occurs during drug administration, is re-administration of the same or similar drug possible?
  - For patients with mild HSR to non-platinum agents, careful re-administration of the same drug is suggested following confirmation of symptom loss after stopping the administration. Grade 2 (↑); level of evidence: C; consensus: 63%* *Rate for grade 1
  - For patients with mild HSR to platinum agents, desensitization therapy for the same drug or alternation with other platinum agents is suggested after the establishment of a system that can immediately cope with serious complications, including cardiopulmonary arrest. Grade 2 (↑); level of evidence: C; consensus: 89%
  - For patients with severe HSR to chemotherapy, non-administration of the same or similar drug is recommended. Grade 1 (↓↓); level of evidence: B; consensus: 100%[10]
- What are the recommended intervals for post-treatment surveillance?
  - The following intervals are suggested after the start of initial treatment: Years 1–2: an interval of 1–3 months Years 3–5: an interval of 3–6 months Year 6 onward: an interval of 1 year Grade 2 (↑); level of evidence: C; consensus: 94%[10]

- Are medical interview, pelvic examination, serum tumor marker measurement, and diagnostic imaging during ovarian cancer follow-up recommended?
  - Medical interview, pelvic examination, and transvaginal ultrasonography are recommended during every patient's visit. Grade 1 (↑↑); level of evidence: C; consensus: 94%
  - Serum tumor marker measurement and computed tomography are recommended to be conducted, as necessary. Grade 1 (↑↑); level of evidence: C; consensus: 100%[10]
- For asymptomatic patients with elevation in serum cancer antigen 125 (CA125) level during ovarian cancer follow-up, is an intervention recommended?
  - It is suggested not to intervene based only on an elevation in the serum level of CA125, a tumor marker. Grade 2 (↓); level of evidence: B; consensus: 95%[10]
- Is hormone replacement therapy (HRT) recommended during treatment or ovarian cancer follow-up?
  - HRT is recommended for patients exhibiting symptoms or those aged < 45 years. Grade 1 (↑↑); level of evidence: B; consensus: 59%[10]
- For carriers of BRCA1/2 variants who have not developed breast cancer, is risk-reducing salpingo-oophorectomy recommended?
  - Following the review and approval by the ethics committee, the performance of risk-reducing salpingo-oophorectomy by gynecologic oncologists in cooperation with clinical geneticists in a facility where genetic counseling and pathologists' cooperation are available is recommended. Grade 1 (↑↑); level of evidence: A; consensus: 100%[10]

b) Recurrent epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer

- For patients with platinum-resistant recurrence, what is the recommended chemotherapy regimen?
  - A single agent without cross-resistance to previous treatment is suggested. Grade 2 (↑); level of evidence: B; consensus: 100%
  - The addition of bevacizumab to a cytotoxic agent is suggested. Grade 2 (↑); level of evidence: B; consensus: 100%[10]
- For patients with platinum-sensitive recurrence, what is the recommended chemotherapy regimen?
  - Combination chemotherapy with a platinum agent is recommended. Grade 1 (↑↑); level of evidence: A; consensus: 100%

- The addition of bevacizumab to the combination chemotherapy followed by bevacizumab maintenance therapy is recommended. Grade 1 (↑↑); level of evidence: B; consensus: 100%[10]
- Olaparib is recommended for patients with BRCA1/2 variants after tumor regression by platinum-based chemotherapy. Grade 1 (↑↑); level of evidence: B; consensus: 100%
- Olaparib is suggested for patients identified to have no variants after BRCA testing as well as those with or without BRCA1/2 variants after tumor regression due to platinum-based chemotherapy. Grade 2 (↑); level of evidence: B; consensus: 85%[10]

- For patients with recurrence, is surgery recommended?
  - For patients with platinum-sensitive recurrence, secondary debulking surgery is suggested to be performed when it is thought that the lesion can possibly be resected completely. Grade 2 (↑); level of evidence: C; consensus: 100%
  - For patients with platinum-resistant recurrence, surgery is suggested to be not performed, except for the purpose of symptom relief or in cases with resectable solitary lesion. Grade 2 (↓); level of evidence: C; consensus: 92%[10]
- For patients with unresectable recurrence, is radiation therapy recommended?
  - Radiation therapy is suggested for the purpose of pain relief or hemostasis. Grade 2 (↑); level of evidence: B; consensus: 100%
  - Radiation therapy for brain metastasis is suggested to relieve the symptoms and improve the prognosis. Grade 2 (↑); level of evidence: B; consensus: 92%[10]
- For patients with ovarian cancer who have an ileus, is surgery or medication recommended?
  - A surgical solution accounting for eligibility and risk of surgery is suggested for physical obstruction to improve emesis and vomiting. Grade 2 (↑); level of evidence: C; consensus: 100%
  - Corticosteroids, octreotide, or both are suggested to relieve emesis and vomiting. Grade 2 (↑); level of evidence: C; consensus: 100%[10]
- For patients with massive ascites, is medication or ascites drainage recommended?
  - Diuretic agent, ascites drainage, or concentrated ascites reinfusion therapy with consideration of patients' condition is suggested for symptom relief. Grade 2 (↑); level of evidence: C; consensus: 92%[10]

- For patients being considered for chemotherapy beyond third-line chemotherapy, is further chemotherapy recommended?
  - After adequate discussion with the patients and careful assessment of their condition, the administration of chemotherapy with different regimens is suggested if they are judged to be less disadvantageous owing to their adverse effects. Grade 2 (↑); level of evidence: C; consensus: 100%[10]

1.4.2 Society for Immunotherapy of Cancer (2023)

The Society for Immunotherapy of Cancer (SITC) released in 2023 clinical practice guidelines on immunotherapy for the treatment of gynecological cancer[11]. The key treatment recommendations relevant for ovarian cancer are outlined in the following sections:

a) Emerging immunotherapy strategies for ovarian cancer

- For all patients with ovarian cancer, clinical trial enrollment should be offered, as feasible.
- NGS testing should be offered to all patients with newly diagnosed ovarian cancer (LE:2).
- For patients with recurrent TMB-H and/or MSI-H/ dMMR ovarian tumors with no satisfactory alternative treatment options, treatment with ICIs should be considered (LE:3).
- Tumor PD-L1 expression should not be used to inform treatment decisions for ICI use in ovarian cancer (LE:2)[11].

1.5 Systematic Reviews/Meta-Analyses

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on ovarian 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 ovarian cancer are constantly being updated with the many clinical trials and treatment alternatives emerging in the market.

1.6 Secondary and Tertiary Resources

The international guidelines detailed in previous sections being most updated, a detailed search of secondary and tertiary resources for additional guidelines, such as Google Scholar, the Ovid Health Technology Assessment Database, the National Institute for Health and Care Research Journals Library, and UpToDate did not yield any additional data that hasn't already been described.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Carboplatin

Table 21. Carboplatin Drug Information

Scientific Name Carboplatin[14]	
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)	C56
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 5 or 6 on day 1 every 3 weeks or Target AUC 2 once weekly
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 chemotherapy; 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)	Primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with paclitaxel ± bevacizumab (preferred treatment); or with docetaxel, liposomal doxorubicin, and ifosfamide (carcinosarcoma). Second-line treatment of ovarian cancer, in patients with platinum sensitive disease in combination with gemcitabine, or paclitaxel, or liposomal doxorubicin ± bevacizumab (preferred regimens). Other combinations in this setting include docetaxel, or oxaliplatin.
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 ovarian cancer. This is probably because carboplatin is a long-established standard of care in ovarian cancer. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Carboplatin

Carboplatin is recommended as a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with paclitaxel ± bevacizumab (preferred treatment). It can also be used in this setting in combination with docetaxel, liposomal doxorubicin, and ifosfamide (carcinosarcoma). Carboplatin is also used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease in combination with gemcitabine, or paclitaxel, or liposomal doxorubicin ± bevacizumab (preferred regimens). Other combinations in this setting include docetaxel, or oxaliplatin.

There is no data issued by HTA bodies regarding its use.

2.1.2 Cisplatin

Table 22. Cisplatin Drug Information

Scientific Name Cisplatin[15]	
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)	C56
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; Intraperitoneal
Dose (Adult) [DDD]*	**IV:** 75 to 100 mg/m^2 once every 3 to 4 weeks **or** 75 mg/m^2 every 3 weeks (in combination with paclitaxel) **Intraperitoneal**: 100 mg/m^2 on day 2 of a 21-day treatment cycle (in combination with IV and intraperitoneal paclitaxel) for 6 cycles
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)	Cisplatin (intraperitoneal) is used part of the IV/IP therapy in combination with IV/IP paclitaxel as a primary treatment of optimally debulked stage II–III ovarian cancer. Primary treatment of carcinosarcoma in combination with ifosfamide. Second-line treatment of ovarian cancer, in patients with platinum sensitive disease in combination with gemcitabine.
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 ovarian cancer. This is probably because cisplatin's use is limited to IP chemotherapy and a few protocols. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Cisplatin

In ovarian cancer, cisplatin (intraperitoneal) is used as part of the IV/IP therapy in combination with IV/IP paclitaxel for the management of optimally debulked stage II–III disease. It can also be used in combination with ifosfamide in carcinosarcoma. Cisplatin is also used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease in combination with gemcitabine.

There is no data issued by HTA bodies regarding its use.

2.1.3 Cyclophosphamide

Table 23. Cyclophosphamide Drug Information

Scientific Name **Cyclophosphamide**[16]	
Trade Name(s) on Saudi Market	Endoxan
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered
FDA approved/off label	No
EMEA approved/off label	No

MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Alkylating Agent (Nitrogen Mustard)
SFDA Registration Number (New)	Endoxan 200 mg vial: 17-16-81 Endoxan 500 mg vial: 18-16-81 Endoxan 1 g vial: 19-16-81 Endoxan 50 mg tablet: 14-16-81
ATC Code	L01AA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for solution for injection; sugar-coated tablet
Route of Administration	Intravenous; oral
Dose (Adult) [DDD]*	IV: 750mg/m^2 every 3 weeks PO: Days 1-28: Cyclophosphamide 50mg orally daily.
Dose (Pediatrics)	N/A
Adjustment	<u>Renal impairment prior to treatment initiation</u>: - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl 10 to 29 mL/minute: Administer 75% or 100% of normal dose. - CrCl <10 mL/minute: Administer 50%, 75%, or 100% of normal dose. - Hemodialysis, intermittent (thrice weekly): Administer 50% or 75% of the normal dose (on dialysis days, administer after hemodialysis). - Peritoneal dialysis: Administer 75% of the normal dose. - CRRT: Administer 100% of the normal dose. <u>Hepatic impairment prior to treatment initiation</u>: No dosage adjustment necessary.
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A

CU (Concurrent Use)	To be used in as a single agent or in combination with bevacizumab; 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 4,000 mg/m^2
ST (Step Therapy)	Second-line treatment of platinum-resistant disease either orally in combination with bevacizumab (preferred) or IV.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	4,000 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: neutropenia, fever, diarrhea, nausea, vomiting, alopecia, bone marrow suppression. - Most serious: acute respiratory distress syndrome (ARDS), multi-organ failure, hemorrhagic cystitis, heart failure.
Drug Interactions*	Amiodarone: Cyclophosphamide may enhance the risk of pulmonary toxicity of Amiodarone (Risk C) Azathioprine: May enhance the hepatotoxic effect of Cyclophosphamide (Risk C) Lenograstim: May enhance the adverse/toxic effect of Cyclophosphamide (Risk D) Live Vaccines: Immunosuppressants (Cytotoxic Chemotherapy) may enhance the adverse/toxic effect of Live Vaccines (Risk X)
Special Population	N/A
Pregnancy	Birth defects (including malformations of the skeleton, palate, limbs, and eyes), miscarriage, fetal growth retardation, and fetotoxic effects in the newborn (including anemia,

	gastroenteritis leukopenia, pancytopenia, and severe bone marrow hypoplasia) have been reported. Chemotherapy should not be administered during the first trimester, after 35 weeks' gestation, or within 3 weeks of planned delivery.
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for 1 week after the last cyclophosphamide dose.
Contraindications	Known hypersensitivity to the product or its components. Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	CBC with differential and platelets, BUN, serum electrolytes, serum creatinine, urinalysis. Pregnancy status. Hepatitis B screening.
Precautions	- Hypersensitivity - Hepatic impairment - Renal impairment
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 cyclophosphamide in ovarian cancer. This is probably because cyclophosphamide's use is limited in disease management, restricted to platinum refractory disease. Moreover, the drug is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion statement - Cyclophosphamide

In ovarian cancer, cyclophosphamide is used in the second-line setting, for the management of platinum-resistant disease either orally in combination with bevacizumab (preferred) or IV.

There is no data issued by HTA bodies regarding its use.

2.1.4 Ifosfamide

Table 24. Ifosfamide Drug Information

Scientific Name Ifosfamide[17]	
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)	C56
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]*	3000 mg/m^2 in combination with carboplatin 1200 mg/m^2-1500 mg/m^2 on Days 1-5 in combination with cisplatin 1600 mg/m^2 on Days 1-3 in combination with paclitaxel 1000 mg/m^2-2000 mg/m^2 on Days 1-5 as a single agent
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 in combination with other chemotherapy agents; 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)	Primary treatment for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer of **carcinosarcoma histology** (Stage I-IV) used in combination with carboplatin or cisplatin or paclitaxel. Second-line treatment of ovarian cancer for refractory disease, used as a single agent.
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*	3000 mg/m^2
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 ovarian cancer. This is probably because ifosfamide's role is limited in disease management, restricted for carcinosarcoma or relapsed disease. Moreover, the drug is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion Statement – Ifosfamide

In ovarian cancer, ifosfamide is a primary treatment for Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer of carcinosarcoma histology (Stage I-IV) used in combination with carboplatin or cisplatin or paclitaxel. It is also a treatment option in the second-line setting for refractory disease, used as a single agent.

There is no data issued by HTA bodies regarding its use.

2.1.5 Oxaliplatin

Table 25. Oxaliplatin Drug Information

Scientific Name Oxaliplatin[18]	
Trade Name(s) on Saudi Market	Oxaliplatin Medac, Eloxatin, Batipan, Platroxin, Xaltin, Xaltipine, Oxaliplatin AqVida
SFDA Classification	Prescription
SFDA approved Indication	Yes, Oxaliplatin Medac, 2010; Eloxatin, 2017; Batipan, 2019, 2020; Platroxin, 2019; Xaltin, 2019; Xaltipine, 2021; Oxaliplatin AqVida, 2023
FDA approved / off label	Yes, 2002
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating Agent
SFDA Registration Number (New)	Oxaliplatin Medac: 1-463-10 (50mg); 2-463-10 (100mg); 3-463-10 (200mg) Eloxatin: 54-23-17 (50mg); 55-23-17 (100mg) Batipan: 5-5251-19 (100mg); 5-5251-20 (50mg) Platroxin : 25-5035-19 (100mg); 26-5035-19 (50mg) Xaltin : 13-5223-19 (50mg); 14-5223-19 (100mg) Xaltipine: 0703210585 (100mg); 0703210586 (50mg) Oxaliplatin AqVida : 1901233127 (200mg); 1901233128 (100mg); 1901233129 (50mg)
ATC Code	L01XA03
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous

Dose (Adult) [DDD]*	85 mg/m^2 in combination with 5-FU; cycles are repeated every 2 weeks 130 mg/m^2 once every 3 weeks (as a single agent or in combination with capecitabine)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥30 mL/min: No dosage adjustment - CrCl 20 to <30 mL/min: 75% to 100% of the usual dose - CrCl <20 mL/minute: 75% of the dose - Hemodialysis/PD/CRRT/ PIRRT: Avoid use due to the lack of data
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 chemotherapy [5-FU/leucovorin or capecitabine (± bevacizumab) or capecitabine or with docetaxel/bevacizumab]; 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 130 mg/m^2
ST (Step Therapy)	Primary treatment of Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer, used in combination with 5-FU/leucovorin or capecitabine (± bevacizumab) (preferred regimens), or with docetaxel/bevacizumab. Second-line treatment of platinum sensitive disease, used as a single agent or, for mucinous carcinoma, in combination with 5-FU/leucovorin or capecitabine (± bevacizumab). Second-line treatment of platinum-resistant disease, used as a single agent.
EU (Emergency Use Only)	N/A

PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	130 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Abdominal pain, anorexia, constipation, diarrhea, nausea, stomatitis, vomiting, anemia, leukopenia, thrombocytopenia, increased AST/ALT, increased bilirubin, fatigue, headache, insomnia, pain, peripheral neuropathy, pain, cough, dyspnea, fever - Most serious: Neutropenia, reversible posterior leukoencephalopathy syndrome, pulmonary fibrosis
Drug Interactions*	- Risk X: BCG Products, Brivudine, Cladribine, Dipyrone, Fexinidazole, - Risk D: Deferiprone, Lenograstim, Lipegfilgrastim, Palifermin, Ropeginterferon Alfa-2b, Taxane derivatives, Topotecan
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Oxaliplatin is present in breast milk. Breastfeeding is not recommended during oxaliplatin treatment
Contraindications	Hypersensitivity to oxaliplatin, other platinum-containing compounds, or any component of the formulation
Monitoring Requirements	CBC with differential, blood chemistries, including serum creatinine, ALT, AST, and bilirubin, electrolytes, INR and PT (in patients on oral anticoagulant therapy) ECG monitoring in patients at risk for cardiac toxicities Neurologic evaluation prior to each dose and periodically thereafter. Monitor for signs/symptoms of hypersensitivity, pulmonary toxicity,

	posterior reversible encephalopathy syndrome, neuropathy, bleeding, and GI toxicity
Precautions	- Bone marrow suppression - Cardiotoxicity - Extravasation - Hemorrhage - Hepatotoxicity - Hypersensitivity - Neuropathy - Posterior reversible encephalopathy syndrome - Pulmonary toxicity - Rhabdomyolysis
Black Box Warning	- Hypersensitivity/Anaphylactic 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 oxaliplatin in ovarian cancer.

Conclusion Statement – Oxaliplatin

In ovarian cancer, oxaliplatin is a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer of Mucinous carcinoma (stage IC) histology, used in combination with 5-FU/leucovorin or capecitabine (± bevacizumab) (preferred regimens), or with docetaxel/bevacizumab. Docetaxel/oxaliplatin/bevacizumab is also an alternative treatment option for patients with Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer.

Oxaliplatin is also a treatment option in the second-line setting for platinum sensitive disease, used as a single agent or, for mucinous carcinoma, in combination with 5-FU/leucovorin or capecitabine (± bevacizumab). It is also a treatment option in the second-line setting for platinum-resistant disease, used as a single agent.

There is no data issued by HTA bodies regarding its use.

2.2 Antimetabolites

2.2.1 5-Fluorouracil (5-FU)

Table 26. 5-Fluorouracil Drug Information

Scientific Name 5-Fluorouracil[19]	
Trade Name(s) on Saudi Market	Fluorouracil (Hospira); Fluorouracil Ebewe; Floryl
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1997
FDA approved / off label	Yes, 1962
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Fluorouracil Hospira: 22-237-97 (500mg) Fluorouracil Ebewe: 16-355-01 (500mg); 18-355-01 (1g) 42-355-07 (5g) Floryl: 15-5223-19 (5g); 16-5223-19 (1g); 17-5223-19 (500mg); 18-5223-19 (250mg)
ATC Code	L01BC02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	400mg/m^2 IV push followed by 1200 mg/m^2/day for 2 days as a continuous infusion over 24 hours; cycles are repeated every 2 weeks
Dose (Pediatrics)	N/A
Adjustment	Renal/Hepatic Impairment (Adult): There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits*	MD, ST, PE, CU, QL

AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with leucovorin/oxaliplatin (± bevacizumab); 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 1000 mg/m^2
ST (Step Therapy)	Primary treatment of Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal of Mucinous carcinoma (stage IC) histology, used in combination with leucovorin/oxaliplatin (± bevacizumab) (preferred regimen). Second-line treatment of mucinous carcinoma in platinum sensitive disease, used in combination with leucovorin/oxaliplatin (± bevacizumab).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Daily dose not to exceed 1000 mg/m^2
Maximum Daily Dose Pediatrics*	Daily dose not to exceed 1000 mg/m^2
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide,

	Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, 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 fluorouracil is present in breast milk. The manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the breastfeeding patient.
Contraindications	N/A
Monitoring Requirements	CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants). Monitor for signs/symptoms of palmar-plantar erythrodysesthesia syndrome, cardiotoxicity, CNS toxicity, stomatitis, diarrhea, and hyperammonemic encephalopathy. Promptly evaluate any symptoms suggestive of cardiotoxicity. Consider monitoring ECG in patients on concomitant QT prolonging medications.
Precautions	- Bone marrow suppression - Cardiotoxicity

	- GI toxicity - Hand-foot syndrome - Hyperammonemic encephalopathy - Neurotoxicity - Dihydropyrimidine dehydrogenase deficiency - Warfarin
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 5-FU in ovarian cancer.

Conclusion Statement – 5-FU

In ovarian cancer, 5-FU is a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal of Mucinous carcinoma (stage IC) histology, used in combination with leucovorin/oxaliplatin (± bevacizumab) (preferred regimen). 5-FU is also a treatment option in the second-line setting for mucinous carcinoma in platinum sensitive disease, used in combination with leucovorin/oxaliplatin (± bevacizumab).

There is no data issued by HTA bodies regarding its use.

2.2.2 Capecitabine

Table 27. Capecitabine Drug Information

Scientific Name Capecitabine[20]	
Trade Name(s) on Saudi Market	Xeloda, Dirogit, Capecitabine SPC, Aceda, Pitacro, Emcap, Xelobine, Catabina
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2004
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, 2001
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent

Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Xeloda: 250-24-04 (150mg); 251-24-04 (500mg) Dirogit: 189-172-18 (500mg) Capecitabine SPC: 1-5171-18 (150mg); 2-5171-18 (500mg) Aceda: 7-5223-18 (500mg); 8-5223-18 (150mg) Pitacro: 2611200294 (500mg); 2611200293 (150mg) Emcap: 1510200212 (500mg) Xelobine: 2202210536 (500mg); 2202210537 (150mg) Catabina: 0706210768 (500mg)
ATC Code	L01BC06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Ovarian, fallopian tube, or peritoneal cancer, platinum-refractory:** 1,000 mg/m^2 twice daily on days 1 to 14 of a 3-week cycle until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal/Hepatic Impairment (Adult): There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits*	MD, ST, CU, 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 chemotherapy [oxaliplatin (± bevacizumab)] 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 not to exceed 2500 mg/m^2 (to be given in two divided doses)
ST (Step Therapy)	Primary treatment of Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal of Mucinous carcinoma (stage IC) histology, used in combination with oxaliplatin (± bevacizumab) (preferred regimen). Second-line treatment of platinum-sensitive disease, used as a single agent or, for mucinous carcinoma, in combination with oxaliplatin (± bevacizumab). Second-line treatment of platinum-resistant disease, used as a single agent.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose not to exceed 2500 mg/m^2 (to be given in two divided doses)
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Aminolevulinic Acid, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab,

	Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Dihydropyrimidine dehydrogenase deficiency, Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if capecitabine is present in breast milk. Breastfeeding is not recommended by the manufacturer during treatment and for 1 week after the last capecitabine dose.
Contraindications	Known hypersensitivity to capecitabine, fluorouracil, or any component of the formulation.
Monitoring Requirements	CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants). Pregnancy status Hydration status Monitor for signs/symptoms of diarrhea, dehydration, hand-foot syndrome, new or worsening serious skin reactions, stomatitis, hepatotoxicity, nephrotoxicity, and cardiotoxicity, cardiotoxicity.

	Consider monitoring ECG in patients on concomitant QT-prolonging medications. Monitor adherence.
Precautions	- Hepatotoxicity - Kidney Impairment - Fluorouracil/leucovorin previous therapy - Proton pump inhibitors - Dihydropyrimidine dehydrogenase deficiency - Older adults
Black Box Warning	Vitamin K antagonist interaction
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 capecitabine in ovarian cancer.

Conclusion Statement – Capecitabine

In ovarian cancer, capecitabine is a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal of Mucinous carcinoma (stage IC) histology, used in combination with oxaliplatin (± bevacizumab) (preferred regimen). Capecitabine is also a treatment option in the second-line setting for platinum-sensitive disease, used as a single agent or, for mucinous carcinoma, in combination with oxaliplatin (± bevacizumab). It is also a treatment option in the second-line setting for platinum-resistant disease, used as a single agent.

There is no data issued by HTA bodies regarding its use.

2.2.3 Gemcitabine

Table 28. Gemcitabine Drug Information

Scientific Name Gemcitabine[21]	
Trade Name(s) on Saudi Market	Gemcitabine Ebewe, Citabol, Gemcitabine Jazeera, Gemzar, Citarox, Gebtin, Gemcitabine Glenmark, Gemcitabine BOS
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2011

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, 2006
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Gemcitabine Ebewe: 48-355-11 (1g); 50-355-11 (200mg) Citabol: 3-796-15 (1g); 4-796-15 (200mg) Gemcitabine Jazeera: 0712222984 (200mg); 0712222985 (1g) Gemzar:1-5396-19 (200mg) Citarox: 1-5251-19 (200mg); 10-5251-20 (1g) Gebtin: 72-5286-20 (1g); 73-5286-20 (200mg) Gemcitabine Glenmark: 1-5438-20 (200mg); 2-5438-20 (1000mg) Gemcitabine BOS: 0301221548 (1g)
ATC Code	L01BC05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous, Intravesicular instillation
Dose (Adult) [DDD]*	**Ovarian cancer, advanced:** 1,000 mg/m^2 over 30 minutes days 1 and 8; repeat cycle every 21 days
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥30 mL/min: No adjustment necessary - CrCl <30 mL/min: No adjustment necessary. However, increased risk of hematologic toxicity - Hemodialysis/ PD/CRRT/ PIRRT: No dosage adjustment necessary Hepatic Impairment (Adult):

	- Transaminases elevated (with normal bilirubin or total bilirubin <1.6 mg/dL): No dosage adjustment necessary - Serum bilirubin >1.6 mg/dL: Use initial dose of 800 mg/m^2; may escalate if tolerated - Total bilirubin ≥1.6 mg/dL: May begin with 80% of the usual gemcitabine dose and increase the dose if tolerated
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 chemotherapy [carboplatin (± bevacizumab), or cisplatin] 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 dose per day 1000 mg/m^2
ST (Step Therapy)	Second-line treatment of ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin (± bevacizumab), or cisplatin (preferred regimens), or as a single agent. Second-line treatment of platinum resistant disease as a single agent (preferred), or in combination with bevacizumab or cisplatin (not in platinum refractory disease).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	1000 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia,

	neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, 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, radiation therapy recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if gemcitabine is present in breast milk. Breastfeeding is not recommended during treatment and for at least 1 week after the last gemcitabine dose.
Contraindications	Known hypersensitivity to gemcitabine or any component of the formulation
Monitoring Requirements	CBC with differential and platelet count; LFTs, renal function, electrolytes, Pulmonary function

	Monitor for signs/symptoms of capillary leak syndrome, hemolytic uremic syndrome, hepatotoxicity, hypersensitivity, posterior reversible encephalopathy syndrome, and pulmonary toxicity.
Precautions	- Bone marrow suppression - Capillary leak syndrome - Hemolytic uremic syndrome - Hepatotoxicity - Hypersensitivity - Posterior reversible encephalopathy syndrome - Pulmonary toxicity
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 gemcitabine in ovarian cancer.

Conclusion Statement – Gemcitabine

Gemcitabine is used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin (± bevacizumab), or cisplatin (preferred regimens), or as a single agent. It is also used in the second-line setting of platinum resistant disease as a single agent (preferred), or in combination with bevacizumab or cisplatin (not in platinum refractory disease).

There is no data issued by HTA bodies regarding its use.

2.2.4 Pemetrexed

Table 29. Pemetrexed Drug Information

Scientific Name Pemetrexed[22]	
Trade Name(s) on Saudi Market	Pemitra ; Pemetrexed SPC ; Pemitax ; Alimta ; Almetra ; Alix ; Pemetrexed EPC
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017

FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Pemitra : 2310222780 Pemetrexed SPC : 1907233889 Pemitax : 0410200179 Alimta : 14-5117-19 Almetra : 80-5286-20 Alix : 1612211484 Pemetrexed EPC : 2711222935 (500 mg); 2711222934 (100 mg)
ATC Code	QL01BA04
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	500 mg/m^2 on day 1 of each 21-day cycle
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥45 mL/minute: No dosage adjustment necessary. - CrCl <45 mL/minute: Use is not recommended by the manufacturer (an insufficient number of patients have been studied for dosage recommendations). - Kidney toxicity during treatment: Withhold pemetrexed until CrCl is ≥45 mL/minute.
Prescribing edits*	AGE, MD, ST, PE, CU, QL
AGE (Age Edit)	No used in the pediatric population
CU (Concurrent Use)	To be used with antiemetics; To be used with folic acid/vitamin B12 supplementation

G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum dose per day 500 mg/m^2
ST (Step Therapy)	Second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	500 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Desquamation, skin rash Anorexia, diarrhea, nausea, stomatitis, vomiting; Anemia, neutropenia, fatigue, pharyngitis - Most serious: Febrile neutropenia, Pulmonary embolism
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, 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, radiation therapy recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy

Lactation	It is not known if pemetrexed is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last pemetrexed dose.
Contraindications	Severe hypersensitivity to pemetrexed or any component of the formulation
Monitoring Requirements	- CBC with differential and platelets - Renal function tests, total bilirubin, ALT, AST (periodic) - Pregnancy status - Monitor for signs/symptoms of mucositis and diarrhea, pulmonary toxicity, dermatologic toxicity, and radiation recall
Precautions	- Bone marrow suppression - Cutaneous reactions - GI toxicity - Hypersensitivity - Nephrotoxicity - Pulmonary toxicity - Radiation recall - Renal impairment - Third space fluids - Ibuprofen may reduce the clearance of pemetrexed
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 pemetrexed in ovarian cancer.

Conclusion Statement – Pemetrexed

Pemetrexed is used in the second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent.

There is no data issued by HTA bodies regarding its use.

2.3 Antimicrotubular Agents

2.3.1 Docetaxel

Table 30. Docetaxel Drug Information

Scientific Name Docetaxel[23]	
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)	C56
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]*	60-75 mg/m^2 every 3 weeks (in combination with carboplatin) for up to 6 cycles **or** 35 mg/m^2 (maximum dose: 70 mg) weekly for 3 weeks followed by a 1-week rest (in combination with carboplatin).
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 chemotherapy (carboplatin, or oxaliplatin/bevacizumab) To be used with anti-emetics and anti-allergic medications
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)	Primary treatment of Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with carboplatin, or oxaliplatin/bevacizumab. Second-line treatment of ovarian cancer, in patients with platinum resistant disease, as a single agent (preferred option).
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 ovarian cancer.

Conclusion Statement – Docetaxel

Docetaxel is a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with carboplatin, or oxaliplatin/bevacizumab. Docetaxel is also used in the second-line setting of ovarian cancer, in patients with platinum resistant disease, as a single agent (preferred option).

There is no data issued by HTA bodies regarding its use.

2.3.2 Paclitaxel

Table 31. Paclitaxel Drug Information

Scientific Name Paclitaxel[24]	
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)	C56
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]*	135-175 mg/m^2 over 3 hours every 3 weeks **or** 80 mg/m^2 over 1 hour on days 1, 8, and 15 every 3 weeks
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)	Can be used as a single agent or in combination with chemotherapy (c.f ST) To be used with anti-emetics and anti-allergic medications
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)	Primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer: - In combination with carboplatin ± bevacizumab (preferred treatment). - In combination with ifosfamide for carcinosarcoma - As part of the IV/IP therapy in combination with IP cisplatin for

	the management of optimally debulked stage II–III disease. Second-line treatment of recurrent ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin ± bevacizumab (preferred regimen) or as a single agent. Second-line treatment of platinum-resistant ovarian cancer as a single agent.
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 ovarian cancer. This is probably because paclitaxel is an established standard of care in ovarian cancer. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Paclitaxel

Paclitaxel is recommended as a primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with carboplatin ± bevacizumab (preferred treatment). It can also be used in this setting in combination with ifosfamide in carcinosarcoma. Paclitaxel can be used as part of the IV/IP therapy in combination with IP cisplatin for the management of optimally debulked stage II–III disease. Paclitaxel is also used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin ± bevacizumab (preferred regimen) or as a single agent. It is also used in the setting of platinum-resistant disease as a single agent.

There is no data issued by HTA bodies regarding its use.

2.3.3 Paclitaxel (Albumin-Bound)

Table 32. Paclitaxel Drug Information

Scientific Name **Nanoparticle albumin bound paclitaxel (nabpaclitaxel)** [25]	
Trade Name(s) on Saudi Market	Abraxane
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2020
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Taxane derivative
SFDA Registration Number (New)	9-5550-22
ATC Code	L01CD01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	

Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	260 mg/m^2 on day 1 of a 21-day cycle for 6 to 8 cycles **or** 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): *refer to specific protocols*
Prescribing edits*	AGE, MD, ST, PE, CU, QL
AGE (Age Edit)	Not used in pediatrics
CU (Concurrent Use)	Can be used as a single agent or in combination with chemotherapy (carboplatin) To be used with anti-emetics
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 260 mg/m^2
ST (Step Therapy)	Second-line treatment of recurrent ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin or as a single agent. Second-line treatment of platinum-resistant ovarian cancer as a single agent.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	260 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: ECG abnormality, edema, alopecia, skin rash, dehydration, hypokalemia, increased gamma-glutamyl transferase, constipation, decreased appetite, diarrhea, dysgeusia, nausea and vomiting, urinary tract infection, anemia, bone marrow depression,

	neutropenia, thrombocytopenia, increased AST/ALT, infection, depression, headache, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, visual disturbances, fever, Increased serum creatinine, cough, dyspnea, epistaxis - Most serious: Cardiac failure, significant cardiovascular event, febrile neutropenia, visual disturbances
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
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends patients not breastfeed during therapy and for 2 weeks following the last paclitaxel (protein bound) dose.

Contraindications	Baseline neutrophil count of <1,500/mm^3; history of severe hypersensitivity reaction to paclitaxel (protein bound) or any component of the formulation.
Monitoring Requirements	CBC with differential; monitor hepatic function. Pregnancy status. Monitor infusion site. Monitor for signs/symptoms of neuropathy, hypersensitivity, pneumonitis, and infection/sepsis. Monitor for ocular toxicity
Precautions	- Bone marrow suppression - Cardiovascular effects - Extravasation - Hypersensitivity - Neuropathy - Ocular effects - Pneumonitis - Sepsis
Black Box Warning	- Neutropenia
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield to any guidance for albumin-bound paclitaxel in ovarian cancer.

Conclusion Statement – Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is used in the second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent or in combination with carboplatin (in platinum-sensitive patients).

There is no data issued by HTA bodies regarding its use.

2.3.4 Vinorelbine

Table 33. Vinorelbine Drug Information

Scientific Name Vinorelbine[26]	
Trade Name(s) on Saudi Market	Navelbine
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1996
FDA approved / off label	Yes, 1962
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Vinca Alkaloid
SFDA Registration Number (New)	1-5798-23 (10mg); 2-5798-23 (50mg)
ATC Code	L01CA04
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Ovarian cancer, relapsed:** 25 mg/m^2 every 7 days **or** 30 mg/m^2 days 1 and 8 of a 21-day treatment cycle until disease progression or unacceptable toxicity.
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): - Serum bilirubin ≤2 mg/dL: Administer 100% of dose. - Serum bilirubin 2.1 to 3 mg/dL: Administer 50% of dose - Serum bilirubin >3 mg/dL: Administer 25% of dose
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with anti-emetics
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 not to exceed 25 mg/m^2
ST (Step Therapy)	Second-line treatment of ovarian cancer (platinum sensitive or resistant) as a single agent.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose not to exceed 25 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Neurotoxicity, peripheral neuropathy, Alopecia, Nausea, vomiting, constipation, diarrhea, Neutropenia, leukopenia, anemia, Increased serum aspartate aminotransferase, Injection site reaction pain at injection site, Asthenia, Increased serum creatinine - Most serious: intestinal necrosis, intestinal obstruction, intestinal perforation, paralytic ileus, bone marrow depression, hepatotoxicity, neurotoxicity, febrile neutropenia, sepsis, pulmonary toxicity
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, 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	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if vinorelbine is present in breast milk. The manufacturer does not recommend breastfeeding during treatment and for 9 days after the final vinorelbine dose.
Contraindications	N/A
Monitoring Requirements	- CBC with differential and platelet count (prior to each dose, and after treatment), hepatic function tests. - Pregnancy status. - Monitor for new-onset pulmonary symptoms, for neuropathy, for signs/symptoms of constipation/ileus. - Monitor infusion site.
Precautions	- Bone marrow suppression - Extravasation - Gastrointestinal toxicity - Hepatotoxicity - Neuropathy - Pulmonary toxicity
Black Box Warning	- 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 to any guidance for vinorelbine in ovarian cancer.

Conclusion Statement – Vinorelbine

Vinorelbine is used in the second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent.

There is no data issued by HTA bodies regarding its use.

2.4 Hormone Therapy

2.4.1 Anastrozole

Table 34. Anastrozole Drug Information

Scientific Name Anastrozole[27]	
Trade Name(s) on Saudi Market	Arimidex; Tabidex; Anastralex; Anadex ; Anastrozole
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2000
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Aromatase inhibitor
SFDA Registration Number (New)	Arimidex : 49-7-00 Tabidex : 9-5223-18 Anastralex : 78-249-18 Anadex : 3-5685-23 Anastrozole : 12-5015-18
ATC Code	L02BG03
Pharmacological Class (ASHP)	68:16.08 – Antiestrogens
Drug Information	
Dosage Form	Film-coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	1 mg once daily until disease progression or unacceptable toxicity
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, PE, QL
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)	Maximum daily dose: 1 mg
ST (Step Therapy)	Preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I

	endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Maintenance treatment of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy. Second-line treatment of ovarian cancer (platinum sensitive or resistant).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	1 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Angina pectoris, hypertension, ischemic heart disease, vasodilation, skin rash, hot flash, gastrointestinal distress, nausea, vomiting, depression, fatigue, headache, mood disorder, arthralgia, arthritis, asthenia, osteoporosis, increased cough, pharyngitis - Most serious: Acute myocardial infarction, cerebral ischemia, deep vein thrombosis, thromboembolic disease, venous thrombosis, vaginal hemorrhage, endometrial carcinoma, hepatitis
Drug Interactions*	Risk X: Estrogen Derivatives; Tamoxifen Risk C: Methadone; Levomethadone
Special Population	N/A
Pregnancy	Pregnancy Category X
Lactation	It is not known if anastrozole is present in breast milk. The manufacturer does not recommend breastfeeding during therapy or for 2 weeks after the last anastrozole dose.

Contraindications	Hypersensitivity to anastrozole or any component of the formulation.
Monitoring Requirements	- Bone mineral density at baseline and periodically thereafter - Total cholesterol and LDL - Pregnancy status - Monitor adherence
Precautions	- Hepatic impairment
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 anastrozole in ovarian cancer.

Conclusion statement – Anastrozole

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is a preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Hormone therapy can also be used in the maintenance setting of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy.

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is also used in the second-line setting of ovarian cancer (platinum sensitive or resistant).

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

2.4.2 Exemestane

Table 35. Exemestane Drug Information

Scientific Name Exemestane[28]	
Trade Name(s) on Saudi Market	Aromasin ; Aromaplex ; Xemetan ; Arexa ; Ezoloc
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2003
FDA approved/off label	Yes
EMEA approved/off label	Yes

MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Aromatase inhibitor
SFDA Registration Number (New)	Aromasin : 0901233077 Aromaplex : 2408234049 Xemetan : 86-370-18 Arexa : 20-5223-19 Ezoloc: 434-212-19
ATC Code	L02BG06
Pharmacological Class (ASHP)	68:16.08 – Antiestrogens
Drug Information	
Dosage Form	Coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	25 mg once daily
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, PE, QL
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)	Maximum daily dose: 25 mg
ST (Step Therapy)	Preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Maintenance treatment of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy. Second-line treatment of ovarian cancer (platinum sensitive or resistant).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	25 mg

Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, alopecia, hyperhidrosis, hot flash, nausea, Lymphocytopenia, Increased serum alkaline phosphatase, depression, fatigue, headache, insomnia, pain, arthralgia - Most serious: Acute myocardial infarction, angina pectoris, ischemic heart disease, lymphedema, increased liver enzymes, Heart failure, thromboembolism
Drug Interactions*	Risk X: Estrogen Derivatives; Tamoxifen Risk D: CYP3A4 Inducers (Strong); St John's Wort Risk C: Methadone; Levomethadone; CYP3A4 Inducers (Moderate)
Special Population	N/A
Pregnancy	Pregnancy Category C
Lactation	It is not known if exemestane is present in breast milk. The manufacturer does not recommend breastfeeding during therapy or for 1 month after the last exemestane dose.
Contraindications	Hypersensitivity to exemestane or any component of the formulation.
Monitoring Requirements	- 25-hydroxy vitamin D levels (at baseline). - Assess bone mineral density at baseline and during therapy in patients with, or at risk for osteoporosis - Pregnancy status
Precautions	- Decreased bone mineral density - Lymphopenia - Elevations of AST, ALT, alkaline phosphatase, and gamma glutamyl transferase >5 times ULN
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 anastrozole in ovarian cancer.

Conclusion statement – Anastrozole

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is a preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Hormonal therapy can also be used in the maintenance setting of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy.

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is also used in the second-line setting of ovarian cancer (platinum sensitive or resistant).

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

2.4.3 Letrozole

Table 36. Letrozole Drug Information

Scientific Name Letrozole[29]	
Trade Name(s) on Saudi Market	Femaplex ; Rozlet ; Marlet ; Femara ; Trezol ; Letara ; Xorola ; Letrazan
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2016
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Aromatase inhibitor
SFDA Registration Number (New)	Femaplex : 2408234052 Rozlet : 413-212-19 ; 0709234153 Marlet : 103-370-18 Femara : 132-9-16 Tresol : 3010222835 Letara : 1906222219

	Xorola : 3-5251-19 Letrazan : 1-5260-19
ATC Code	L02BG04
Pharmacological Class (ASHP)	68:16.08 – Antiestrogens
Drug Information	
Dosage Form	Film-coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	2.5 mg once daily until disease progression or unacceptable toxicity
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, PE, QL
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)	Maximum daily dose: 2.5 mg
ST (Step Therapy)	Preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Maintenance treatment of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy. Second-line treatment of ovarian cancer (platinum sensitive or resistant).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	2.5 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, flushing, diaphoresis, night sweats, hot flash, hypercholesterolemia, weight gain, nausea, dizziness, fatigue, arthralgia, arthritis, asthenia, back

	pain, bone fracture, ostealgia, osteoporosis, cough, dyspnea - Most serious: Acute myocardial infarction, angina pectoris, cardiac failure, cerebrovascular accident, hemorrhagic stroke, thromboembolic disease, transient ischemic attacks, vaginal hemorrhage, endometrial hyperplasia
Drug Interactions*	Risk X: Tamoxifen Risk C: Methadone; Levomethadone; Nintedanib
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if letrozole is present in breast milk. The manufacturer does not recommend breastfeeding during therapy or for 3 weeks after the last letrozole dose.
Contraindications	Hypersensitivity to letrozole or any component of the formulation.
Monitoring Requirements	- Hepatic function tests (at baseline) - Consider monitoring cholesterol panel and bone mineral density - Pregnancy status - Monitor adherence
Precautions	- CNS depression - Increased cholesterol
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 anastrozole in ovarian cancer.

Conclusion statement – Anastrozole

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is a preferred treatment option for Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Hormonal therapy can also be used in the maintenance setting of Stage I-IV Low-

grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy.

Hormone therapy with aromatase inhibitors (anastrozole, letrozole, exemestane) is also used in the second-line setting of ovarian cancer (platinum sensitive or resistant).

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

2.4.4 Megestrol Acetate

Table 37. Megestrol Acetate Drug Information

Scientific Name Megestrol Acetate[30]	
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]*	800 mg/day orally for 4 weeks and then 400 mg/day until tumor progression (off-label use; based on published studies).
Adjustment	N/A Use with caution in renal impairment
Prescribing edits*	AGE, MD, ST, PE, QL
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)	800 mg per day
ST (Step Therapy)	Second-line treatment for recurrent ovarian cancer (platinum sensitive or resistant)
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 ovarian cancer.

Conclusion statement – Megestrol acetate

Megestrol acetate is used as a hormone therapy option in the second-line setting of ovarian cancer (platinum sensitive or resistant) (off-label; based on published studies).

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

2.4.5 Tamoxifen

Table 38. Tamoxifen Drug Information

Scientific Name Tamoxifen[31]	
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)	C56
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: 3-206-101 (10 mg; 30 tabs); 4-206-101 (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]*	20 mg twice daily
Adjustment	N/A Chronic dialysis: No dosage adjustment necessary
Prescribing edits*	AGE, MD, ST, PE, QL
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)	Maximum daily dose: 60 mg
ST (Step Therapy)	Hormone therapy (less preferred) treatment option for Stage I-IV Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. Maintenance hormone therapy of Stage I-IV Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy. Second-line treatment for recurrent ovarian cancer (platinum sensitive or resistant).
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 are 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 ovarian cancer.

Conclusion statement – Tamoxifen

Tamoxifen is a (less preferred) hormone therapy treatment option for Stage I-IV Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer. It can also be used in the maintenance setting of Stage I-IV Low-grade serous (stage IC)/Grade I endometrioid (stage IC) ovarian/fallopian tube/primary peritoneal cancer after treatment with chemotherapy.

It can also be used in the second-line setting of ovarian cancer (platinum sensitive or resistant).

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

2.5 Immune Checkpoint Inhibitors (ICIs)

2.5.1 Pembrolizumab

Table 39. Pembrolizumab Drug Information

Scientific Name Pembrolizumab[32]	
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)	C56
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. It 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, 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)	To be used in patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase.
QL (Quantity Limit)	Maximum daily dose 400 mg
ST (Step Therapy)	Second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent in patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase
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)

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

Conclusion Statement – Pembrolizumab

Pembrolizmuab is used in the second-line setting of ovarian cancer (platinum sensitive or resistant) as a single agent in patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥ 10 mutations/megabase.

2.6 PARP Inhibitors

2.6.1 Olaparib

Table 40. Olaparib Drug Information

Scientific Name **Olaparib**[33]	
Trade Name(s) on Saudi Market	Lynparza
SFDA Classification	Prescription
SFDA Approved Indication	Yes, 2021
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	PARP Inhibitor
SFDA Registration Number (New)	1402210511 (100 mg); 1402210512 (150 mg)
ATC Code	L01XX46
Pharmacological Class (ASHP)	68:16.08 – Antiestrogens
Drug Information	
Dosage Form	Film-coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Ovarian cancer, advanced, *BRCA* - mutated , first-line maintenance therapy (monotherapy):** 300 mg twice daily until disease progression or unacceptable toxicity or completion of 2 years of therapy.

	Ovarian cancer, advanced, homologous recombination deficient-positive, first-line maintenance therapy (combination therapy): 300 mg twice daily (in combination with bevacizumab) until disease progression or unacceptable toxicity or completion of 2 years of therapy. **Ovarian cancer, recurrent, *BRCA*-mutated, maintenance therapy:** 300 mg twice daily until disease progression or unacceptable toxicity.
Adjustment	Renal Impairment (Adult): - CrCl >50 mL/minute: No dosage adjustment necessary. - CrCl 31 to 50 mL/minute: *Tablets:* Reduce dose to 200 mg twice daily. - CrCl ≤30 mL/minute/ End-stage kidney disease: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Hepatic Impairment (Adult): - Mild to moderate impairment (Child-Turcotte-Pugh classes A, B): No dosage adjustment necessary. - Severe impairment (Child-Turcotte-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	AGE, MD, CU, ST, PE, PA, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	Olaparib can be given as a single agent or in combination with bevacizumab (if received bevacizumab-containing therapy).
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	BRCA mutation

	Homologous recombination deficient-positive
QL (Quantity Limit)	Maximum daily dose: 300 mg BID
ST (Step Therapy)	Maintenance therapy in patients with BRCA -mutated, and/or homologous recombination deficient-positive, newly diagnosed stage II–IV disease (high-grade serous, grade 2/3 endometrioid, or BRCA1/2-mutated clear cell carcinoma or carcinosarcoma) if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. Maintenance therapy in patients with BRCA -mutated recurrent disease if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARP inhibitor. 3rd line treatment for advanced recurrent ovarian cancer (platinum sensitive or platinum resistant) for patients with deleterious germline BRCA-mutated who have been treated with two or more lines of chemotherapy
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	300 mg BID
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Skin rash; Hypomagnesemia; Abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, dyspepsia, nausea, stomatitis, vomiting; Urinary tract infection; Anemia, increased MCV, leukopenia, neutropenia, thrombocytopenia; Influenza; Dizziness, fatigue, headache; Arthralgia, back pain, myalgia; Increased serum creatinine, bronchitis, cough, dyspnea,

	nasopharyngitis, rhinitis, sinusitis, upper respiratory tract infection - Most serious: Venous thromboembolism, Lymphocytopenia, myelodysplastic syndrome, myeloid leukemia
Drug Interactions*	Risk X: BCG (Intravesical); Bitter Orange; Cladribine; CYP3A4 Inducers; Dipyrone; Fexinidazole; Grapefruit Juice Risk D: CYP3A4 Inhibitors; Deferiprone; Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if olaparib is present in breast milk. The manufacturer does not recommend breastfeeding during therapy or for 1 month after the last anastrozole dose.
Contraindications	N/A
Monitoring Requirements	- CBC at baseline and monthly thereafter, or as clinically indicated - Renal function. - Monitor for signs/symptoms of venous thrombosis, pulmonary embolism, and pneumonitis - Monitor for signs of acute myeloid leukemia/myelodysplastic syndrome - Pregnancy status - Monitor adherence
Precautions	- Hypersensitivity - Pulmonary toxicity - Secondary malignancy - Thromboembolic events
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**), and Institute for Quality and Efficiency in Health Care (**IQWIG**),

HTA review and recommendations of olaparib in ovarian cancer treatment options.

Table 41. Olaparib HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Olaparib	HAS[34,35]	07/2021: **Favorable opinion for reimbursement in combination with bevacizumab** for the **maintenance** treatment of adult patients with **advanced (FIGO stages III and IV) high-grade epithelial ovarian**, fallopian tube or primary peritoneal cancer who are in response (complete or partial) **following completion of first-line platinum-based chemotherapy** in combination with bevacizumab and whose cancer is associated with **homologous recombination deficiency (HRD) positive status** defined by either a BRCA1/2 mutation and/or genomic instability. - **Therapeutic improvement compared to bevacizumab as monotherapy**. - The results from a subgroup analysis that was preplanned, but not incorporated in the methods to take into consideration inflation of the α overall alpha risk, suggesting the superiority of the olaparib + bevacizumab combination, compared to bevacizumab as monotherapy, in terms of **progression-free survival** (HR=0.33 [CI95%: 0.25-0.45]), with respective medians of 37.2 months and 17.7 months, in a phase 3, randomized, double-blind study; - **Higher toxicity**, with the occurrence of grade ≥ 3 adverse events in more than one in two patients (58.1%, including 34% treatment-related), permanent discontinuation of treatment due to an adverse event in 20.9% of patients (including 18% treatment-related) and, in particular, the onset of myelodysplastic syndrome/acute myeloid leukemia - The Transparency Committee considers that olaparib, in combination with bevacizumab, provides a **minor clinical added value (CAV**

		IV) compared to bevacizumab as monotherapy 12/2019: **Favorable opinion** for **reimbursement** in the **maintenance** treatment of patients with advanced **BRCA-mutated ovarian cancer who have responded to first-line chemotherapy**. - The clinical benefit of olaparib is **substantial** in the maintenance indication. - Demonstrated **superiority of olaparib in terms of progression-free survival** compared to placebo (median not reached in the olaparib group vs 13.8 months in the placebo group; HR = 0.30; 95% CI [0.23; 0.41]; $_p$ < 0.0001), without any demonstrated superiority on overall survival following the interim analysis scheduled in the protocol - Safety profile of olaparib, characterized primarily by **gastrointestinal** and **hematological** events but absence of long-term safety data - The committee considers that olaparib provides a **minor clinical added value (CAV IV)** in the care pathway for the treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian , fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
Olaparib	NICE[36-38]	07/2023: Olaparib is **recommended** as an option for the **maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian**, fallopian tube, or primary peritoneal cancer in adults whose cancer has responded to platinum-based chemotherapy, only if: • they have a **BRCA1 or BRCA2 mutation** • they have had **2 or more courses of platinum-based chemotherapy**. o Olaparib improves progression-free survival and overall survival compared with placebo.

		○ The most likely cost-effectiveness estimate is within what NICE considers an acceptable use of NHS resources. 04/2021: **Olaparib plus bevacizumab** is **recommended** for use within the Cancer Drugs Fund as an option for **maintenance treatment of advanced (FIGO stages 3 and 4) high-grade epithelial ovarian**, fallopian tube or primary peritoneal cancer in adults when: • there has been a **complete or partial response after first-line platinum-based chemotherapy plus bevacizumab**, and • the cancer is associated with **homologous recombination deficiency (HRD)**. ○ There is an ongoing clinical trial comparing maintenance treatment with olaparib plus bevacizumab with placebo plus bevacizumab in people whose cancer has responded to first-line platinum-based chemotherapy plus bevacizumab. ○ Early results suggest that it improves how long people live without their cancer getting worse. The evidence suggests that the treatment effect is bigger in people whose disease is HRD-positive. However, there is uncertainty about how olaparib plus bevacizumab affects the length of time people live. ○ The uncertainty in the clinical evidence means that the cost-effectiveness estimates are very uncertain, so the treatment is not recommended for routine use in the NHS. ○ If the treatment does increase the length of time people live, it has the potential to be cost effective. Further trial results will help to address the uncertainties in the clinical-and cost effectiveness estimates. ○ Therefore, olaparib plus bevacizumab maintenance treatment is recommended for use within the Cancer Drugs Fund while further data are collected. 04/2019: **Olaparib plus bevacizumab** is **recommended** for use within the Cancer Drugs Fund as an option for **maintenance treatment of advanced (FIGO stages 3 and 4) high-grade**

		epithelial ovarian, fallopian tube or primary peritoneal cancer in adults when: • there has been a **complete or partial response after first-line platinum-based chemotherapy plus bevacizumab**, and • the cancer is associated with **homologous recombination deficiency (HRD)**. o An ongoing clinical trial shows that olaparib delays disease progression. But it is not known whether people having olaparib live longer because people in the trial have not been followed up for long enough. o The currently available clinical trial evidence does not show a significant difference in overall survival between olaparib and placebo. o This makes the estimates of cost effectiveness very uncertain. Therefore, olaparib is not recommended for routine use in the NHS. o If olaparib increases the length of time people live it has the potential to be cost effective, but more evidence from the ongoing trial is needed to address the uncertainties. Therefore, it is recommended for use in the Cancer Drugs Fund, while further data are collected.
Olaparib	CADTH[39,40]	12/2019: CADTH **recommends the reimbursement** of **olaparib monotherapy** if cost-**effectiveness can be improved** to an acceptable level through a reduction in price. o Reimbursement should be for the **maintenance treatment** of adult patients with **newly diagnosed, advanced, BRCA-mutated, high grade epithelial ovarian**, fallopian tube, or primary peritoneal cancer who are **in response** (complete or partial) to **first-line platinum-based chemotherapy**, as per SOLO-1 trial. o Patients must have received at least 4 cycles of platinum-based chemotherapy. Maintenance olaparib should begin within 8 weeks of the last platinum dose. Reimbursement should be for patients with good performance status. o There is a net clinical benefit of olaparib maintenance treatment compared with placebo, based on a statistically significant

		improvement in PFS, no detrimental effect on quality of life, and a manageable toxicity profile. 09/2017: CADTH **recommends reimburse**ment of **olaparib** conditional on the **cost effectiveness being improved** to an acceptable level. o Reimbursement should be for olaparib monotherapy **maintenance treatment** of adult patients with **platinum-sensitive relapsed BRCA-mutated** (germline or somatic as detected by approved testing) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have completed **at least two previous lines of platinum-based chemotherapy** and are in radiologic response (complete or partial response) to their most recent platinum-based chemotherapy regimen as per the SOLO-2 trial. o Patients must have received at least four cycles of their most recent platinum-based chemotherapy. Maintenance therapy with olaparib should begin within eight weeks of the last dose of platinum-based chemotherapy. o There is a net clinical benefit of olaparib maintenance treatment compared with placebo, based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), no appreciable detrimental effect on quality of life (QoL), and a manageable but not insignificant toxicity profile. o Olaparib, at the submitted price, and given the high level of uncertainty in the magnitude of long-term overall survival benefit, is not cost-effective in this population compared with best supportive care.
Olaparib	IQWIG[41,42]	02/2023: **Maintenance therapy** of adult patients with **advanced** (FIGO stages III and IV) **high-grade epithelial ovarian cancer** who are **in response** (complete or partial) following completion of **first-line platinum-based chemotherapy in combination with bevacizumab** and whose tumor is associated with HRD-positive status o Patients with no evidence of disease after PDS and patients with no evidence of

		disease or complete response after chemotherapy: **indication of considerable added benefit** o Patients with no evidence of disease after IDS and patients with partial: **indication of lesser benefit** 07/2023: **No hint of an added benefit** of olaparib in **comparison with niraparib**

Conclusion statement – Olaparib

PARP inhibitors are used as a maintenance therapy in patients with ***BRCA* -mutated, and/or homologous recombination deficient-positive**, newly diagnosed stage II–IV disease (high-grade serous, grade 2/3 endometrioid, or BRCA1/2-mutated clear cell carcinoma or carcinosarcoma) if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. Olaparib can be given as a single agent or in combination with bevacizumab (if received bevacizumb-containing therapy).

They are also used as a maintenance therapy in patients with ***BRCA* -mutated** recurrent disease if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARP inhibitor.

Olaparib can also be used as a 3rd line treatment for advanced recurrent ovarian cancer (platinum sensitive or platinum resistant) for patients with deleterious germline BRCA-mutated who have been treated with two or more lines of chemotherapy (off-label use; more data needed to support the use in this setting-mentioned in NCCN guidelines as Category 3 recommendation).

All HTA organisms **support the reimbursement of olaparib** for the **maintenance** treatment of patients with **newly diagnosed**, **advanced (FIGO stages 3 and 4), BRCA-mutated**, high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are **in response (complete or partial) to first-line platinum-based chemotherapy**.

- Patients must have received at least **four cycles** of their most recent platinum-based chemotherapy. Maintenance therapy with olaparib should begin **within eight weeks** of the last dose of platinum-based chemotherapy
- There is a **net clinical benefit** of olaparib maintenance treatment compared with placebo, based on a statistically significant improvement in PFS, no detrimental effect on quality of life, and a manageable toxicity profile.
- HAS, NICE, and IQWIG support both the use of **olaparib monotherapy** and the **combination of olaparib plus bevacizumab** in this maintenance indication.

- CADTH mentions that a condition for olaparib reimbursement is that **cost-effectiveness should be improved to an acceptable level** through a **reduction in price**. They note that given the high level of uncertainty in the magnitude of long-term overall survival benefit, olaparib is not cost-effective compared with best supportive care.
- CADTH also supports the use of olaparib monotherapy in the maintenance setting of **relapsed BRCA-mutated** high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have completed **at least two previous lines of platinum-based chemotherapy** and are in radiologic response (complete or partial response) to their most recent platinum-based chemotherapy regimen.

2.7 Topoisomerase Inhibitors

2.7.1 Doxorubicin

Table 42. Doxorubicin Drug Information

Scientific Name **Doxorubicin**[43]	
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)	C56
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]*	75 mg/m^2 every 21 days for 6 cycles
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/Pediatric): - 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. Renal Impairment (Pediatric): - CrCl <50 mL/minute: No dosage adjustment necessary. - Hemodialysis: Supplemental dose is not necessary.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	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 advanced recurrent ovarian cancer (platinum sensitive or resistant) as a single agent.
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*	Cumulative lifetime limit: 400 mg/m^2
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, mucositis, 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 ovarian neoplasms. This is probably because doxorubicin has a limited role in the management of ovarian cancer. Moreover, the drug is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion Statement – Doxorubicin

Doxorubicin is used in the second-line setting of advanced recurrent ovarian cancer (platinum sensitive or resistant) as a single agent.

There is no data issued by HTA bodies regarding its use.

2.7.2 Doxorubicin Liposomal

Table 43. Doxorubicin Liposomal Drug Information

Scientific Name Pegylated liposomal doxorubicin[44]	
Trade Name(s) on Saudi Market	Deroxi
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2023
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Anthracycline; Topoisomerase II inhibitor
SFDA Registration Number (New)	1505233641
ATC Code	L01DB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	50 mg/m^2 once every 28 days until disease progression or unacceptable toxicity. 30 mg/m^2 on day 1 every 28 days (in combination with carboplatin ± bevacizumab) for up to 6 cycles, followed by bevacizumab maintenance (if used with chemotherapy) 40 mg/m^2 once every 28 days (as a single agent or in combination with bevacizumab) until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): - Bilirubin >1.2 to <3 mg/dL: Reduce dose to 75% of the original dose. - Bilirubin 3 to 5 mg/dL: Reduce dose to 50% of the original dose.

	- Bilirubin >5 mg/dL: Use is not recommended.
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 carboplatin and/or bevacizumab. 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)	50 mg/m^2 per day/per cycle
ST (Step Therapy)	Primary treatment for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with carboplatin. Second-line treatment of ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin ± bevacizumab (preferred regimen). Second-line treatment (preferred) for patients with platinum resistant disease either as a single agent or in combination with bevacizumab.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	50 mg/m^2 per day/per cycle
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Cardiomyopathy, fatigue, headache, palmar-plantar erythrodysesthesia, skin rash, alopecia, nausea, stomatitis, vomiting, diarrhea, constipation, mucous membrane disease, dyspepsia,; Thrombocytopenia, anemia, neutropenia; infection, asthenia, back pain, pharyngitis, dyspnea, fever, infusion-related reaction - Most serious: Deep vein thrombosis

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	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	It is not known if doxorubicin (liposomal) is present in breast milk. Breastfeeding should be discontinued during doxorubicin (liposomal) treatment.
Contraindications	History of severe hypersensitivity (including anaphylaxis) to doxorubicin (liposomal), conventional doxorubicin, or any component of the formulation.

Monitoring Requirements	- CBC with differential and platelet count, liver function tests. - Assess left ventricular function with ECG or multigated acquisition scan prior to and during treatment to detect acute changes; monitor after treatment to detect delayed cardiotoxicity. - Pregnancy status - Monitor infusion site. - Monitor for infusion reactions, hand-foot syndrome, stomatitis, and oral ulceration/discomfort suggestive of secondary oral malignancy.
Precautions	- Bone marrow suppression - Cardiomyopathy - Infusion-related reactions - Palmar-plantar erythrodysesthesia (hand-foot syndrome) - Secondary malignancy
Black Box Warning	- Cardiomyopathy - Infusion-related 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 liposomal doxorubicin in ovarian cancer.

Conclusion Statement – Liposomal Doxorubicin

Liposomal doxorubicin is a primary treatment option for Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with carboplatin. It is also used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease in combination with carboplatin ± bevacizumab (preferred regimen). It is also a preferred treatment option for patients with platinum resistant disease either as a single agent or in combination with bevacizumab.

There is no data issued by HTA bodies regarding its use.

2.7.3 Etoposide

Table 44. Etoposide Drug Information

Scientific Name Etoposide[45]	
Trade Name(s) on Saudi Market	Etoposid Ebewe, Lastet
SFDA Classification	Prescription
SFDA approved Indication	Yes, Etoposid Ebewe, 2001; Lastet 2001
FDA approved / off label	Yes, 1983
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Podophyllotoxin derivative, Topoisomerase II inhibitor
SFDA Registration Number (New)	25-355-01 (Etoposid Ebewe 100 mg) 26-355-01 (Etoposid Ebewe 200 mg) 2-202-01 (Lastet 100 mg)
ATC Code	L01CB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Oral (in ovarian cancer)
Dose (Adult) [DDD]*	50 mg PO BID If previous neutropenia, or age greater than or equal to 70, or heavily pre-treated: 50 mg PO BID alternating with 50 mg PO once daily
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl >50 mL/min: No adjustment required. - CrCl 15 to 50 mL/min: Administer 75% of dose - CrCl <15 mL min: Data not available; consider further dose reductions - Hemodialysis: Reduce dose by 50%; not removed by hemodialysis - PD: Administer 50% of dose; supplemental dose is not necessary

	- CRRT: Administer 75% of dose Hepatic Impairment (Adult): - Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose Renal Impairment (Pediatric): - GFR >50 mL/min/1.73 m^2: No adjustment - GFR 10 to 50 mL/minute/1.73 m^2: 75% of dose - GFR <10 mL/minute/1.73 m^2: 50% of dose - Hemodialysis/PD (after dialysis on dialysis days): 50% of dose - CRRT: 75% of dose and reduce for hyperbilirubinemia Hepatic Impairment (Pediatric): - Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose
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 100 mg/m^2
ST (Step Therapy)	Second-line treatment of platinum resistant ovarian cancer as a single agent (preferred option).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	100 mg/m^2
Maximum Daily Dose Pediatrics*	100 mg/m^2
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, nausea and vomiting, anorexia, diarrhea, leukopenia, thrombocytopenia, anemia - Most serious: leukopenia, thrombocytopenia, anemia, anaphylactoid reaction
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine,

	Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, CycloSPORINE, CYP3A4 Inducers (Strong), 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. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Etoposide is present in breast milk. Concentrations are below the limit of detection 24 hours after the last dose (Azuno 1995). The manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of treatment to the mother
Contraindications	Hypersensitivity to etoposide or any component of the formulation
Monitoring Requirements	CBC with differential, liver function (bilirubin, ALT, AST), albumin, renal function tests Monitor vital signs (BP); monitor for signs of an infusion reaction. Monitor for secondary malignancies
Precautions	- Bone marrow suppression

	- Extravasation - Hypersensitivity - Hypotension - Secondary malignancies
Black Box Warning	- Experienced physician - 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 etoposide in ovarian cancer.

Conclusion Statement – Etoposide

Etoposide (oral) is used in the second-line setting of platinum resistant ovarian cancer as a single agent (preferred option).

There is no data issued by HTA bodies regarding its use.

2.7.4 Irinotecan

Table 45. Irinotecan Drug Information

Scientific Name Irinotecan[46]	
Trade Name(s) on Saudi Market	Irinotecan (Jazeera), Campto, Imtus, Tecana
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, 2013
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Camptothecin; Topoisomerase I Inhibitor
SFDA Registration Number (New)	Irinotecan (Jazeera): 1810222747 (100mg); 1810222748 (40mg) Campto: 7-5381-22 (100mg)

	Imtus: 1-5197-19 (40mg); 2-5197-19 (100mg) Tecana: 6-5251-19 (100mg)
ATC Code	L01XX19
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Concentrate for solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Ovarian cancer, recurrent:** *Platinum- and taxane-resistant*: 100 mg/m^2 days 1, 8, and 15 every 4 weeks (as a single-agent) for up to 6 cycles. *Platinum- refractory/resistant:* Initial: 50 mg/m^2 on days 1 and 8 every 3 weeks (in combination with gemcitabine) until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - GFR <10 mL/minute: Initiate with 50% to 66% of the original dose; increase if tolerated - Hemodialysis: Although the manufacturer does not recommend use, may initiate with 50% to 66% of the original dose; increase if tolerated Hepatic impairment (Adult): - Liver metastases with normal hepatic function: No dosage adjustment necessary. - Bilirubin >ULN to ≤2 mg/dL: Consider reducing initial dose by 1 dose level. - Bilirubin >2 mg/dL: Use is not recommended. Renal/Hepatic Impairment (Pediatric): *Refer to individual protocols* (adjustment suggested)
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 cisplatin (clear cell sarcoma); 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 350 mg/m^2
ST (Step Therapy)	Second-line treatment of ovarian cancer, for platinum sensitive clear cell carcinoma (in combination with cisplatin), and for platinum refractory disease as a single agent.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	350 mg/m^2
Maximum Daily Dose Pediatrics*	*Refer to specific protocols*
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Vasodilation, cholinergic syndrome, pain, dizziness, insomnia, headache, alopecia, diaphoresis, skin rash, weight loss, dehydration, diarrhea, nausea, abdominal pain, vomiting, abdominal cramps, anorexia, constipation, mucositis, flatulence, stomatitis, anemia, neutropenia, thrombocytopenia, increased LFTs, infection, weakness, back pain, dyspnea, cough, rhinitis, fever - Most serious: Febrile neutropenia, hemorrhage, neutropenic infection, abdominal distention
Drug Interactions*	- Risk X: Abrocitinib, Atazanavir, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Itraconazole, Ketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ritlecitinib, Sacituzumab Govitecan, Tacrolimus (Topical), Talimogene Laherparepvec,

	Tertomotide, Tofacitinib, Upadacitinib, UGT1A1 Inhibitors, Vaccines (Live) - Risk D: COVID-19 Vaccine (mRNA), CYP3A4 Inducers (Strong), Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, St John's Wort, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Irinotecan and its metabolites are present in breast milk. The manufacturer does not recommend breastfeeding during therapy and for 7 days after the last irinotecan dose.
Contraindications	Severe hypersensitivity to irinotecan or any component of the formulation
Monitoring Requirements	- CBC with differential, platelet count, and hemoglobin with each dose; bilirubin, electrolytes (with severe diarrhea) - Pregnancy status - Monitor for cholinergic reactions; bowel movements and hydration status - Monitor for signs/symptoms of pulmonary toxicity - Monitor for hypersensitivity reactions; monitor infusion site for signs of inflammation. - Consider UGT1A1 genotype testing for the *28 and *6 alleles to

	determine UGT1A1 metabolizer status
Precautions	- Bone marrow suppression - Diarrhea - Extravasation: Irritant - Hypersensitivity - Pulmonary toxicity - Renal toxicity
Black Box Warning	- Diarrhea - 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 irinotecan in ovarian cancer.

Conclusion Statement – Irinotecan

Irinotecan is used in the second-line setting of ovarian cancer, for platinum sensitive clear cell carcinoma (in combination with cisplatin), and for platinum refractory disease as a single agent.

There is no data issued by HTA bodies regarding its use.

2.7.5 Topotecan

Table 46. Topotecan Drug Information

Scientific Name Topotecan[47]	
Trade Name(s) on Saudi Market	Hycamtin
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2016
FDA approved / off label	Yes, 2007
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	No
Indication (ICD-10)	C56
Drug Class	Antineoplastic agent
Drug Sub-class	Camptothecin; Topoisomerase I Inhibitor

SFDA Registration Number (New)	3-5773-23
ATC Code	L01XX17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Ovarian cancer, metastatic:** IV: 1.5 mg/m^2/day for 5 consecutive days every 21 days, continue until disease progression or unacceptable toxicity **or** 1.25 mg/m^2/day for 5 days every 21 days until disease progression or unacceptable toxicity or a maximum of 12 months or (weekly administration; off-label dosing) 4 mg/m^2 on days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity or a maximum of 12 months
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): Baseline: Initial dosing: - CrCl 46 to 60 mL/minute: Administer 80% of usual dose. - CrCl 31 to 45 mL/minute: Administer 75% of dose. - CrCl ≤30 mL/minute: Administer 70% of dose. Renal Impairment (Pediatric): *Baseline: Initial dosing*: - CrCl >40 mL/minute/1.73 m^2: No adjustment necessary. - CrCl 20 to 40 mL/minute/1.73 m^2: Administer 50% of dose. - CrCl <20 mL/minute/1.73 m^2: Hold doses until renal function recovers (CrCl >20 mL/minute/1.73 m^2). *During therapy:* - CrCl >60 mL/minute/1.73 m^2: No adjustment necessary.

	- CrCl 40 to 60 mL/minute/1.73 m^2: Administer 50% of dose. - CrCl 20 to <40 mL/minute/1.73 m^2: Administer 25% to 50% of dose. - CrCl <20 mL/minute/1.73 m^2: Hold doses until renal function recovers (CrCl >20 mL/minute/1.73 m^2). - Hemodialysis: Avoid use. - Continuous ambulatory peritoneal dialysis (CAPD): Avoid use - Continuous renal replacement therapy (CRRT): 0.75 mg/m^2
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 bevacizumab or sorafenib. 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/cycle dose: 4 mg/m^2
ST (Step Therapy)	Second-line setting of ovarian cancer in patients with platinum resistant disease (preferred option)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	4 mg/m^2
Maximum Daily Dose Pediatrics*	*Refer to specific protocols*
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Fatigue, alopecia, nausea, diarrhea, vomiting, anorexia, anemia, neutropenia, thrombocytopenia - Most serious: Febrile neutropenia, bone marrow depression, intestinal obstruction
Drug Interactions*	- Risk X: BCG Products, Cladribine, Dipyrone, Fexinidazole, Lasmiditan, Leniolisib, Pacritinib, P-glycoprotein/ABCB1 Inhibitors, Pimecrolimus, Sparsentan,

	Taurursodiol, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Velpatasvir, Voxilaprevir - Risk D: Adagrasib, Deferiprone, Erdafitinib, Fosphenytoin-Phenytoin, Granulocyte Colony-Stimulating Factors, Lenograstim, Lipegfilgrastim, Palifermin, Platinum derivatives, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	It is not known if topotecan is present in breast milk. The manufacturer recommends lactating females not breastfeed during therapy and for 1 week following the last topotecan dose.
Contraindications	Severe hypersensitivity to topotecan or any component of the formulation
Monitoring Requirements	- CBC with differential and platelet count, renal function tests, bilirubin - Pregnancy status - Monitor for symptoms of interstitial lung disease; diarrhea symptoms/hydration status; monitor infusion site
Precautions	- Bone marrow suppression - Extravasation: Irritant - Gastro-intestinal toxicity - Hypersensitivity - Neutropenic enterocolitis - Pulmonary toxicity - Renal impairment
Black Box Warning	- 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 topotecan in ovarian cancer.

Conclusion statement - Topotecan

Topotecan ± bevacizumab is used in the second-line setting of ovarian cancer in patients with platinum resistant disease (preferred option). Sorafenib/Topotecan is also an alternative treatment option in this setting.

There is no data issued by HTA bodies regarding its use.

2.8 Tyrosine Kinase Inhibitors

2.8.1 Dabrafenib

Table 47. Dabrafenib Drug Information

Scientific Name Dabrafenib mesylate[48]	
Trade Name(s) on Saudi Market	Tafinlar
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered, 2018
FDA approved/off label	Yes (Solid tumors, BRAF V600E mutation)
EMEA approved/off label	Yes (Solid tumors, BRAF V600E mutation)
MHRA approved/off label	Yes (Solid tumors, BRAF V600E mutation)
PMDA approved/off label	Yes (Solid tumors, BRAF V600E mutation)
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	BRAF Kinase Inhibitor
SFDA Registration Number (New)	Tafinlar 75 mg: 25-665-18 (120 tabs); 26-665-18 (28 tabs) Tafinlar 50 mg: 23-665-18 (120 tabs); 24-665-18 (28 tabs)
ATC Code	L01XE23
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	

Dosage Form	Hard capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	**Solid tumors, unresectable or metastatic, with BRAF V600E mutation:** 150 mg twice daily, approximately every 12 hours (in combination with trametinib); continue until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): eGFR <15 mL/minute/1.73 m^2: There are no dosage adjustments provided in the manufacturer's labeling. Hepatic Impairment (Adult): Moderate (bilirubin >1.5 to 3 times ULN and any AST) to severe (bilirubin >3 to 10 times ULN and any AST) impairment: No dosage adjustments provided in the manufacturer's labeling.
Prescribing Edits*	MD, ST, PE, PA, 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)	Used for BRAF V600E mutation positive tumors
QL (Quantity Limit)	Maximum daily dose 150 mg BID
ST (Step Therapy)	Second-line treatment of progressive locoregional unresectable/metastatic disease for **patients with positive BRAF V600E mutation.**
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	150 mg BID
Maximum Daily Dose Pediatric*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, hyperkeratosis, palmar-plantar erythrodysesthesia, skin rash, squamous cell carcinoma of skin,

	xeroderma, hyperglycemia, hyponatremia, hypophosphatemia, constipation, papilloma, Increased serum alkaline phosphatase, chills, headache, arthralgia, back pain, myalgia, cough, fever, - Most serious: Squamous cell carcinoma of skin, basal cell carcinoma of skin, bullous rash, malignant melanoma, keratoacanthoma, malignant neoplasm, pancreatitits
Drug Interactions*	CYP3A4 Substrates; QT prolonging agents
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if dabrafenib is present in breast milk. Breastfeeding is not recommended by the manufacturer during dabrafenib treatment and for 2 weeks after the last dabrafenib dose.
Contraindications	N/A
Monitoring Requirements	- BRAF V600K or V600E mutation status - Serum glucose, electrolytes, renal function - Pregnancy status - Periodic dermatologic evaluations - Monitor for febrile drug reactions and signs/symptoms of infections. - For patients receiving combination therapy with trametinib: Hepatic function; CBC; left ventricular ejection fraction; Monitor for signs/symptoms of hemorrhage, venous thromboembolism, interstitial lung disease, hemophagocytic lymphohistiocytosis and retinal pigment epithelial detachment or retinal vein occlusion
Precautions	- Cardiomyopathy - Dermatologic toxicity - Febrile reactions

	- Hemophagocytic lymphohistiocytosis - Hemorrhage - Hyperglycemia - Malignancy - Ocular toxicity - QT prolongation - Venous thromboembolism - Glucose-6-phosphate dehydrogenase deficiency
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of dabrafenib/trametinib for the treatment of ovarian cancer.**

Conclusion Statement – Dabrafenib

Dabrafenib (in combination with trametinib) is a second-line treatment option for recurrent Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer (platinum sensitive or refractory) in patients with BRAF V600E mutation. There is no HTA data for its use in this indication.

2.8.2 Entrectinib

Table 48. Entrectinib Drug Information

Scientific Name Entrectinib[49]	
Trade Name(s) on Saudi Market	Rozlytrek
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered, 2022
FDA approved/off label	Yes (Solid tumors with NTRK gene fusion)
EMEA approved/off label	Yes (Solid tumors with NTRK gene fusion)
MHRA approved/off label	Yes (Solid tumors with NTRK gene fusion)
PMDA approved/off label	Yes (Solid tumors with NTRK gene fusion)
Indication (ICD-10)	C56

Drug Class	Antineoplastic Agent
Drug Sub-Class	Tropomyosin Receptor Kinase (TRK) Inhibitor
SFDA Registration Number (New)	Rozlytrek 100 mg: 0301221550 Rozlytrek 200 mg: 0301221552
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Hard capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	**Solid tumors, locally advanced or metastatic, *NTRK* gene fusion–positive:** 600 mg once daily until disease progression or unacceptable toxicity.
Dose (Pediatrics)	N/A
Adjustment	Renal impairment prior to treatment initiation: No dosage adjustment is necessary. Hepatic impairment prior to treatment initiation: No dosage adjustment is necessary. Hepatic toxicity during treatment: - Grade 3: Withhold entrectinib until recovery to ≤ grade 1 or to baseline; resume at the same dose if recovery occurs within 4 weeks. Permanently discontinue entrectinib if recovery does not occur within 4 weeks. For recurrent grade 3 toxicity, resume at a reduced dose if toxicity resolves within 4 weeks. - Grade 4: Withhold entrectinib until recovery to ≤ grade 1 or to baseline; resume at a reduced dose if recovery occurs within 4 weeks. Permanently discontinue entrectinib if recovery does not occur within 4 weeks. Permanently discontinue for recurrent grade 4 toxicity.

	- ALT or AST >3 times ULN with concurrent total bilirubin >1.5 times ULN (in the absence of cholestasis or hemolysis): Permanently discontinue entrectinib.
Prescribing Edits*	MD, ST, PE, PA, 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)	Used for *NTRK* gene fusion–positive tumors
QL (Quantity Limit)	Maximum daily dose 600 mg
ST (Step Therapy)	Second-line treatment of progressive locoregional unresectable/metastatic disease for **patients with positive NTRK gene fusion.**
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	600 mg
Maximum Daily Dose Pediatric*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, fatigue, dizziness, hyperuricemia, hypernatremia, anemia, dyspnea - Most serious: pulmonary embolism, cardiac failure, myocarditis, suicidal ideation
Drug Interactions*	CYP3A4 Inducers (Moderate/Strong): May decrease the serum concentration of Entrectinib (Risk X) CYP3A4 Inhibitors (Moderate/Strong): May increase the serum concentration of Entrectinib (Risk D) Domperidone: QT-prolonging agents may enhance the QTc-prolonging effect of Domperidone (Risk D) Grapefruit juice: May increase the serum concentration of Entrectinib (Risk X) Levoketoconazole/Posaconazole: QT-prolonging CYP3A4 Substrates may

	enhance the QTc-prolonging effect of Levoketoconazole (Risk X)
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, in utero exposure to entrectinib may cause fetal harm.
Lactation	It is not known if entrectinib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for 7 days after the last entrectinib dose.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	NTRK gene fusion status prior to initiation LFTs (at baseline and periodically) Left ventricular ejection fraction prior to initiation Pregnancy status prior to initiation Hepatitis B screening
Precautions	- Cardiac effects - CNS effects - Fractures - Hepatotoxicity - Hyperuricemia - Ocular toxicity - QT interval prolongation
Black Box Warning	N/A
REMS	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of entrectinib in NTRK fusion positive solid tumors treatment options by the following agencies/institutes/authorities: NICE, CADTH, and PBAC as applicable (no specific guidance issued for ovarian neoplasms).

Table 49. Entrectinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Entrectinib	NICE[50]	**08/2020:** Entrectinib is **recommended** for use within the Cancer Drugs Fund as an option for

		treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumors in adults and children 12 years and older if: ▪ the disease is locally advanced or metastatic or surgery could cause severe health problems and ▪ they have not had an NTRK inhibitor before and ▪ they have no satisfactory treatment options. It is recommended only if the conditions in the managed access agreement for entrectinib are followed.
	HAS[51]	**07/2021: Unfavorable opinion** for reimbursement in adult and pediatric patients 12 years of age and older with solid tumors expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options.
	IQWIG[52]	**11/2020:** The data presented by the company are **insufficient** in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib.

Conclusion Statement – Entrectinib

Entrectinib is a second-line treatment option for recurrent Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer (platinum sensitive or refractory) in patients with NTRK gene fusion-positive tumors. The guidance by HTA bodies is for the management of **NTRK gene fusion positive solid tumors in general**; however, there is no data related specifically to ovarian cancer.

2.8.3 Larotrectinib

Table 50. Larotrectinib Drug Information

Scientific Name Larotrectinib[53]	
Trade Name(s) on Saudi Market	Vitrakvi
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered, 2020
FDA approved/off label	Yes (Solid tumors with NTRK gene fusion)

EMEA approved/off label	Yes (Solid tumors with NTRK gene fusion)
MHRA approved/off label	Yes (Solid tumors with NTRK gene fusion)
PMDA approved/off label	No
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Tropomyosin Receptor Kinase (TRK) Inhibitor
SFDA Registration Number (New)	Vitrakvi 25 mg capsule: 2004200055 Vitrakvi 100 mg capsule: 2004200060 Vitrakvi 20 mg/mL solution: 2004200059
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Capsule; oral solution
Route of Administration	Oral
Dose (Adult) [DDD]*	**Solid tumors (with neurotrophic tyrosine receptor kinase [NTRK] gene fusion):** 100 mg twice daily until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal impairment prior to treatment initiation: No dosage adjustment necessary. Hepatic impairment prior to treatment initiation: - Mild impairment (Child-Pugh class A): No dosage adjustment necessary. - Moderate to severe impairment (Child-Pugh classes B and C): Reduce the initial larotrectinib dose by 50%. Hepatic toxicity during treatment: Grade 3 or 4 hepatic adverse reactions: Withhold larotrectinib until adverse reaction resolves to baseline or grade 1; if resolution occurs within 4 weeks, resume at the next lower dosage level.

	Discontinue permanently if the adverse reaction does not resolve within 4 weeks or if unable to tolerate larotrectinib after 3 dose reductions.
Prescribing Edits*	MD, ST, PE, PA, 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)	Solid tumors with NTRK gene fusion
QL (Quantity Limit)	Maximum dose 100 mg BID
ST (Step Therapy)	Second-line treatment of progressive locoregional unresectable/metastatic disease for **patients with positive NTRK gene fusion.**
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	100 mg BID
Maximum Daily Dose Pediatric*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, rash, hypoalbuminemia, anemia, increased LFTs - Most serious: pneumonia, myasthenia
Drug Interactions*	CYP3A4 Inducers (Strong): May decrease the serum concentration of Larotrectinib (risk D). CYP3A4 Inhibitors (Strong): May increase the serum concentration of Larotrectinib (risk D). Grapefruit Juice: May increase the serum concentration of Larotrectinib (risk D).
Special Population	N/A
Pregnancy	Based the mechanism of action and available human and animal data, larotrectinib may cause fetal harm if administered to a pregnant female.
Lactation	It is not known if larotrectinib is present in breast milk. Due to the potential for adverse events in a

	breastfed infant, breastfeeding is not recommended during therapy and for 1 week after the final larotrectinib dose.
Contraindications	Known hypersensitivity to the product or its components
Monitoring Requirements	- LFTs (at baseline and periodically) - Pregnancy status - Hepatitis B screening prior to initiation
Precautions	- CNS effects - Fractures - Hepatotoxicity
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of larotrectinib in NTRK fusion positive solid tumors treatment options by the following agencies/institutes/authorities: NICE, CADTH, and PBAC as applicable (no specific guidance issued for ovarian neoplasms).

Table 51. Larotrectinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Larotrectinib	NICE[54]	**05/2020**: Larotrectinib is **recommended** for use within the Cancer Drugs Fund as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumors in adults and children if: ▪ the disease is locally advanced or metastatic or surgery could cause severe health problems and ▪ they have no satisfactory treatment options. It is recommended only if the conditions in the managed access agreement for larotrectinib are followed.
	CADTH[55]	**09/2021: Reimbursed** by public drug plans for treating adult and pediatric patients with locally advanced or metastatic solid tumors who have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, or where surgical

		resection is likely to result in severe morbidity and have no satisfactory treatment options, but only if certain conditions are met: ▪ reimbursed as single-agent therapy if it is prescribed by a clinician with expertise in the use of antineoplastic drugs. ▪ the cost is reduced.
	PBAC[56]	**03/2022:** The PBAC **recommended** the listing of Larotrectinib for the treatment of patients with tropomyosin receptor kinase (NTRK) fusion tumors that are either unresectable locally advanced, metastatic, or locally advanced and unsuitable for surgery.

Conclusion Statement – Larotrectinib

Larotrectinib is a second-line treatment option for recurrent Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer (platinum sensitive or refractory) in patients with NTRK gene fusion-positive tumors. HTA bodies recommend the use of Larotrectinib – some with certain conditions – for the management of **NTRK gene fusion positive solid tumors in general**; however, there is no data related specifically to ovarian cancer.

2.8.4 Selpercatinib

Table 52. Selpercatinib Drug Information

Scientific Name Selpercatinib[57]	
Trade Name(s) on Saudi Market	Retevmo
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered, 2022; data on ovarian tumors not available
FDA approved/off label	Yes (Solid tumors, RET fusion-positive)
EMEA approved/off label	Yes (Solid tumors, RET fusion-positive)
MHRA approved/off label	Yes (Solid tumors, RET fusion-positive)
PMDA approved/off label	No
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	RET Kinase Inhibitor
SFDA Registration Number (New)	2806222274 (40 mg) 2806222275 (80 mg; 120 tabs) 2806222276 (80 mg; 60 tabs)

ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	**Solid tumors, RET fusion-positive:** Patients ≥50 kg: 160 mg twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity. Patients <50 kg: 120 mg twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - eGFR ≥15 mL/minute: No dosage adjustment necessary. - End-stage renal disease: There are no dosage adjustments provided in the manufacturer's labeling (has not been established). Hepatic Impairment (Adult): <u>Hepatic impairment at treatment initiation:</u> *Mild (total bilirubin ≤ ULN with AST > ULN or total bilirubin >1 to 1.5 times ULN with any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) impairment:* No initial dosage adjustment necessary. Monitor for adverse reactions. *Severe impairment (total bilirubin >3 to 10 times ULN and any AST):* Current dose of 120 mg twice daily or 160 mg twice daily: Reduce dose to 80 mg twice daily. Monitor for adverse reactions. <u>Hepatotoxicity during treatment:</u> Grade 3 or 4: Withhold selpercatinib and monitor AST and ALT once weekly until resolves to grade 1 or baseline. Resume selpercatinib with the dose

	reduced by 2 dose levels; monitor AST and ALT once weekly. After a minimum of 2 weeks without recurrence, increase selpercatinib dose by 1 dose level. Then, after a minimum of 4 weeks without recurrence, increase selpercatinib to dose taken prior to the onset of grade 3 or 4 AST or ALT elevation.
Maximum Daily Dose Adults*	N/A
Prescribing Edits*	MD, ST, PE, PA, 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)	Used for RET positive tumors
QL (Quantity Limit)	Maximum 160 mg BID
ST (Step Therapy)	Second-line treatment of progressive locoregional unresectable/metastatic disease for **patients with RET fusion-positive tumors.**
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	160 mg BID
Maximum Daily Dose Pediatric*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, hypertension, prolonged QT interval, skin rash; decreased serum albumin, calcium, glucose, magnesium, sodium, hypothyroidism; increased serum cholesterol, glucose, potassium; abdominal pain, constipation, diarrhea, nausea, vomiting, xerostomia; decreased hemoglobin, neutrophils, platelets; hemorrhage, lymphocytopenia, increased transaminases, bilirubin, fatigue, headache, arthralgia, increased serum creatinine, cough, dyspnea - Most serious: Severe hepatic disease, hypersensitivity reaction,

	interstitial lung disease, pleural effusion, pneumonitis, sepsis, QT interval prolongation
Drug Interactions*	QT-prolonging agents, CYP3A4 Inducers, P-glycoprotein/ABCB1 substrates
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, in utero exposure to selpercatinib may cause fetal harm.
Lactation	It is not known if selpercatinib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last selpercatinib dose.
Contraindications	N/A
Monitoring Requirements	- Evaluate RET gene fusion - Transaminases - QT interval, electrolytes, and thyroid-stimulating hormone/thyroid function - Pregnancy status - Blood pressure - Monitor for signs/symptoms of pulmonary toxicity, hypersensitivity, hemorrhage, impaired wound healing, and tumor lysis syndrome.
Precautions	- Tumor Lysis Syndrome - Elevations in serum creatinine - RET gene status for patient selection
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 selpercatinib in ovarian cancer (HTA recommendations available covered small cell lung cancer and thyroid cancer in patients with RET fusion positive tumors).

Conclusion Statement – Selpercatinib

Selpercatinib is a second-line treatment option for recurrent Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer (platinum sensitive or refractory) in patients with **RET fusion-positive tumors.**

There is no data issued by HTA bodies regarding its use in ovarian cancer.

2.8.5 Sorafenib

Table 53. Sorafenib Drug Information

Scientific Name **Sorafenib**[58]	
Trade Name(s) on Saudi Market	Nexavar, Sorafenib BOS
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered
FDA approved/off label	Yes
EMEA approved/off label	Yes
MHRA approved/off label	Yes
PMDA approved/off label	Yes
Indication (ICD-10)	C56
Drug Class	Antineoplastic Agent
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	Nexavar: 1407210864 Sorafenib BOS: 2408222547
ATC Code	L01XE05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Film-Coated Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	400 mg twice daily
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): - Mild to moderate (Child-Pugh class A and B) impairment: No dosage adjustment is necessary. - Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the

	manufacturer's labeling (has not been studied).
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 topotecan
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 BID
ST (Step Therapy)	Second-line treatment of ovarian cancer in patients with platinum resistant disease.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	400 mg BID
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, alopecia, pruritus, rash, xeroderma, palmar-plantar erythrodysesthesia, hypoalbuminemia, hypocalcemia, hypophosphatemia, increased amylase, increased TSH, weight loss, abdominal pain, anorexia, constipation, decreased appetite, diarrhea, GI hemorrhage, increased lipase, nausea, stomatitis, vomiting, anemia, neutropenia, thrombocytopenia, increased INR, hemorrhage, hepatic insufficiency, increased LFTs, fatigue, headache, peripheral sensory neuropathy, voice disorder, pain, asthenia, dyspnea, fever - Most serious: Hemorrhage, hepatic insufficiency, cardiac failure, ischemic heart disease, prolonged QT interval, squamous cell carcinoma of skin,
Drug Interactions*	- Risk X: BCG Products, Cladribine, Dipyrone, Fexinidazole, Lasmiditan

	, Leniolisib, Pacritinib, P-glycoprotein/ABCB1 Inhibitors, Pimecrolimus, Sparsentan, Taurursodiol, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Velpatasvir, Voxilaprevir - Risk D: Adagrasib, Deferiprone, Erdafitinib, Fosphenytoin-Phenytoin, Granulocyte Colony-Stimulating Factors, Lenograstim, Lipegfilgrastim, Palifermin, Platinum derivatives, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	It is not known if sorafenib is present in breast milk. The manufacturer recommends discontinuing breastfeeding during sorafenib treatment and for 2 weeks after the final sorafenib dose.
Contraindications	Known severe hypersensitivity to sorafenib or any component of the formulation
Monitoring Requirements	- CBC with differential electrolytes (magnesium, potassium, calcium), phosphorus, lipase and amylase levels; LFTs. - Pregnancy status - Monitor blood pressure, ECG in patients at risk for prolonged QT interval. - Monitor for signs/symptoms of bleeding, GI perforation, hand-foot skin reaction and other dermatologic toxicities, heart failure, and/or impaired wound healing.

	- Monitor adherence.
Precautions	- Bleeding - Cardiovascular events - Dermatologic toxicity - Gastro-intestinal perforation - Hepatotoxicity - Hypertension - QT prolongation - Thyroid impairment - Wound healing complications
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 sorafenib in ovarian cancer.

Conclusion statement - Sorafenib

Sorafenib (in combination with topotecan) is a treatment option in the second-line setting of ovarian cancer in patients with platinum resistant disease.

There is no data issued by HTA bodies regarding its use in this setting.

2.9 Vascular Endothelial Growth Factor (VEGF) Inhibitors

2.9.1 Bevacizumab

Table 54. Bevacizumab Drug Information

Scientific Name Bevacizumab[59]	
Trade Name(s) on Saudi Market	Avastin; Zirabev; Mvasi
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered
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)	C56

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 10 mg/kg every 2 weeks
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
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)	Used in both the first-line and second-line setting in the management of ovarian neoplasms.
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 Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), and Canadian Agency for Drugs and Technologies in Health (**CADTH**) HTA review and recommendations of bevacizumab in ovarian cancer treatment options.

Table 55. Bevacizumab HTA Analysis

Medication	Agency	Date – HTA Recommendation
Bevacizumab	HAS[60]	10/2016: The **addition of bevacizumab to carboplatin and to paclitaxel** has demonstrated a **modest effect on PFS**, without impacting the overall survival, but with an addition of adverse events such as bleeding, arterial hypertension and gastrointestinal perforations compared to carboplatin and paclitaxel. - Bevacizumab initially administered simultaneously with a carboplatin + paclitaxel chemotherapy, then continued in monotherapy, retains a minor improvement of actual clinical benefit (IACB IV) in the therapeutic strategy of for **advanced stage ovarian cancer (FIGO stage IIIB to IV) in first-line treatment**.

		- HAS recommends continued **inclusion on the list of reimbursable products** for hospital use.
Bevacizumab	NICE[61,62]	05/2013: **Bevacizumab in combination with gemcitabine and carboplatin** is **not recommended** within its marketing authorization, that is, for treating people with the **first recurrence of platinum-sensitive advanced ovarian cancer** (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents. o The Committee concluded that no overall survival benefit for bevacizumab plus gemcitabine and carboplatin had been shown in the OCEANS trial, but the results could have been confounded by post-progression therapies. o The Committee noted that the results for the intention-to treat population at the September 2010 cut-off date gave a difference in median PFS of 4 months in favor of bevacizumab and this was statistically significant. o The Committee agreed that the manufacturer's base-case ICER, using the September 2010 overall survival data of £149,000 per QALY gained, was likely to be an optimistic cost-effectiveness estimate and that the most plausible ICER could be much higher than this. 05/2013: **Bevacizumab in combination with paclitaxel and carboplatin** is **not recommended for first-line treatment of advanced ovarian cancer** (FIGO stages IIIB, IIIC and IV epithelial ovarian, fallopian tube or primary peritoneal cancer). o The Committee concluded that the **overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218** because of the uncertainty related to the extent to which patients received bevacizumab after progression. o The Committee noted that there was an apparent differential response, with little benefit shown in the stage III population with optimally debulked cancer (difference in

		median PFS 1.6 months in favor of bevacizumab) compared with the population with stage III suboptimally debulked cancer (difference in median PFS 6.8 months) or stage IV cancer (difference in median PFS 3.4 months). o The difference in median PFS in favor of bevacizumab using the censored data from GOG-0218 was 6 months. The Committee concluded that bevacizumab plus paclitaxel and carboplatin improved PFS compared with paclitaxel and carboplatin alone and that, of the available data, the censored PFS data are more relevant to UK clinical practice. o The Committee noted that the manufacturer's base-case ICER was approximately £144,000 per QALY gained. The Committee considered the Evidence Review Group (ERG)'s exploratory analyses, which examined the changes in the ICER with a treatment duration of 15 months or a time horizon of 25 years or both, and gave a range of ICERs from £128,000 to £161,000 per QALY gained.
Bevacizumab	CADTH[63]	03/2023: It was **not clear from the studies in the review whether bevacizumab plus chemotherapy does or does not improve overall survival compared to chemotherapy alone** (or with placebo) for **recurrent platinum-sensitive** ovarian cancer. o Most studies in this review found that bevacizumab plus chemotherapy results in longer progression-free survival than chemotherapy alone (or with placebo) for recurrent platinum-sensitive ovarian cancer. o Most studies in this review found that bevacizumab plus chemotherapy had a more beneficial effect on treatment response than chemotherapy alone (or with placebo) for recurrent platinum-sensitive ovarian cancer. o There was no difference in quality of life, based on 1 randomized controlled trial, and no clear differences in adverse events reported between

		bevacizumab plus chemotherapy or chemotherapy alone (or with placebo).

Conclusion Statement – Bevacizumab

Bevacizumab is used in the primary treatment of Stage II-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer in combination with paclitaxel/carboplatin followed by maintenance bevacizumab (preferred treatment). It is also used this setting for mucinous carcinoma (stage IC) histology, in combination with oxaliplatin/5-FU/leucovorin or oxaliplatin/capecitabine (preferred regimens). Docetaxel/oxaliplatin/bevacizumab followed by maintenance bevacizumab is also an alternative treatment option for patients with Stage I-IV Epithelial Ovarian/Fallopian Tube/Primary Peritoneal cancer.

Bevacizumab is also used in the second-line setting of ovarian cancer, in patients with platinum sensitive disease, used as a single agent or in combination with carboplatin/gemcitabine, or carboplatin/paclitaxel, or carboplatin/liposomal doxorubicin (preferred regimens). Other combinations in this setting include with oxaliplatin/5-FU/leucovorin or oxaliplatin/capecitabine for patients with recurrent platinum sensitive mucinous carcinoma.

Bevacizumab is also used in the second-line setting of platinum resistant ovarian cancer, as a single agent, or in combination with oral cyclophosphamide, or liposomal doxorubicin, or paclitaxel, or topotecan (preferred regimens). Other combinations in this setting include with carboplatin/gemcitabine, carboplatin/paclitaxel, or carboplatin/liposomal doxorubicin (not for platinum refractory disease).

Bevacizumab has received mixed reviews from HAS, NICE, and CADTH in the ovarian cancer indication:

- **HAS recommends the reimbursement** of bevacizumab **in addition to paclitaxel/carboplatin** in the **first-line setting of advanced ovarian cancer**, citing however a **modest improvement in PFS without impacting OS**, a minor clinical benefit, and an addition of **adverse events** such as hypertension and gastrointestinal perforations compared to paclitaxel/carboplatin.
- **NICE** on the other hand **doesn't recommend the use of bevacizumab in this setting**, citing that the overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218 because of the uncertainty related to the extent to which patients received bevacizumab after progression. The committee however noted that there was an apparent differential response, with little benefit shown in the stage III population with optimally debulked cancer. NICE gave a range of ICERs from £128,000 to £161,000 per QALY gained.

- **NICE** also **doesn't support the reimbursement** of bevacizumab in combination with gemcitabine and carboplatin for the **first recurrence of platinum-sensitive advanced ovarian cancer** (including fallopian tube and primary peritoneal cancer).
- A recent CADTH review of published studies data concluded that **it was not clear** from the studies whether **bevacizumab plus chemotherapy does or does not improve overall survival** compared to chemotherapy alone (or with placebo) for recurrent platinum-sensitive ovarian cancer.

Section 3.0 Key Recommendations Synthesis

A. Primary Treatment

These recommendations are primarily based on data from patients with the most common subtypes—**high-grade serous and grade 2 and 3 endometrioid carcinoma**; treatment for less common ovarian cancers will be discussed separately in section C.

Primary treatment for presumed ovarian, fallopian tube, or primary peritoneal cancer usually consists of appropriate **surgical staging** and **debulking surgery**, followed in most (but not all) patients by **systemic chemotherapy**[6-10].

- Ovarian cancer is staged according to the joint 2017 **International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Node, Metastasis (TNM)** classification system[6-10].
- An open laparotomy is recommended for most patients, but minimally invasive techniques may be appropriate in certain circumstances.
- For some patients with early-stage disease, surgery alone (followed by observation) may be sufficient as primary treatment.
- For certain histologic subtypes, adjuvant therapy with hormonal agents are options that may be considered.
- Neo-adjuvant chemotherapy (NACT) with interval debulking surgery (IDS) should be considered in patients with advanced-stage ovarian cancer who are not good candidates for upfront primary debulking surgery (PDS) due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced[6-10].

A.1. Surgery

- For most patients presenting with suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, initial surgery should include a **hysterectomy** (if uterus present) and bilateral salpingo-oophorectomy **(BSO)** with comprehensive staging and debulking as indicated[6-10].
- This is the recommended approach for stage IA–IV if optimal cytoreduction appears feasible, the patient is a surgical candidate, and fertility is not a concern.
- For patients with early-stage disease who wish to preserve fertility, less extensive surgery may be an option.
- **NACT with IDS** should be considered for patients with advanced-stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced[6-10].

- Patients treated with NACT and IDS should also receive **postoperative adjuvant chemotherapy**[6-10].

A.2. Management after Primary Surgery

- Most patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer should receive **adjuvant systemic chemotherapy** after primary surgery[6-10].
- Postoperative **observation** is an option for select patients with **stage I disease**, depending on cancer histologic type and substage (i.e. grade 2 endometrioid, Stage IA-IB). This approach is only possible in patients who have had resection of all disease and complete surgical staging to rule out the possibility of clinically occult disease that would result in upstaging[6-10].
- Several options are possible for postoperative treatment (within 6 weeks) in patients with advanced epithelial cancers: platinum-based intravenous (IV) chemotherapy, platinum-based intravenous/intraperitoneal (IV/IP) chemotherapy, and platinum-based IP chemotherapy plus bevacizumab[6-10].
- The recommended options for platinum-based IV chemotherapy to treat stage II–IV epithelial disease are: **paclitaxel (175 mg/m²)/carboplatin (AUC 5-6) (every 3 weeks)** (preferred), **paclitaxel (60 mg/m²)/carboplatin (AUC 2) (weekly)**, **dose-dense paclitaxel (80 mg/m²) Days 1, 8, and 15 + carboplatin AUC 5–6 Day 1 (every 3 weeks)**, **carboplatin/liposomal doxorubicin**, **docetaxel/carboplatin** (Recommendation Level A, Evidence Level II) [6-10].
- Based on results from GOG-0218 and ICON7, the international guidelines include **bevacizumab-containing regimens** as options for first-line chemotherapy following cytoreductive surgery (**carboplatin/paclitaxel/bevacizumab**, followed by **bevacizumab maintenance**) for patient with **Stage II and higher disease**[6-10].
- **Intravenous/Intraperitoneal (IV/IP) chemotherapy** is a treatment option for patients with **optimally debulked (<1 cm residual) stage III disease** (Recommendation Level A, Evidence Level II) [6-10].
  - The NCCN guidelines note that patients with optimally debulked stage II disease may also receive IP chemotherapy, as the panel has decided that many of the regimens tested in stage III–IV should also be offered to patients with stage II disease[5].
  - The IV/IP protocol consists of **Paclitaxel 135 mg/m² as a continuous infusion over 3 or 24 hours on Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m² IP Day 8** (Recommendation Level A, Evidence Level II) [6-10].

- Adjuvant therapy options for **patients >70 years and those with comorbidities** include: carboplatin AUC 5 (single agent), paclitaxel (135 mg/m^2)/carboplatin (AUC 5) every 3 weeks, paclitaxel (60 mg/m^2)/carboplatin (AUC 2) weekly (Recommendation Level A, Evidence Level II) [6-10].

A.3. Neoadjuvant Chemotherapy

- For advanced-stage epithelial ovarian cancer, including fallopian tube and primary peritoneal cancers, the best outcomes have been observed in patients whose primary treatment included **complete resection of all visible disease** and **combination chemotherapy**[6-10].
- For most patients presenting with suspected advanced-stage malignant ovarian, fallopian tube, or primary peritoneal cancer, initial surgery should include a hysterectomy and BSO with comprehensive staging and debulking as indicated.
- PDS is the recommended approach for advanced-stage disease if the patient is a surgical candidate, optimal cytoreduction (residual disease <1 cm [R1] and preferably removal of macroscopic disease [R0]) appears feasible, and fertility is not a concern.
- **NACT with IDS** should be considered for patients with **advanced-stage disease who are not good candidates for PDS** due to advanced age, frailty, poor performance status, comorbidities, or disease that is unlikely to be optimally cytoreduced[6-10].
- Neoadjuvant therapy should be considered for patients with **bulky disease** that is unlikely to be optimally cytoreduced by up-front surgery.
- A wide variety of platinum-based regimens have been used in clinical trials testing NACT plus IDS and postoperative chemotherapy: **paclitaxel (175 mg/m^2)/carboplatin (AUC 5-6) (every 3 weeks)** (preferred), **paclitaxel (60 mg/m^2)/carboplatin (AUC 2) (weekly)**, **dose-dense paclitaxel (80 mg/m^2) Days 1, 8, and 15 + carboplatin AUC 5–6 Day 1 (every 3 weeks)**, **carboplatin/liposomal doxorubicin**, **docetaxel/carboplatin** (Recommendation Level A, Evidence Level II) [6-10].
- After 3 to 4 cycles of NACT, patients should be evaluated to determine the likelihood of optimal cytoreduction[6-10].
    - For patients whose disease responded to NACT and are likely to have optimal cytoreduction, IDS with completion hysterectomy/BSO and cytoreduction should be performed.
    - Those with stable disease after 3 to 4 cycles of NACT can consider IDS (with completion hysterectomy/BSO, and cytoreduction), but also should consider either 1) switching to treatment for persistent/recurrent disease; or 2) treatment with additional cycles of NACT (to a total of ≥6 cycles), then re-evaluating to determine

whether to perform IDS (with completion hysterectomy/BSO, and cytoreduction) or switch to therapy for persistent/recurrent disease; The option to continue on beyond 6 cycles is usually reserved for those who are tolerating therapy and have signs that a response may be achieved, such as those whose CA-125 is continuing to fall.

- Patients who experience disease progression during NACT should switch to therapy for persistent/recurrent disease[6].

- Regardless of the number of cycles of NACT received, IDS should always be followed by **adjuvant chemotherapy**. For all patients who undergo NACT plus IDS, a minimum of **6 cycles** of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS. Patients with stable disease who are tolerating therapy may continue past 6 cycles[6-10].

A.4. Hyperthermic Intraperitoneal Chemotherapy at the Time of IDS

- Hyperthermic intraperitoneal chemotherapy (HIPEC) is a technique in which chemotherapy is delivered in a heated solution perfused throughout the peritoneal space.
- HIPEC is a treatment option to consider at the time of IDS in patients with stage III disease treated with NACT for patients who have response or stable disease after NACT (3 cycles preferred, but 4–6 allowed)[6].
- All patients treated with NACT and IDS (± HIPEC) should receive postoperative chemotherapy.
- The HIPEC chemotherapy agent is **cisplatin, 100 mg/m²** (Recommendation Level A, Evidence Level II)[6].

A.5. Maintenance Options After First-Line Chemotherapy

- For patients who have completed primary surgery and systemic therapy, the recommended options for the treatment of patients who have completed primary therapy include:
- **Stage I disease**: observation (Recommendation Level A, Evidence Level II) [6-10]
- **Stage II-IV disease**:

- *BRCA 1/2 mutated*[6-10]*:*
  - Observation (Recommendation Level A, Evidence Level II)
  - **Olaparib** (Recommendation Level A, Evidence Level I)
  - **Bevacizumab + Olaparib** (Recommendation Level A, Evidence Level I; in patients who received bevacizumab with chemotherapy)
  - **Niraparib** (Recommendation Level A, Evidence Level I)
- *BRCA status wild-type or unknown*[6-10]*:*
  - Observation (Recommendation Level A, Evidence Level II)

- Bevacizumab + Olaparib for patients with genomic instability (Recommendation Level A, Evidence Level II)
- Niraparib (Recommendation Level A, Evidence Level II)

B. Recurrent Disease

- **Platinum-based combination chemotherapy** is recommended (Recommendation Level A, Evidence Level I) for a total of **6 cycles** for **platinum-sensitive recurrence**[6-10].
- For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred **single agent** is **carboplatin** or **cisplatin** (Recommendation Level A, Evidence Level II) [6-10].
- **Preferred combinations** for **platinum-sensitive recurrent disease** include: carboplatin/paclitaxel (Recommendation Level A, Evidence Level I), carboplatin/liposomal doxorubicin (Recommendation Level A, Evidence Level I), carboplatin/weekly paclitaxel (Recommendation Level A, Evidence Level II), carboplatin/albumin-bound paclitaxel (for taxane hypersensitivity) (Recommendation Level A, Evidence Level II), carboplatin/docetaxel (Recommendation Level A, Evidence Level II), carboplatin/gemcitabine (which has been shown to improve PFS) (Recommendation Level A, Evidence Level II), cisplatin/gemcitabine (Recommendation Level A, Evidence Level II), or carboplatin/gemcitabine/bevacizumab (Recommendation Level A, Evidence Level II) [6-10].
- For **platinum-resistant disease**, **non-platinum–based agents** or regimens are preferred (i.e., docetaxel, oral etoposide, gemcitabine, weekly paclitaxel with or without pazopanib, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel/bevacizumab, topotecan with or without bevacizumab) (Recommendation Level A, Evidence Level II); sequential therapy using single agents is typically used[6-10].
- **Other potentially active agents** include capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), pemetrexed, and vinorelbine (Recommendation Level A, Evidence Level II) [6-10].
- **Immunotherapy drugs** including pembrolizumab and dorstarlimab are mentioned in the NCCN guidelines as treatment options for patients with recurrent disease with MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/megabase (platinum sensitive or resistant) (Recommendation Level A, Evidence Level II) [6,11].
- **Targeted therapy options** are also mentioned for recurrent disease (platinum sensitive or resistant) (Recommendation Level A, Evidence Level II)[6]:
  - Dabrafenib + trametinib (for BRAF V600E-positive tumors)
  - Entrectinib or larotrectinib (for NTRK gene fusion-positive tumors

- Selpercatinib (for RET gene fusion-positive tumors)

C. Less Common Ovarian Cancers

C.1 Clear Cell Carcinoma

- Clear cell carcinomas are considered high-grade tumors. Most clear cell carcinomas are negative for WT1 and estrogen receptors.
- Primary treatment for these patients includes completion **surgery** with comprehensive **staging** followed by **postoperative therapy**[6-10]. Fertility-sparing surgery is not recommended for stage IA to C clear cell carcinomas. Lymphadenectomy has been shown to improve survival.
- For patients with *stage IA to IC disease*, recommended postoperative treatment is the **standard IV taxane-carboplatin regimens** (with paclitaxel or docetaxel) used for high-grade serous ovarian cancer[6-10].
- For patients with *stage II to IV* clear cell carcinoma, postoperative treatment is **standard regimens used for epithelial ovarian cancer** (e.g., IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin).
- Patients with advanced clear cell carcinoma have a poor prognosis.
- Data suggest that **6 or 3 cycles** of postoperative chemotherapy are equivalent for patients with clear cell carcinoma[6-10].

C.2 Mucinous Carcinoma

- Mucinous tumors are unusual because they may be very large cystic masses that may fill the abdomen and pelvis; this presentation often suggests mucinous histology.
- Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year DFS is about 80% to 90%.
- Primary treatment for these patients includes completion **surgery** with comprehensive **staging** followed by **postoperative therapy** or **observation**[6-10].
- An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors.
- The additional workup includes a **GI tract evaluation and CEA level** for patients with mucinous histology to determine whether patients have either occult GI primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries[6].
- Postoperative **observation** and **monitoring** are recommended for patients with **stage IA or IB** mucinous tumors because most of these tumors are benign or borderline.

- For patients with **stage IC mucinous carcinomas**, postoperative options include: 1) **observation**; 2) **IV carboplatin with either paclitaxel or docetaxel**; 3) **5-FU/leucovorin/oxaliplatin** (GI regimen); or 4) **capecitabine/oxaliplatin** (GI regimen) (Recommendation Level A, Evidence Level II) [6-10].
- Some clinicians find the GI regimens appropriate because mucinous carcinomas of the ovary are similar to GI tumors[6].
- For patients with **stages II to IV mucinous carcinomas**, postoperative options include: 1) **chemotherapy** using the regimens for **epithelial ovarian cancer** (e.g., **IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin**); 2) **5-FU/leucovorin/oxaliplatin** (GI regimen); or 3) **capecitabine/oxaliplatin** (GI regimen) (Recommendation Level A, Evidence Level II)[6].
- Recommendations for **recurrence** therapy for mucinous carcinomas include: 1) **5-FU/leucovorin/oxaliplatin with or without bevacizumab** (Recommendation Level B, Evidence Level II for bevacizumab); or 2) **capecitabine/oxaliplatin** (Recommendation Level A, Evidence Level II)[6].

C.3 Low-Grade Serous Carcinoma (LGSC)

- Low-grade serous carcinoma is a subtype of serous carcinoma that is considered pathologically distinct from the more commonly diagnosed high-grade serous carcinoma and represents less than 5% of epithelial ovarian cancers.
- Activating mutations in the mitogen-activated protein kinase (MAPK) pathway are frequently identified in low-grade, but not high-grade, serous carcinomas.
- Primary treatment for low-grade serous carcinomas is comprised of completion **surgery** with comprehensive **staging**, followed by **adjuvant therapy** or **observation**[6-10].
- Low-grade serous carcinomas often **respond poorly to chemotherapy** compared with high-grade serous carcinomas; therefore, neoadjuvant chemotherapy is less favored for patients with low-grade serous carcinoma[6].
- Postoperative observation is an option for patients with stage IA and IB disease (Recommendation Level A, Evidence Level II) and for those with stage IC disease (Recommendation Level B, Evidence Level II) [6].
- Several adjuvant systemic therapy options, including **paclitaxel/platinum-containing regimens**, are recommended for patients with stage IC or stage II–IV disease, although there are limited data on systemic therapy regimens in patients with low-grade serous carcinoma in general[6].
- Patients with low-grade serous carcinomas may also benefit from **maintenance hormone therapy** following adjuvant chemotherapy, with

letrozole, anastrozole, exemestane, leuprolide acetate, or tamoxifen (Recommendation Level B, Evidence Level II) [6].

- **Adjuvant hormone therapy** is mentioned in the NCCN guidelines as a potential substitute for adjuvant chemotherapy for these patients. However, as there are no supporting prospective data, this is a category 2B recommended option in the guidelines[6].
- Unfortunately, patients with low-grade serous carcinoma, particularly those with advanced stage disease, may experience disease relapse.
  - Secondary cytoreduction can be considered for patients with a long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction.
  - Systemic therapy is another option for this patient population; however, the guidelines emphasize that there is no standard sequencing of drugs for recurrent disease.
  - Importantly, recent studies have suggested that **MEK inhibitors** have activity in recurrent low-grade serous carcinoma. The NCCN panel recommends trametinib as a category 2A option for patients with recurrent low-grade serous carcinoma[6].
  - In June 2022, the U.S. Food and Drug Administration granted accelerated approval to selective **BRAF inhibitor dabrafenib** in combination with trametinib for the treatment of adult and pediatric patients (6 years and older) with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options[6].

D. HTA Recommendations

HTA recommendations were found for olaparib and bevacizumab in ovarian cancer.

All HTA organisms **support the reimbursement of olaparib** for the **maintenance** treatment of patients with **newly diagnosed**, **advanced (FIGO stages 3 and 4), BRCA-mutated**, high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are **in response (complete or partial) to first-line platinum-based chemotherapy**.

- Patients must have received at least **four cycles** of their most recent platinum-based chemotherapy. Maintenance therapy with olaparib should begin **within eight weeks** of the last dose of platinum-based chemotherapy
- There is a **net clinical benefit** of olaparib maintenance treatment compared with placebo, based on a statistically significant improvement in PFS, no detrimental effect on quality of life, and a manageable toxicity profile.

- HAS, NICE, and IQWIG support both the use of **olaparib monotherapy** and the **combination of olaparib plus bevacizumab** in this maintenance indication.
- CADTH mentions that a condition for olaparib reimbursement is that **cost-effectiveness should be improved to an acceptable level** through a **reduction in price**. They note that given the high level of uncertainty in the magnitude of long-term overall survival benefit, olaparib is not cost-effective compared with best supportive care.
- CADTH also supports the use of olaparib monotherapy in the maintenance setting of **relapsed BRCA-mutated** high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have completed **at least two previous lines of platinum-based chemotherapy** and are in radiologic response (complete or partial response) to their most recent platinum-based chemotherapy regimen.

Bevacizumab has received mixed reviews from HAS, NICE, and CADTH in the ovarian cancer indication:

- **HAS recommends the reimbursement** of bevacizumab **in addition to paclitaxel/carboplatin** in the **first-line setting of advanced ovarian cancer**, citing however a **modest improvement in PFS without impacting OS**, a minor clinical benefit, and an addition of **adverse events** such as hypertension and gastrointestinal perforations compared to paclitaxel/carboplatin.
- **NICE** on the other hand **doesn't recommend the use of bevacizumab in this setting**, citing that the overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218 because of the uncertainty related to the extent to which patients received bevacizumab after progression. The committee however noted that there was an apparent differential response, with little benefit shown in the stage III population with optimally debulked cancer. NICE gave a range of ICERs from £128,000 to £161,000 per QALY gained.
- **NICE** also **doesn't support the reimbursement** of bevacizumab in combination with gemcitabine and carboplatin for the **first recurrence of platinum-sensitive advanced ovarian cancer** (including fallopian tube and primary peritoneal cancer).
- A recent CADTH review of published studies data concluded that **it was not clear** from the studies whether **bevacizumab plus chemotherapy does or does not improve overall survival** compared to chemotherapy alone (or with placebo) for recurrent platinum-sensitive ovarian cancer.

Section 4.0 Conclusion

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

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

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. 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):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	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

II. 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.

III. What information are available in the notes?

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

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. 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/

VI. 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

I- Level of Evidence Adopted:

Grade of research	
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

II. NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category C	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

All recommendations are category 2A unless otherwise indicated.

III. NCCN Categories of Preference

Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for ovarian cancers guideline search:

Query	Filters	Search Details	Results
(((((Ovarian Neoplasms[Title/Abstract]) OR (Ovarian Neoplasms[MeSH Major Topic])) OR (Hereditary Breast and Ovarian Cancer Syndrome[MeSH Major Topic])) OR (Hereditary Breast[Title/Abstract] AND Ovarian Cancer Syndrome[Title/Abstract])) OR (Carcinoma, Ovarian Epithelial[Title/Abstract])) OR (Carcinoma, Ovarian Epithelial[MeSH Major Topic])	Guideline, in the last 5 years	("ovarian neoplasms"[Title/Abstract] OR "ovarian neoplasms"[MeSH Major Topic] OR "hereditary breast and ovarian cancer syndrome"[MeSH Major Topic] OR ("hereditary breast"[Title/Abstract] AND "ovarian cancer syndrome"[Title/Abstract]) OR "carcinoma ovarian epithelial"[Title/Abstract] OR "carcinoma, ovarian epithelial"[MeSH Major Topic]) AND ((y_5[Filter]) AND (guideline[Filter]))	56

Appendix D. Treatment Algorithms

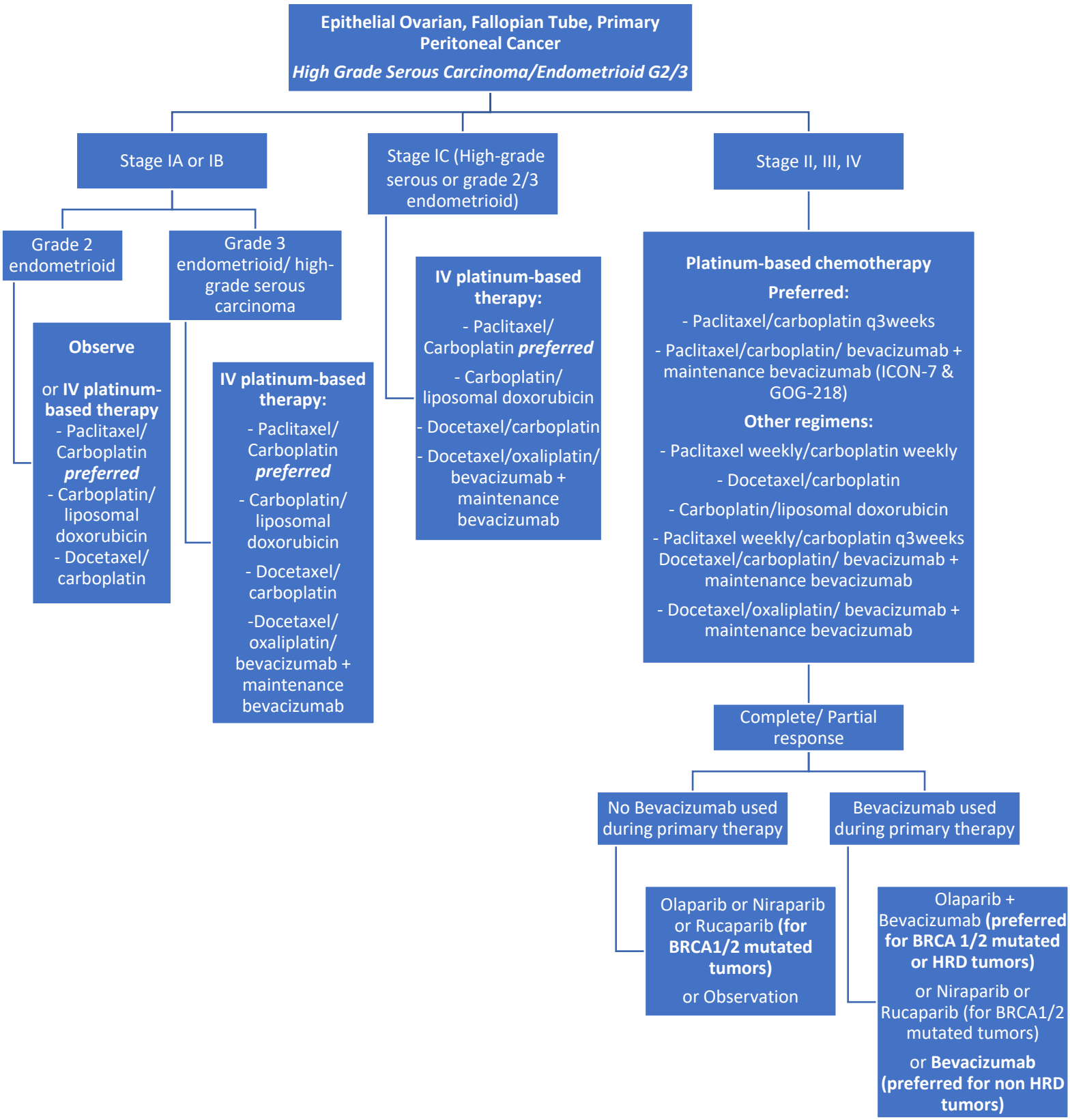

Figure 7. *Management of Epithelial Ovarian, Fallopian Rube, Primary Peritoneal Cancer (HGSC and Endometrioid Histologies)*

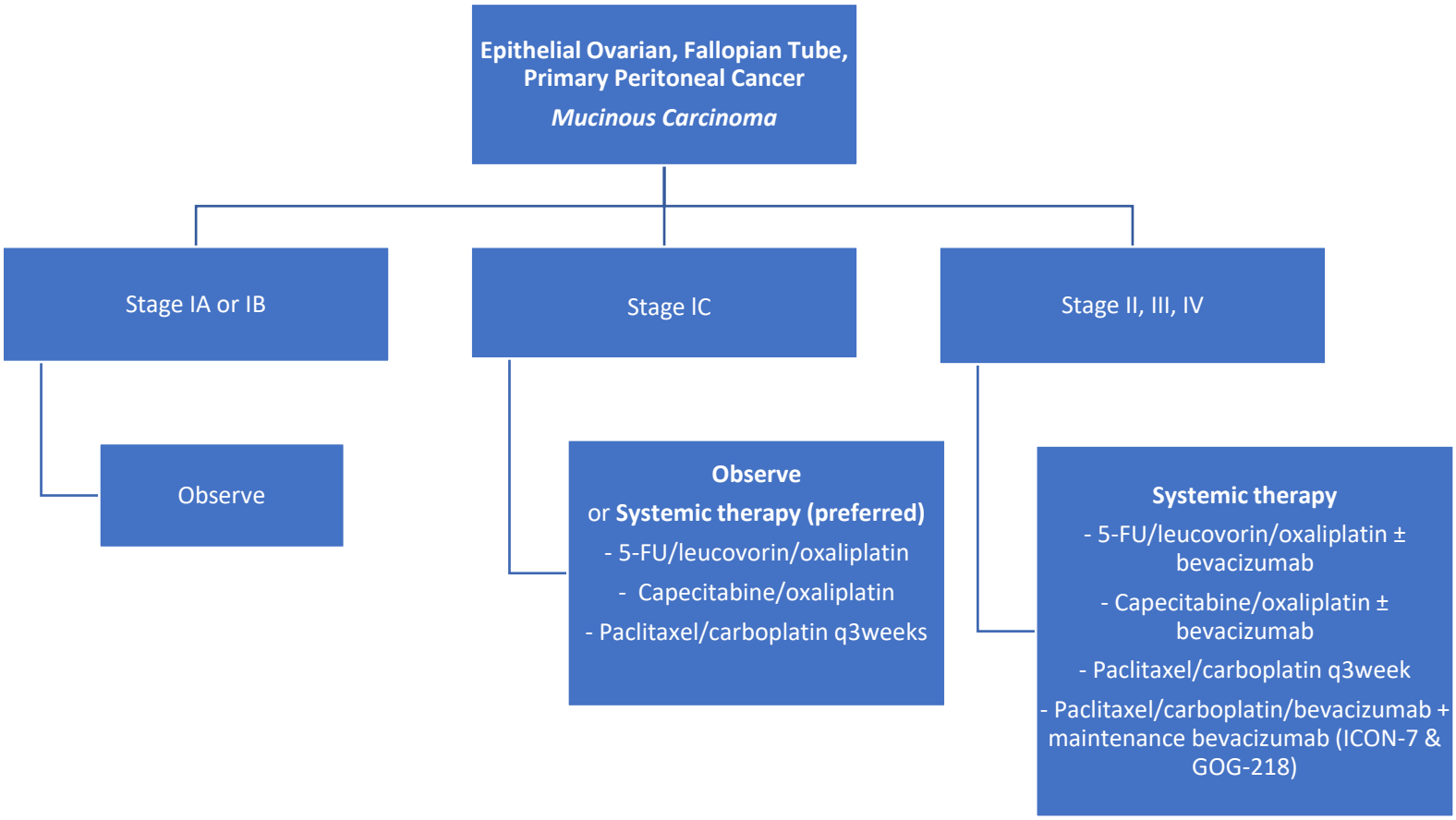

Figure 8. *Management of Epithelial Ovarian, Fallopian Rube, Primary Peritoneal Cancer (Mucinous Carcinoma Histology)*

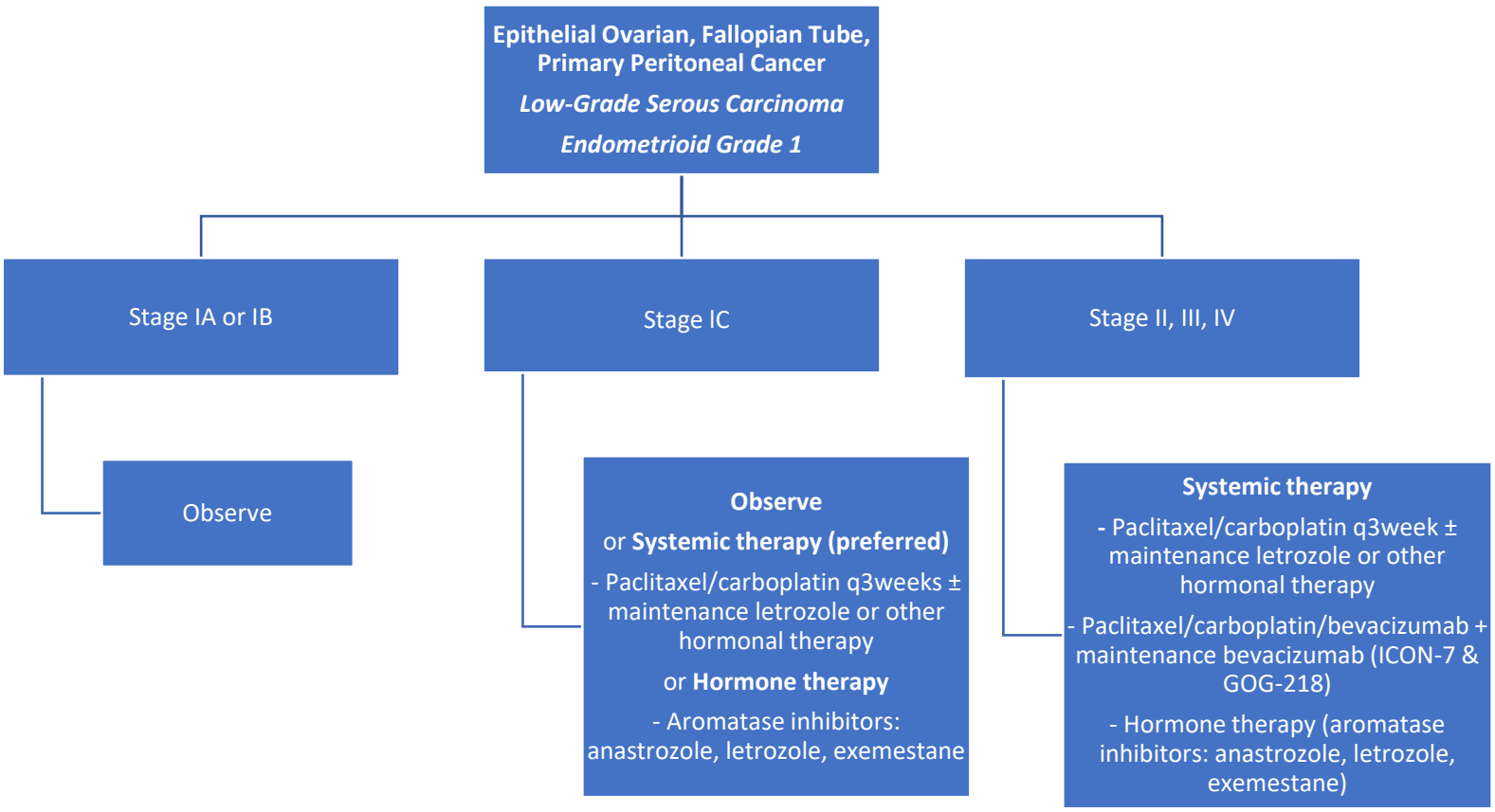

Figure 9. *Management of Epithelial Ovarian, Fallopian Rube, Primary Peritoneal Cancer (Low Grade Serous Carcinoma/Endometrioid Grade 1 Histologies)*

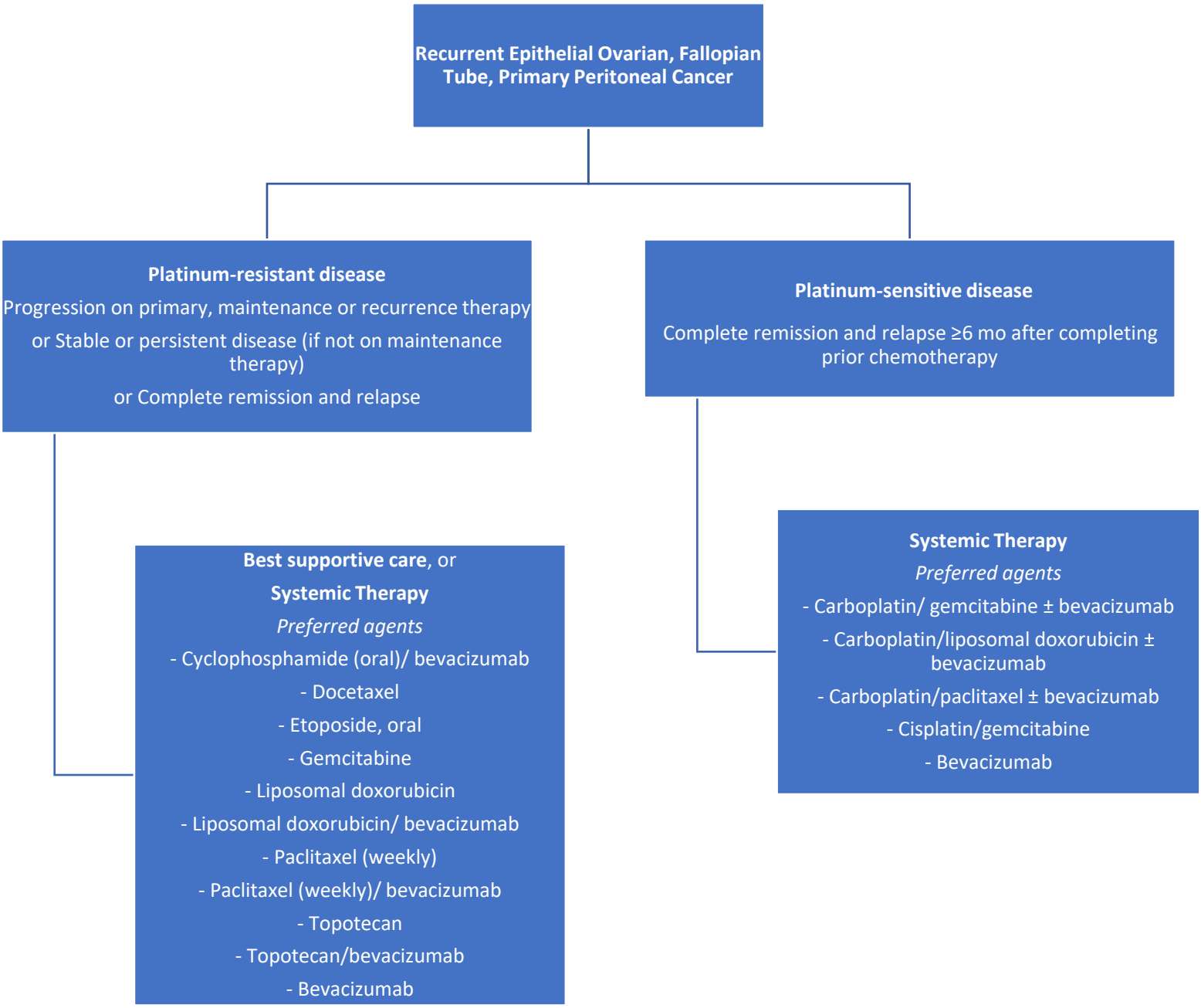

Figure 10. *Management of Recurrent Epithelial Ovarian, Fallopian Rube, Primary Peritoneal Cancer*