Treatment of ovarian cancer: From the past to the new era (Review)

KHALED ALROSAN[1], AMJAD Z. ALROSAN[1], GHAITH B. HEILAT[2], ALAA F. ALROUSAN[3], OMAR S. GAMMOH[4], ABDELRAHIM ALQUDAH[1], SABA MADAE'EN[1] and MOHAMMED J. ALROUSAN[5]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, The Hashemite University, Zarqa 13133, Jordan; [2]Department of General Surgery and Urology, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan; [3]Faculty of Pharmacy, Jordan University of Science and Technology, Irbid 22110, Jordan; [4]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Yarmouk University, Irbid 21163, Jordan; [5]Department of General surgery, King Fahad Specialist Hospital, Tabuk 47717, Saudi Arabia

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Abstract. Ovarian cancer is the most lethal malignancy among female genital cancers, primarily due to the non-specific symptoms, late-stage diagnosis and poor prognosis. Thus, there is a need for accurate and precise diagnostic methods to improve overall survival rates. The aim of the present review was to provide a comprehensive overview of ovarian cancer, including its epidemiology, clinical presentation, etiology, risk factors, staging and diagnostic techniques, in addition to examining the therapeutic approaches, including cytoreductive surgery and adjuvant treatments, while highlighting the mechanisms of resistance to such interventions. Advancements in molecular profiling and a deeper understanding of ovarian tumorigenesis have led to the introduction of novel therapeutic agents currently in clinical use or under clinical investigation. These innovations may improve the management of ovarian cancer, potentially improving survival outcomes.

Contents

Correspondence to: Dr Khaled Alrosan, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, The Hashemite University, 453J+5C5 Damascus Highway, Zarqa 13133, Jordan
E-mail: kalrosan@hu.edu.jo; rousankhaled@yahoo.com

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1. Introduction

Ovarian cancer is the seventh most common type of cancer in female patients (1-4) and the third most common gynecological cancer, following cervical and uterine cancer (5). Although ovarian cancer ranks eighth as a cause of cancer-associated mortality in female patients globally (3,6), it is the most lethal among gynecological tumors (2,3,6,7). Ovarian cancer has a lifetime risk of 1.3% (6) with ~314,000 new cases and ~207,000 mortalities globally each year, based on data from 2020 (8,9). In the United States, >22,000 new cases of ovarian cancer are diagnosed each year, with 14,000 deaths attributed to the disease (1,10). Ovarian cancer is uncommon in young patients, especially those <30 years old; however, the risk rises with age, with a sharp increase in patients ≥50 years old (2). There are also geographical variations, with the highest prevalence in the United States and northern Europe, and the lowest prevalence in Japan (3). Notably, ethnicity also has an impact on the prevalence of ovarian cancer and the incidence of mortality (1). The highest incidence is observed in Caucasian patients with ~12 cases per 100,000 individuals, and the lowest incidence is observed in African-American patients with ~0.4 cases per 100,000 individuals (3).

Symptoms. The term 'silent killer' has been given to ovarian cancer due to its high mortality rate, which is attributed to the inapparent tumor growth, delayed onset of symptoms and inadequate screening, often leading to an advanced-stage diagnosis in the first instance (5). Furthermore, ovarian cancer is generally associated with non-specific symptoms. The symptoms are common and include abdominal bloating, abdominal pain, frequent urination, early satiety and changes in bowel habits. However, because these symptoms are often mild or seem ordinary, patients may not seek medical attention, which can lead to delays in diagnosis (2). Ovarian cancer is uncommon, and a general physician may only encounter a case every 5 years (11). This rarity, combined with the commonality of the symptoms, creates notable challenges for both physicians and patients. For example, physicians frequently misinterpret these symptoms, attributing them to conditions such as irritable

bowel syndrome, stress or gastritis. At the same time, patients may not recognize the seriousness of these symptoms, further contributing to delays in diagnosis (12). As such, the overlap of ovarian cancer symptoms with more common conditions, along with a lack of awareness, often results in misdiagnosis and delayed treatment.

Risk factors. Momenimovahed *et al* (5) have classified the risk factors that are associated with ovarian cancer into three main categories: Predisposing, protective and controversial. The predisposing factors include age (more common in patients aged >65 years), menstrual-associated factors, endometriosis, family history of breast or ovarian cancer, BRCA gene mutations (Table I), Lynch syndrome and lower socioeconomic status.

Age is a key predisposing factor for ovarian cancer, with a higher incidence in women >65 years and a median diagnosis age of 63 years. Early-onset ovarian cancer, occurring between 18 and 30 years, accounts for <5% of cases and is usually diagnosed at a localized stage. By contrast, late-onset ovarian cancer is often identified at advanced stages with metastasis, indicating a more favorable prognosis for early-onset cases (13).

A thorough assessment of family history is key for identifying hereditary risks, primarily in cases associated with hereditary breast and ovarian cancer and Lynch syndrome. This evaluation includes analyzing cancer diagnoses in first- and second-degree relatives, particularly those with ovarian, breast, prostate or pancreatic cancer, as well as early-onset or bilateral malignancy, which may indicate pathogenic variants in BRCA1, BRCA2 or mismatch repair genes. The genes that are highly associated with ovarian cancer are listed in Table I. Understanding familial cancer patterns aids risk stratification, enabling personalized interventions such as enhanced surveillance, prophylactic surgery, targeted therapies [such as poly(ADP-ribose) polymerase (PARP) inhibitors] and genetic counseling (14).

Protective factors include multiparity, advanced maternal age at first childbirth, contraceptive use and lactation, which are associated with a reduced risk of ovarian cancer (5). Factors whose associations with ovarian cancer remain inconsistent or debated, include age at menarche and menopause, pregnancy characteristics, pelvic inflammatory disease, hormone replacement therapy, infertility treatment, dietary and nutritional patterns, obesity, physical activity, and the consumption of alcohol, caffeine and tobacco (5).

Etiology. The development of ovarian cancer remains to be elucidated and determining the exact pathophysiology is hampered by the heterogeneous nature of the disease, which includes a variety of histological types with distinct behaviors and features. Several hypotheses have been proposed to explain the etiology of ovarian cancer, including the incessant ovulation (repeated ovulatory cycles cause damage to the ovarian epithelium, increasing cancer risk), inflammation (highlights the role of chronic pelvic inflammation in stimulating carcinogenesis; androgen/progesterone and gonadotropin hypotheses, propose that hormonal imbalances may stimulate abnormal cellular growth (15). The tubal origin hypothesis suggests that many high-grade serous ovarian cancers may actually originate from the epithelial cells of the fallopian tubes (16) . However, a definitive scientific consensus has yet to be established.

Types of ovarian cancer. Primary ovarian malignancies are classified in three primary forms (epithelial, germ cell, and sex cord). Of all ovarian malignancies, ~95% are epithelial cancers. Epithelial cancers are hypothesized to originate from the single-cell layer covering the ovary (2). According to histology, serous [high-grade serous ovarian carcinoma (HGSOC) or low-grade serous ovarian carcinoma (LGSOC)], clear-cell, endometrioid and mucinous tumors are the four most prevalent forms of ovarian cancer, with HGSOC being the most common, accounting for 70-80% of all epithelial subtypes (2). The unique biology and responses to different treatments allow further stratification of the subtypes (17). The remaining 5% of all ovarian cancers consist of sex and germ cell cancers. Germ cell tumors are rare, accounting for 3% of cases of ovarian cancer, and they are most commonly diagnosed in younger patients, typically between the ages of 10 and 30 years. Sex cord-stromal malignancies are the rarest ovarian neoplasms, accounting for <2% of primary ovarian tumors. They are typically benign and frequently identified early during development (2).

Staging and diagnosis. Ovarian cancer is characterized by a low 5-year survival rate (1). The 5-year survival rate for patients with early-stage ovarian cancer (stages I and II) is 70%, but this drops to <20% in patients with advanced-stage cancer (stages III and IV) (7,16). The International Federation of Gynecology and Obstetrics (FIGO) was the first association to develop a staging system for gynecological cancer. The current FIGO staging system combines ovarian, fallopian tube and peritoneum cancer classifications, and considers findings obtained primarily through surgical exploration (Table II) (18).

The understanding of ovarian cancer biology has advanced and is now based on histological characteristics and the molecular phenotype (19). The first step in diagnosis is to obtain a thorough medical history from the patient to determine any family history of ovarian and other types of cancer (18). If ovarian cancer is detected early in the development process, the chances of successful treatment are higher (20). Screening tests must be performed multiple times to ensure early, cost-effective treatment while minimizing unnecessary interventions (21). Due to its role in oncogenesis and metastasis, the cancer antigen-125 (CA-125) test has been widely used for ovarian cancer screening and differentiation from benign conditions, making it a key focus in developing antitumor strategies (18,19).

While >90% of patients with advanced-stage cancer exhibit elevated CA-125 levels in the blood, 50-60% of patients with stage I ovarian cancer exhibit elevated CA-125 levels (6,16). A potential explanation for the low serum concentration of CA-125 in patients with partial epithelial ovarian cancer (EOC) may be the development of circulating immune complexes, which may interfere with detection (19). However, CA-125 testing has limitations. Studies have reported false positives, with ~1% of healthy individuals showing elevated CA-125 levels (>35 U/ml) and 5% of patients with benign conditions also exhibiting increased levels (20,22). Furthermore, CA-125 levels vary due to factors such as differences in ethnicity, pregnancy, the

Table I. Genes associated with ovarian cancer.

Gene	Location	mRNA and protein	Function	Interactions	Expression	Genotype-phenotype association
BRCA1 and BRCA2	BRCA1, 17q21; BRCA2, 13q12.3 (270).	BRCA1 encodes a protein of 1,863 amino acids; BRCA2 encodes a protein of 3,418 amino acids; both are involved in DNA repair (271).	HR repair of DNA double-stranded breaks and maintaining genomic stability; regulation of cell cycle checkpoints and transcription (272).	BRCA1 interacts with RAD51, BARD1 and DNA repair proteins; BRCA2 directly binds RAD51 to facilitate its function in DNA repair (273).	Ubiquitously expressed in tissue with active DNA repair; mutations impair their function, leading to genomic instability (273).	Germline mutations are strongly associated with HBOC; BRCA1 mutations are more frequently associated with HGSOC; BRCA2 mutations are associated with a lower predisposition to ovarian cancer (275).
TP53	17p13.1 (276).	53 kDa nuclear phosphoprotein that serves as a tumor suppressor (277).	Regulates apoptosis, cell cycle arrest and DNA repair in response to cellular stress (278).	Interacts with MDM2, which regulates its stability, and proteins involved in cell cycle control and apoptosis (279).	Mutated TP53 expression is upregulated in nearly all HGSOCs, resulting in loss of function or gain of oncogenic properties (270).	Mutations are associated with a more aggressive phenotype and poor survival rates (274).
RAD51	17q22 (280).	Protein of 339 amino acids involved in HR repair (271).	Facilitates strand exchange during HR (272).	Interacts with BRCA1, BRCA2 and DNA repair proteins to ensure genomic integrity (270).	Upregulation in ovarian cancer is associated with resistance to chemo therapy (274).	Germline mutations are associated with hereditary ovarian cancer and may influence the response to PARP inhibitors (281).
ARID1A	1p36.11 (276).	Protein involved in chromatin remodeling as part of the SWI/SNF complex (278).	Regulating gene expression by modifying chromatin structure; DNA repair, cell cycle control and differentiation (282).	Functions in conjunction with chromatin-modifying proteins such as SMARCA4 (270).	Frequently mutated in ovarian clear cell and endometrioid ovarian carcinoma, leading to loss of expression (283).	Loss of function is associated with tumor progression and poor prognosis in ovarian cancer, particularly in clear cell and endometrioid subtypes (284).
PTEN	10q23.3 (285).	Phosphatase protein that regulates the PI3K/AKT pathway (272).	Serves as a tumor suppressor by dephosphorylating phosphoinositide, inhibiting cell proliferation and survival pathways (274).	Interacts with proteins, including AKT, PDK1 and mTOR, to regulate cell signaling pathways (286).	Loss of expression is associated with increased oncogenic signaling (270).	Loss of function is associated with increased cell proliferation, survival and tumorigenesis; in ovarian cancer, PTEN mutations are associated with endometrioid and clear cell carcinomas (287).
KRAS and BRAF	KRAS, 12p12.1; BRAF, 7q34 (288).	KRAS encodes a 21 kDa GTPase; BRAF encodes an 84 kDa serine/threonine kinase (289).	Part of the RAS/RAF/MEK/ERK signaling pathway, which regulates cell proliferation, differentiation and survival (290).	KRAS activates BRAF, which activates MEK and ERK, leading to downstream signaling (291).	Mutations are commonly found in LGSOC and mucinous ovarian cancer (292).	Mutations are associated with distinct histological subtypes of ovarian cancer and may influence response to targeted therapy such as MEK inhibitors (135).

Table I. Continued.

Gene	Location	mRNA and protein	Function	Interactions	Expression	Genotype-phenotype association
CDKN2A	9p21.3 (293).	Proteins p16INK4a and p14ARF through alternative splicing (294).	p16INK4a inhibits CDK4/6, preventing cell cycle progression; p14ARF stabilizes TP53 by inhibiting MDM2 (295).	p16INK4a interacts with CDK4/6; p14ARF interacts with MDM2 (296).	Frequently inactivated in ovarian cancer through deletion, mutation or promoter methylation (297).	Loss of function is associated with uncontrolled cell cycle progression and tumorigenesis in ovarian cancer (298).
NF1	17q11.2 (299).	320 kDa protein, which functions as a GAP (300).	Negatively regulates the RAS/MAPK pathway, controlling cell proliferation and differentiation (301).	Interacts with RAS proteins to hydrolyze GTP, inactivating RAS signaling (302).	Mutations are found in a subset of ovarian cancer, particularly in HGSOC (303).	Loss of function leads to hyperactivation of the RAS pathway, contributing to tumor growth and progression (304).

HBOC, hereditary breast and ovarian cancer syndrome; HGSOC, high-grade serous ovarian carcinoma; GAP, GTPase-activating protein; LGSOC, low-grade serous ovarian carcinoma; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; RAD51, RAD51 recombinase; ARID1A, AT-rich interaction domain 1A; SWI/SNF, switch/sucrose non-fermentable; SMARCA4, SWI/SNF-related BAF chromatin remodeling complex subunit ATPase 4; PDK1, pyruvate dehydrogenase kinase 1; CDKN2A, CDK inhibitor 2A; MDM2, MDM2 proto-oncogene; NF1, neurofibromin 1; BARD1, BRCA1 associated RING domain 1.

menstrual cycle (particularly the follicular phase), aging and menopause (20,22). This raises questions regarding the application of static cut-off points for CA-125 (20) and makes it an unreliable indicator of ovarian cancer.

Due to its low sensitivity and specificity, research shows that a single CA-125 measurement is insufficient for efficient screening. To improve specificity and early-stage disease detection, an approach with two phases that tracks changes in CA-125 over time and applies transvaginal ultrasound for abnormal increases can be adopted (20). It has previously been demonstrated that the Risk of Ovarian Cancer Algorithm, which combines age and serial CA-125 measurements, can increase the identification of cancer during the early stages (20,23). However, these actions are not effective in decreasing ovarian cancer-associated mortality and are expensive (20). The multivariate index assay, which has been reported to have a lower specificity of 40% and a higher sensitivity of 94% compared with CA-125 assessment alone, incorporates five different markers [CA-125, transferrin, transthyretin (prealbumin), apolipoprotein AI and β-2 microglobulin] to generate a score to assess the likelihood of ovarian cancer in patients with a pelvic mass (19).

In addition to CA-125, >110 other possible protein biomarkers have been assessed separately and in combination. Other potential biomarkers include CA15.3, transthyretin, human epididymal protein 4 (HE4) and CA72.4 (6,16). HE4 is a 124-amino acid glycosylated protein that is elevated in the serum of 60-75% of patients with ovarian cancer and can identify a small percentage of cases that are not detected based on CA-125. Other markers and techniques have been shown to improve ovarian cancer detection, such as the presence of autoantibodies, circulating tumor DNA (ctDNA), microRNAs (miRs/miRNAs), DNA methylation, fallopian tube cytology and tumor DNA detection in cervical screening tests (6,16). Furthermore, it has been demonstrated that membrane-spanning mucin (MUC16) glycoprotein CA-125 is a highly glycosylated protein with a molecular weight of ~5 MDa (16). The ovarian cancer cell surface is the site of cleavage of the extracellular domain of MUC16, which releases CA-125 into the pericellular space and the blood, where it can be detected using an immunoassay (16). Extensive research has demonstrated the association between ovarian cancer and the MUC16 biomarker (17,18).

Furthermore, novel imaging techniques have been assessed for the detection of ovarian cancer, including magnetic resonance imaging (MRI) and relaxometry, superconducting quantum interference device technology (SQUID), microbubbles and light-induced endogenous fluorescence (autofluorescence) (6,16). Although it is more expensive and less widely available, MRI combined with relaxometry improves tissue characterization and offers high-resolution, radiation-free imaging. The use of SQUID is constrained by its technical complexity and requirement for cryogenic equipment, despite the fact that it provides ultra-sensitive detection of magnetic signals from cancer-related biomarkers (24). Although it might be limited in deep pelvic regions, microbubble-enhanced ultrasonography increases visualization of tumor vasculature and aids in early identification in a real-time and cost-effective manner. Autofluorescence imaging uses variations in natural tissue fluorescence to detect cancers. It is quick and non-invasive, but its specificity is low (25).

Table II. International Federation of Gynecology and Obstetrics staging classification for cancer of the ovary, fallopian tube and peritoneum *(18)*.

A, Stage I, tumor confined to ovaries or fallopian tube(s)

Stage	Characteristics
IA	Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
IC1	Surgical spill
IC2	Capsule ruptured before surgery or tumor on the ovarian or fallopian tube surface
IC3	Malignant cells in the ascites or peritoneal washings

B, Stage II, tumor involves one or both ovaries or fallopian tubes with pelvic extension or peritoneal cancer

Stage	Characteristics
IIA	Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues

C, Stage III, tumor involves one or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

Stage	Characteristics
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i)	Metastasis ≤10 mm in greatest dimension
IIIA1(ii)	Metastasis >10 mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastasis beyond the pelvis ≤2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

D, Stage IV, distant metastasis excluding peritoneal metastases

Stage	Characteristics
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

2. Treatment of ovarian cancer

Comorbidities, previous therapy and the specific biology of the disease serve a role in guiding treatment decisions. As 90% of cases of early-stage ovarian cancer are curable, this highlights the importance of early detection and prompt specialist treatment. However, most patients are diagnosed at a later stage, when the effectiveness of targeted agents, such as chemotherapy and surgery, is limited (26). Since choices made during the surgical and medical phases of the disease may impact the prognosis, controlling the cancer and decreasing the symptoms are the primary goals of treatment (27). Furthermore, although the current standard of care for the treatment of ovarian cancer is primary debulking surgery followed by systemic chemotherapy (28,29), the age at presentation, performance status (PS) and stage

at presentation are prognostic factors that influence the therapeutic recommendations (30).

Surgery. Surgical procedures serve a key role in the management of ovarian cancer, functioning as both a diagnostic and therapeutic approach (31). The clinical stage of the disease, histology, specific biology and clinical characteristics of the patient determine the extent of the surgery. Surgery is primarily responsible for cytoreduction and cancer staging. Cytoreductive surgery, which includes primary, interval, second-look and secondary cytoreductive surgery, can be performed at various stages during the course of the treatment (26). The goal of surgeries is to eradicate all macroscopic illnesses or leave no residual illnesses, a state known as R0 (27).

There is a clear association between improved survival results for women with ovarian cancer and complete cytoreduction (R0), which is the removal of all visible tumor burden. After surgery, individuals who have no residual disease have a longer overall survival (OS) and progression-free survival (PFS) than individuals who still have tumor tissue (32). According to Wright *et al* (33), optimal cytoreduction was associated with a median OS time of up to 60 months in cases of advanced ovarian cancer; however, sub-optimal debulking considerably lowered the median OS time to <30 months. These findings underscore the critical importance of achieving complete cytoreduction to enhance patient prognosis.

Beyond its direct therapeutic benefits, surgical intervention also enables the collection of tissue samples for histopathological evaluation and molecular profiling, which are crucial for guiding personalized treatment approaches. For example, BRCA-mutated patients may benefit from PARP inhibitors as part of their treatment regimen (34,35). Furthermore, the combination of surgery with systemic therapies, including chemotherapy and targeted therapies, maximizes treatment efficacy and improves patient outcomes. Given its pivotal role in disease management, surgical intervention represents a necessary component of comprehensive ovarian cancer treatment (36,37).

Of patients with ovarian cancer, ~35% are diagnosed at early stages (FIGO stage I-II) (38,39). The typical course of treatment entails extensive surgical staging to diagnose the condition and determine the extent of the illness (38). In the initial stages, the surgery needs to be staged (or stratified) and the following protocols should be performed: Peritoneal lavage, total hysterectomy with bilateral salpingo-oophorectomy, biopsy of any suspicious areas; resection of any adhesions adjacent to the tumor, infracolic omentectomy and random biopsy of the uterine fundus, bladder peritoneum, right and left pelvic walls, ovarian fossae, right and left colic canals and both hemidiaphragms. Additionally, pelvic lymphadenectomy, along with sampling or dissection of para-aortic and paracaval lymph nodes, should be performed. . Adjuvant chemotherapy should be used if necessary, and the surgery should yield sufficient information for prognostication and staging (27).

In advanced stages, the objective of EOC treatment is to eradicate all visible macroscopic disease, as this has been associated with a higher OS and longer time without disease (27,40). Cytoreductive surgery and platinum-based chemotherapy are the most commonly used treatments for advanced ovarian cancer. Since primary cytoreductive surgery is the gold standard for patients with advanced ovarian cancer and as this surgical outcome is associated with improved OS, the aim of the procedure is to stage the tumor and cytoreduce its volume to the point where there is no gross residual disease >1 cm of tumor (27,41,42). An alternative to primary cytoreductive surgery for patients deemed unsuitable due to insufficient physical fitness or incapacity to resect disease to <1 cm is interval debulking surgery combined with platinum-based neoadjuvant chemotherapy (41).

Chemotherapy. Chemotherapy is a mainstay in the management of ovarian cancer, showing notable effectiveness in different stages and clinical settings (43). Platinum-based agents and taxanes are combined in a standard first-line regimen, resulting in marked response rates, and extending OS and PFS, especially in advanced stages of the disease (37,44). Chemotherapy is important in cases of recurrence; recurrence of platinum-sensitive tumors typically responds to treatment with platinum-based regimens, while non-platinum agents are used in platinum-resistant cancer to mitigate disease progression (45). Furthermore, the integration of chemotherapy with novel therapeutic strategies, such as PARP inhibitors and anti-angiogenic agents, has enhanced its efficacy, particularly in patients with specific genetic profiles such as BRCA mutations (46,47). Clinical trials have demonstrated that these combinations not only improve response rates but also prolong PFS and, in some cases, OS. For instance, the addition of bevacizumab to chemotherapy was associated with a median PFS time improvement of several months in advanced ovarian cancer (48), while PARP inhibitors as maintenance therapy post-chemotherapy reduced the risk of recurrence by up to 70% in BRCA-mutated patients (46). These advancements underscore the evolving role of chemotherapy as a foundational treatment that synergizes with targeted therapies to optimize outcomes for patients with ovarian cancer.

Platinum-based compounds are considered to be the most effective chemotherapeutic drugs in ovarian cancer (28,49). Platinum chemotherapy compounds have been used since the mid-1970s. Cisplatin was the first platinum-based drug, but it had several undesirable side effects, such as nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal tract problems and allergic reactions. Consequently, the development of second-generation platinum led to the 1989 launch of carboplatin, which is equally as effective as cisplatin but has fewer severe side effects, especially regarding nephrotoxicity (50). The guidance on the use of platinum-based chemotherapy for relapsed EOC has changed over time, becoming a limited and occasionally variable time-based approach. If a relapse occurs >6 months after the conclusion of the previous platinum-based treatment, the patient is deemed 'platinum-sensitive' and eligible for further platinum-based chemotherapy. If the gap is <6 months, the patients are considered 'platinum-resistant' and not suitable for platinum-based treatment (44). In the latter case, non-platinum regimens are typically offered. Single-agent non-platinum-based chemotherapy, such as weekly administration of paclitaxel, pegylated liposomal doxorubicin or topotecan, is typically offered to patients who are not eligible for additional platinum-based chemotherapy (44,49). Oral etoposide, tamoxifen, gemcitabine and treosulfan are also potential non-platinum alternatives; however, there is a limited

probability of these medications being effective because of their decreased cytotoxic potency and the development of resistance mechanisms, including enhanced DNA repair and increased drug efflux, these agents show limited efficacy (51). Moreover, their lack of molecular specificity and weakened activity against aggressive tumor subtypes result in lower response rates compared with platinum-based chemotherapy (52).

Adjuvant chemotherapy using carboplatin (area under the curve, 5-6) and paclitaxel (175 mg/m^2) are administered following cytoreductive surgery in accordance with established protocols (53). Typically, 6-8 cycles are given every 21 days (30). While there is some disagreement regarding the optimal number of chemotherapy cycles, to the best of our knowledge, there is no evidence that >6 cycles of post-operative combination chemotherapy improve outcomes for patients with advanced ovarian cancer (28,54). It is advised to start chemotherapy as soon as possible following surgery, usually within 2-4 weeks; longer wait times are associated with worse results (30). Notably, compared with single-agent platinum-based regimens, a combination of platinum-based drugs (containing paclitaxel, gemcitabine or pegylated liposomal doxorubicin) is associated with longer PFS and OS (51). The toxicity profile should be taken into consideration when choosing therapeutic agent combinations (55).

Despite high initial response rates (~70%) with chemotherapy and surgery, recurrence is a notable concern (56). In the 10 years following diagnosis, 80-85% of patients with advanced ovarian cancer experience a relapse (55). The need for additional therapy and their performance status should be considered before beginning treatment for recurrent disease. The next stage is to determine whether platinum is the best option; severe side effects, which include fatigue, arthralgia and neurotoxicity, of chemotherapeutic treatments for ovarian cancer impede the quality of life (55). Thus, investigation of the disease mechanisms requires an understanding of the biology of heterogeneous ovarian cancers. Intrinsic signaling pathways, angiogenesis, hormone receptors and immunological factors are among the possible therapeutic targets being investigated for the treatment of ovarian cancer (56). When chemotherapy is combined with targeted treatments such as bevacizumab and PARP inhibitors, patients with homologous recombination (HR) deficiency (HRD) or BRCA mutations (BRCAms) exhibit improved results once compared with chemotherapy alone (57).

Resistance. Certain patients experience relapses following chemotherapeutic treatments as a result of developing drug resistance mechanisms (58). In ovarian cancer, the initial treatment with carboplatin and paclitaxel as first-line chemotherapy has shown an enhanced complete response rate compared with single agents or platinum based regimens (50). However, recurrence rates are 70-80%, particularly for patients with advanced-stage cancer (50). Notably, patients who receive neoadjuvant carboplatin therapy before surgery are more likely to exhibit platinum resistance. Matsuo *et al* demonstrated a markedly elevated incidence of carboplatin resistance among patients who receive neoadjuvant therapy (33.3%) compared with those undergoing primary cytoreductive surgery (9.2%) (59). Similarly, Rauh-Hain *et al* identified a substantially higher prevalence of carboplatin resistance in patients who underwent neoadjuvant therapy (88.8%) compared with those subjected to primary cytoreductive surgery (55.3%) (60).

The molecular diversity of tumor cells contributes to variations in signaling pathways, involving the activation of oncogenes, inactivation of tumor suppressors and the presence of pro-survival genetic mutations. Consequently, resistance to standard chemotherapy regimens is a hurdle in managing the disease (61) and treating patients effectively (56). Thus, understanding of resistance mechanisms is important for the development of novel therapeutic approaches. There are two primary types of resistance: Intrinsic and acquired (extrinsic) resistance. Nevertheless, accurate discrimination between these forms is difficult (34). Intrinsic resistance pertains to the inherent capability of cancer cells to withstand treatment owing to pre-existing characteristics present before their initial exposure to therapeutic agents. Cell attributes associated with intrinsic chemo-resistance include the capacity to decrease drug uptake, increase drug efflux and elevate the activity of detoxification enzymes such as cytochrome P450 or glutathione (GSH) transferases. Conversely, acquired chemo-resistance can emerge from genetic and epigenetic alterations that enable cancer cells to adapt to the effects induced by chemotherapy, such as stress, DNA damage and apoptosis (22).

In ovarian cancer, a subset of patients possess germline mutations in BRCA1 and/or BRCA2, which are key constituents of the HR pathway, essential for repairing DNA double-strand breaks. Consequently, BRCAms impair the capacity to rectify DNA damage via HR, potentially accounting for the heightened sensitivity of this cancer subtype to platinum-based chemotherapeutic agents (62). Conversely, the p53 protein, which serves a key role in governing the cell cycle, is sensitive to DNA damage incurred during replication, resulting in G_1 arrest and/or apoptosis, thereby inhibiting the generation of defective cells (63). Mutation of the gene responsible for p53 expression in human cancer can result in the loss of p53 function. This enables uncontrolled cell proliferation and confers resistance to agents inducing DNA damage. Consequently, a potential avenue for addressing chemotherapy resistance involves reactivating mutant p53 (64).

Ovarian cancer resistance to chemotherapy is markedly influenced by abnormal transmembrane transport, which includes decreased drug influx and increased drug efflux, leading to decreased intracellular drug concentrations and treatment failure. Platinum-resistant ovarian cancer exhibits diminished drug transport-associated gene and transmembrane transporter expression, resulting in inadequate intracellular platinum accumulation (51,65). miRNAs serve a key role in regulating these transporters by binding to the 3'-untranslated region (UTR) of target genes, thereby modulating their transcription and contributing to drug resistance (66). The solute carrier (SLC) superfamily transporters, such as SLC31A1 and SLC22A1/2/3, are responsible for drug influx. The transport of cisplatin, carboplatin and oxaliplatin by SLC31A1 aids intracellular platinum accumulation (67). Patients with ovarian cancer and low SLC22A2 expression are more likely to develop resistance to platinum drugs as they are unable to absorb as much of the drug (68). While evidence has demonstrated that dysregulated expression of miRNAs and target genes serves a critical role in the initiation, proliferation, survival and chemoresistance of ovarian cancer,

the understanding of how miRNAs contribute to the disease pathology remains limited (69,70). Studies focusing on how miRNAs regulate the pathology of ovarian cancer account for <4% of the total published research, highlighting the need for further investigation (69).

Key efflux transporters include ATP-binding cassette subfamily B member 1 (ABCB1), G member 2 and C. miRNAs, such as miR-27a, miR-451, and miR-298, directly bind to the 3'-UTRs) of ABC transporter mRNAs, thereby inhibiting their translation or promoting mRNA degradation by influencing the expression of genes that encode nuclear receptors, transcription factors and signaling molecules associated with ABC transporters. ABCB1 is the only efflux transporter reported to exhibit elevated expression in resistant ovarian cancer cells, while the expression of other ABC transporters is markedly decreased (71). P-glycoprotein, an ATP-dependent drug efflux pump, is encoded by ABCB1 and upregulated in resistant ovarian cancer cell lines, making it a key factor in resistance to paclitaxel, doxorubicin, sorafenib and PARP inhibitors (72,73). miRNAs, including miR-130a/b, miR-186 and miR-495, bind to the 3'-UTR of ABCB1 to degrade the mRNA or limit translation. Although the exact regulatory mechanism is unknown, upregulated ABCB1 expression decreases miR-21-5p expression (68). In patients with HGSOC who undergo chemotherapy or targeted treatment, a whole-genome study identified that an increase in ABCB1 expression is associated with the transcriptional fusion of ABCB1 and SLC25A40 (74).

Beyond transport mechanisms, drug resistance also results from drug inactivation by metallothionein (MT) and GSH (Table III). These thiol-containing proteins bind platinum-based drugs, rendering them inactive, allowing for drug resistance beyond transport mechanisms. Short hairpin RNA targeting MT reverses the well-established resistance mechanism by decreasing MT binding to cisplatin (68,75). The GSH S-platinum complex formed by GSH and cisplatin lowers intracellular platinum levels (76). This platinum inactivation mechanism is catalyzed by GSH S-transferase and associated with platinum resistance in ovarian cancer (68,77).

3. Novel treatment modalities

Targeted therapy and immunotherapy. Targeted therapy for ovarian cancer utilizes treatments that specifically target the pathways essential for the progression of the disease. By targeting specific proteins, these treatments minimize the adverse effects of cytotoxic treatment on healthy cells. Patients with recurrent disease are typically the first to be assessed for targeted therapy (78). If these treatments demonstrate potential in clinical studies focusing on recurrent diseases, they may be considered a primary treatment option for further investigation. In previous years, targeted therapies, such as PARP inhibitors, antiangiogenic medications and MAPK inhibitors, have been acknowledged as notable advancements in treating ovarian cancer (79,80).

Targeted therapies have revolutionized the treatment of ovarian cancer by focusing on specific biological pathways that drive tumor development and resistance. Bevacizumab and PARP inhibitors are two of the most commonly used targeted treatments (81). Bevacizumab, a VEGF inhibitor, prevents the formation of new blood vessels, decreasing blood supply and slowing tumor growth (82). Bevacizumab can be administered alongside chemotherapy during initial treatment or as maintenance therapy, either alone or in combination with olaparib, a PARP inhibitor. PARP inhibitors block PARP protein, which serves a key role in DNA repair in cancer cells (46,47). Initially developed for patients with mutations in BRCA1 or BRCA2, the use of PARP inhibitors has expanded to patients with other types of DNA repair deficiencies (such as RAD51C (RAD51 Paralog C)/RAD51D (RAD51 Paralog D), ATR (Ataxia Telangiectasia and Rad3-related protein), CHEK1 (Checkpoint Kinase 1)/CHEK2 (Checkpoint Kinase 2), BARD1 (BRCA1 Associated RING Domain 1), BRIP1 (BRCA1 Interacting Protein C-terminal Helicase 1), ATM (Ataxia Telangiectasia Mutated) and PALB2 (Partner and Localizer of BRCA2)) (83). PARP inhibitors approved for use as ovarian cancer treatment are primarily used as maintenance therapy following chemotherapy for advanced ovarian cancer, decreasing the risk of recurrence and tumor progression (84). Previous research has evaluated their effectiveness in broader patient populations, including those with inherited mutations in DNA repair genes, such as partner and localizer of BRCA2 (PALB2), BRCA1-interacting protein C-terminal helicase 1 (BRIP1), RAD51 recombinase paralog C (RAD51C) and RAD51 recombinase paralog D (RAD51D) (85). Additionally, patients without inherited mutations, but with acquired tumor biomarker mutations in DNA repair genes may also benefit from PARP inhibitors (86). There is growing interest in combining PARP inhibitors with immunotherapy or other targeted agents to enhance treatment outcomes (87,88).

Other targeted therapies have been developed for ovarian cancer, particularly for recurrent disease or cases where chemotherapy is ineffective. Mirvetuximab soravtansine (MIRV)-gynx is approved for recurrent ovarian cancer positive for folate receptor α (FRα) (89). Larotrectinib is used to treat metastatic ovarian cancer or cases that cannot be surgically removed and have progressed despite prior treatment, especially if the tumor harbors a neurotrophic receptor tyrosine kinase gene fusion (90). Selpercatinib is prescribed for ovarian cancer with a RET gene fusion, as identified by tumor biomarker testing (91). The integration of these therapies emphasizes the importance of biomarker testing, which can identify patients most likely to respond to precision medicine approaches. Ongoing research continues to explore novel targeted therapies and combination treatment strategies aimed at improving survival and clinical outcomes for patients with ovarian cancer (92-94).

PARP inhibitors. In 2014, the United States Food and Drug Administration (FDA) and European Medication Agency authorized the use of PARP inhibitors for the treatment of ovarian cancer (95). These drugs target EOC that cannot repair DNA through HR, which is key for fixing double-stranded DNA breaks (80,95). Mutations in BRCA1/2 induce HR repair (HRR) pathway deficiencies in tumor cells, which prevent DNA double-stranded breaks from being repaired. PARP inhibitors prevent DNA damage repair in these cells, inducing apoptosis by synthetic lethality (96). Synthetic lethality describes a phenomenon where the presence of a mutated gene, such as one involved in DNA repair, combined with the functional loss

Table III. Mechanisms of resistance to treatment for ovarian cancer.

Drug	Method of resistance	First author/s, year	(Refs.)
Platinum family (carboplatin and cisplatin)	Activation of the Nrf2 pathway	Yang *et al*, 2022	(65)
	Alteration in DNA copy number	Lukanović *et al*, 2022	(29)
	Apoptosis evasion	Lukanović *et al*., 2022	(29)
	Augmented levels of cellular thiols	Lukanović *et al*, 2022	(29)
	Cancer stem cells	Yang *et al*, 2022	(65)
	Changes in drug targets	Lukanović *et al*, 2022	(29)
	Changes in gene expression	Lukanović *et al*, 2022	(29)
	Decreased influx by influx transporter copper transporter 1	Lukanović *et al*, 2022; Yang *et al*, 2022	(29,65)
	Dependence on mitochondrial oxidative phosphorylation for energy supply	Ortiz *et al*, 2022	(305)
	High genomic instability	Lukanović *et al*, 2022	(29)
	Increased DNA damage repair	Lukanović *et al*, 2022; Ortiz *et al*, 2022	(29,305)
	Increased efflux by efflux transporters ATPase copper-transporting a and b	Lukanović *et al*, 2022; Ortiz *et al*, 2022	(29,305)
	Increased cisplatin-induced autophagy	Ortiz *et al*, 2022; Yang *et al*, 2022	(65,305)
	Upregulation and higher enzyme activity of glucose-6-phosphate dehydrogenase	Yang *et al*, 2022	(65)
	Upregulation of de-ubiquitination of proteins targeted for proteasomal degradation	Ortiz *et al*, 2022	(305)
Taxanes (paclitaxel)	Changes in microtubule composition (such as βIII isoform)	Lukanović *et al*, 2022; Ortiz *et al*, 2022	(29,305)
	Evasion of apoptosis and conformational changes in BCL-2 family members	Levit and Tang, 2021; Ortiz *et al*, 2022	(58,305)
	Glutathione S-transferase 1	Levit and Tang, 2021; Ortiz *et al*, 2022	(58,305)
	High metabolism of taxanes (due to upregulating CYP enzymes)	Lukanović *et al*, 2022	(29)
	Hypoxia	Lukanović *et al*, 2022	(29)
	Overactivation of the PI3K/AKT pathway	Ortiz *et al*, 2022	(305)
	P-gp mediated drug efflux	Levit and Tang, 2021; Lukanović *et al*, 2022; Ortiz *et al*, 2022	(29,58, 305)
	Increased rate of DNA repair	Levit and Tang, 2021	(58)
Paclitaxel and cisplatin cross-resistance	Upregulation of cell survival pathways	Ortiz *et al*, 2022	(305)
PARP family	Autophagy	Ortiz *et al*, 2022	(305)
	Upregulation of DNA replication stress markers ATM and ATR	Ortiz *et al*, 2022	(305)
	Increased activation of the Wnt signaling pathway and transcription of β-catenin targets	Ortiz *et al*, 2022	(305)
	Increased expression of neuropilin-1 transmembrane receptor	Ortiz *et al*, 2022	(305)
	P-gp-mediated drug efflux	Ortiz *et al*, 2022	(305)
	DNA repair pathways	Lukanović *et al*, 2022; Ortiz *et al*, 2022	(29,305)
	Upregulation of aldehyde dehydrogenase 1 family member A1	Ortiz *et al*, 2022	(305)
VEGF inhibitors (bevacizumab)	Adaptation of the tumor microenvironment, reflected by the recruitment of progenitor cells, angiogenesis and adapted neovascularization modalities	Lukanović *et al*, 2022	(29)

Table III. Continued.

Drug	Method of resistance	First author/s, year	(Refs.)
	Angiogenesis	Ortiz *et al*, 2022	(305)
	Epithelial-mesenchymal transition	Lukanović *et al*, 2022	(29)
	Increased vessel pericyte coverage	Ortiz *et al*, 2022	(305)
	Lysosomal sequestration of drugs	Lukanović *et al*, 2022	(29)
	Upregulation of ephrin type-B receptor	Ortiz *et al*, 2022	(305)
	Upregulation of genes involved in angiogenic redundancy	Lukanović *et al*, 2022	(29)

CYP, cytochrome P450; P-gp, P-glycoprotein; PARP, poly(ADP-ribose) polymerase; ATM, ataxia-telangiectasia mutated; ATR, ATM-and Rad3-related; Nrf2, nuclear factor erythroid 2-related factor 2.

or inhibition of another gene or its product, leads to a synergistic effect that induces cellular toxicity and cell death (97).

The FDA has approved olaparib as a maintenance treatment for patients with advanced ovarian cancer with a BRCAm who respond well to initial platinum-based chemotherapy (98). Notably, olaparib increased PFS compared with a placebo following a median follow-up of ~41 months. Furthermore, after 7 years of monitoring, a notable improvement in OS was noted in the SOLO1 (trial no. NCT01844986) clinical study (99).

A previous study compared the efficacy of maintenance niraparib with a placebo in patients with advanced ovarian cancer (100,101). In the PRIMA study (trial no. NCT02655016), 733 patients with newly diagnosed advanced ovarian cancer were randomly assigned to receive either maintenance niraparib or a placebo for up to 36 months, or until disease progression. After 3.5 years of follow-up, the improvement in progression-free survival (PFS) with niraparib was significant, confirming PFS as the primary and durable outcome of the trial (101,102). As a first line of maintenance treatment, 384 patients with advanced ovarian cancer were randomized to receive niraparib [individualized starting dose (ISD)] or a placebo in the PRIME trial (NCT03709316). Following a median observation period of 27.5 months, there was a marked increase in PFS with the niraparib (ISD) regimen compared with the placebo (100).

Similarly, the ATHENA-MONO trial (trial no. NCT03522246) compared maintenance rucaparib with a placebo (103). Rucaparib maintenance therapy markedly increased the median PFS compared with the placebo in the HRD-positive patient group after a median follow-up of ~26 months (103,104). Initial research demonstrated that administration of rucaparib resulted in improved PFS outcomes in patients with BRCAm, non-BRCAm/loss of heterozygosity-high cancer and malignancies that test negative for HRD compared with a placebo (103). Preservation therapy with PARP inhibitors is effective when administered initially to patients with BRCAm or tumors exhibiting HRD (103).

While the PARP inhibitor veliparib is in the advanced stages of clinical testing, the FDA has approved four PARP inhibitors to date: Olaparib, rucaparib, niraparib and talazoparib (105). Talazoparib may exert its therapeutic effect by blocking PARP enzyme activity, which leads to PARP1/2 being trapped on damaged DNA (thereby inhibiting DNA repair) (106). The clinical efficacy of olaparib, an oral PARP inhibitor, or cediranib, an oral VEGF inhibitor, in conjunction with durvalumab, has been evaluated in a phase I dose-escalation trial (107). After determining that chemotherapy with avelumab exhibits antitumor activity and acceptable safety, the JAVELIN OVARIAN PARP100 trial (trial no. NCT03642132) proceeded with maintenance treatment combining the two drugs (108). The selective PARP inhibitor saruparib markedly inhibited tumor growth in preclinical models of breast, ovarian, pancreatic and prostate cancer with HRD mutations (109,110). Notably, saruparib exhibited lower toxicity compared with other PARP inhibitors, allowing administration at higher doses (111).

Chemotherapeutic drugs, such as carboplatin and paclitaxel, along with angiogenesis inhibitors, such as bevacizumab, have demonstrated synergistic effects with PARP inhibitors (35,46). Clinical trials evaluate these combinations to optimize treatment strategies (112-114). Although PARP inhibitors have markedly improved the treatment of ovarian cancer, particularly in patients with BRCAm and HRD, their use is hindered. A major challenge is drug resistance (Table III). Adverse effects, including hematological toxicity (anemia, neutropenia and thrombocytopenia) and gastrointestinal problems (nausea, vomiting and diarrhea), further limit treatment adherence (115,116). Furthermore, the high cost of PARP inhibitors restricts access, particularly in low-resource settings, making affordability a concern (117). Another serious risk is the potential development of secondary malignancy during and after treatment with PARP inhibitors (118). To address these challenges, research is exploring combination therapy, novel biomarkers for patient selection and strategies to overcome resistance and enhance PARP inhibitor efficacy (119-121).

Angiogenesis inhibitors. Tumor growth and angiogenesis are facilitated by the production of VEGF (122). Drugs that hinder angiogenesis and the formation of blood vessels are an alternative approach for managing ovarian cancer. As the number of cancerous cells increases in a tumor, the cells experience hypoxia, leading to angiogenesis, which is the formation of new blood vessels (123). VEGF and its receptor enhance endothelial cell proliferation and movement (124). Angiogenesis is involved in initiating and advancing ovarian cancer (123).

Bevacizumab is a monoclonal antibody that targets VEGF-A (124). Phase II trials show improvement in PFS in recurrent ovarian cancer treated with bevacizumab, either alone or in combination with other agents (47,125) Subsequent phase III studies have investigated bevacizumab in both initial treatment and recurrent cases of ovarian cancer, regardless of platinum sensitivity (44,126). Improvements in PFS have been noted in two clinical trials, ICON7 (trial no. NCT0048 3782) (126,127) and GOG218 (trial no. NCT00262847) (126), when using bevacizumab in the primary treatment and maintenance therapy especially for patients at high risk for progression. The outcomes of bevacizumab are moderate and increased the likelihood of intestinal perforation (128). Therefore, bevacizumab is not commonly used as the initial therapeutic option. Furthermore, bevacizumab has been applied in clinical trials, such as OCEANS and AURELIA (trial no. NCT00976911), to extend PFS in platinum-sensitive and platinum-resistant cases of recurrent ovarian cancer when combined with chemotherapy. This suggests that patients with notable ascites or high angiogenic activity are the most likely to benefit from this strategy (44). Notably, increased EGFR expression is associated with a negative prognosis in ovarian cancer (129). Administering carboplatin alongside cetuximab enhanced results in 9 of 26 patients with ovarian or primary peritoneal cancer who were EGFR-positive (130). However, a second round of patient selection was not performed due to the poor response rate.

Although angiogenesis inhibitors have demonstrated promising efficacy in ovarian cancer treatment, patients exhibit adverse effects such as hypertension, proteinuria and gastrointestinal perforation, necessitating careful patient selection (131,132). Therapeutic strategies that combine angiogenesis inhibitors with PARP inhibitors or immunotherapy have been explored to improve clinical outcomes and overcome resistance mechanisms (96).

MAPK inhibitors and miRNAs. MAPK inhibitors are promising therapeutic options for LGSOC (133). LGSOC is frequently driven by mutations in the MAPK signaling pathway, including in BRAF and KRAS. These genetic alterations result in constitutive activity, promoting tumor growth and resistance to conventional chemotherapy (134,135). MAPK pathway inhibitors, particularly MEK inhibitors such as trametinib and binimetinib, have notable efficacy in increasing PFS in patients with LGSOC, as demonstrated in clinical trials such as GOG-281 and MILO (trial no. NCT02101788) (134). In patients with a BRAF V600E mutation or non-mutated ovarian cancer with limited therapeutic options, it is advisable to target MAPK pathways, such as p38 and JNK pathways (136), as this approach is more effective and manageable regarding toxicity. A previous study reported that the upregulation of p38 and JNK was directly associated with the development of resistance to olaparib in ovarian cancer (137). Combining p38 and JNK inhibitors induced notable antitumor effects in both laboratory studies and animal experiments (138), emphasizing the therapeutic potential of MAPK inhibitors in addressing olaparib-resistant human ovarian cancer (139). While MAPK inhibitors show notable potential in ovarian cancer treatment, challenges persist, including the emergence of resistance through pathway reactivation or alternative signaling mechanisms, as well as adverse effects such as rash, diarrhea and fatigue (140). Additional research on combination therapies and biomarker-driven approaches is required to improve their effectiveness and therapeutic value in multiple subtypes of ovarian cancer.

Several miRNAs are dysregulated in numerous types of cancer, and this dysregulated expression is associated with resistance to chemotherapy (141). miR-139-5p serves a crucial role in ovarian cancer, and its expression levels are decreased in ovarian cancer tissues from cisplatin-resistant patients (142). As such, upregulation of miR-139-5p can impede proliferation, decrease resistance to cisplatin and enhance apoptosis in ovarian cancer cells. Furthermore, the combined use of miR-139-5p and MAPK inhibitors decreases cisplatin resistance in ovarian cancer (143). Thus, upregulating miR-139-5p expression may be a promising treatment approach for ovarian cancer (144).

Immunotherapy. Immunotherapy, which is designed to encourage the immune system to identify and eradicate cancerous cells, has become a promising therapeutic option for ovarian cancer; immunotherapeutic strategies, such as immune checkpoint inhibitors (ICIs) and customized vaccinations, improve outcomes in certain patients with ovarian cancer (145).

Dendritic cells are specialized antigen-presenting cells that are essential for initiating and guiding the development of numerous subsets of $CD4^+$ T cells. They activate immune cells to fight against invading pathogens or cancer cells, and the presence of tumors hinders their function (146). TGF-b is a protein released by tumor cells that impedes the ability of cytotoxic CD8 T lymphocytes to eradicate cancer cells (147). Programmed death ligand 1 (PD-L1) is an immunosuppressive ligand, which is produced by tumor cells. PD-L1 induces immunological tolerance by inhibiting T cells through binding to their receptor, programmed cell death protein 1 (PD-1). Additionally, PD-L1 inhibits IL-2 release by interacting with PD-1, inducing T-cell immunity. PD-L1 expression on monocytes in blood samples of patients with ovarian cancer is associated with a poor prognosis (148,149). Antigen-presenting cells have another immunological checkpoint known as cytotoxic T lymphocyte-associated protein 4 (CTLA-4). CTLA-4 binds to CD80, a co-stimulatory factor, and prevents T-cell activation, resulting in cell cycle arrest (150).

Anti-PD-1 and anti-CTLA-4 ICI therapies were first authorized for use in 2011 (such as ipilimumab) to treat malignant melanoma and non-small and renal cell carcinoma. Official authorization for other anti-PD1 therapies, such as nivolumab use was obtained in 2014 (151). In a phase I trial (trial no. NCT00729664), 17 patients with ovarian cancer were treated with a PD-L1 blocking antibody (BMS-936559); 1 patient exhibited a partial response, while disease stability was reported in 2 patients (152). A total of 10% of patients with platinum-resistant ovarian cancer exhibited a sustained complete response in a phase II trial (trial no. UMIN000005714) utilizing nivolumab (anti-PD-1) (153). In the KEYNOTE-028 multicohort phase Ib trial (trial no. NCT02054806), patients with platinum-resistant ovarian cancer treated with pembrolizumab achieved an objective response rate of 11.5%, while 23% of patients experienced stable disease (154). Ipilimumab,

a CTLA-4 blocker, was given as a monotherapy in a phase II trial including patients with platinum-sensitive ovarian cancer (trial no. NCT01611558) (155); 95% of the patients did not survive the induction phase due to disease progression, medication toxicity, mortality or undiscovered factors.

Due to the limited efficacy of immunotherapies that target the PD-1/PD-L1 pathway in ovarian cancer, there is interest in combination treatments that target additional immune checkpoints, such as the T cell immunoreceptor with Ig and ITIM domains (TIGIT)/CD155/DNAX accessory molecule-1 (DNAM-1) pathway. This dual blockade approach may boost T cell and natural killer (NK) cell activity against cancer cells, improve tumor antigen expression and overcome immunosuppression in the tumor microenvironment (156,157). However, more research is required to understand the mechanisms and synergistic benefits of targeting both the PD-1/PD-L1 and TIGIT/CD155/DNAM-1 pathways in ovarian cancer (156). Although immunotherapy has potential in the treatment of ovarian cancer, individual outcomes can vary, and certain patients may not experience notable improvements. Immunotherapy may also result in immune-associated side effects, such as autoimmune responses and inflammation (158).

Combination therapy. Researchers have investigated various combination treatment approaches to enhance clinical outcomes (26,159). Integrating multiple treatment modalities effectively treats ovarian cancer by enhancing the efficacy of each approach (160). These approaches utilize the increasing accessibility of therapeutic drugs and comprehension of the disease biology. The combinations target multiple cancer pathways simultaneously by utilizing DNA-damaging medications, targeted therapy impacting signaling pathways and immunotherapies. Immunotherapy is effective in patients with hypercalcemic small cell carcinoma with high PD-L1 expression and severe ovarian cancer due to their active immune environment (161). A review of 15 clinical trials, involving 945 patients with advanced ovarian cancer, found that PD-1/PD-L1 inhibitors achieve an overall response rate (ORR) of 19%. These inhibitors were significantly more effective when combined with chemotherapy (36% ORR) compared to when used alone (9% ORR) (162). Additionally, patients with platinum-sensitive ovarian cancer responded better to these inhibitors (31% ORR) than those with platinum-resistant disease (19%) ORR (162). Checkpoint-blocking medications have not been successful in treating ovarian cancer despite their efficacy in solid tumors such as melanoma, lung cancer and renal cell carcinoma (163).

It has been demonstrated that elevated intracellular enzyme indoleamine 2,3 dioxygenase (IDO) levels suppress the immunological response (164). Due to its toxic nature, IDO converts tryptophan into kynurenine, enhancing regulatory T cell levels and reducing NK cell levels (165). This results in a weakened immune response, allowing cancer cells to evade immune detection and continue to proliferate. .In a phase I trial (trial no. NCT01191216), 41% of patients with various metastatic solid tumors achieved disease stability. By comparison, 18% had a partial response when given a combination of docetaxel and the IDO inhibitor indoximod (146,166). Phase II research on using an IDO1 inhibitor + tamoxifen to treat recurrent EOC and primary peritoneal and fallopian tube carcinoma was discontinued because there was no notable difference in responses between the treatment and control groups (167).

Combining ICIs with cytotoxic medications is a rational approach to enhance tumor immunogenicity and improve the effectiveness of ICIs. For example, a phase II trial investigated the efficacy of combining nivolumab with bevacizumab in recurrent ovarian cancer (168). The combination demonstrated clinical effectiveness, with an overall response rate (ORR) of 28.9% and a PFS of 8.1 months. Atezolizumab is being evaluated in various cancer types in ongoing phase III trials that combine it with chemotherapy and/or bevacizumab. OS and investigator-assessed PFS are co-primary outcomes in the IMagyn050 study (NCT03038100) (169,170). Evaluation of atezolizumab effectiveness in combination with platinum-based chemotherapy with concurrent and maintenance bevacizumab is the primary goal of the ATALANTE study (NCT02891824) (170).

Additionally, ICIs have been studied in combination with PARP inhibitors, as reported in the TOPACIO/KEYNOTE-162 trial (trial no. NCT02657889). Niraparib + pembrolizumab achieved a 25% ORR and 68% disease control rate (DCR) in patients with platinum-resistant recurrent ovarian cancer, with patients with BRCAm showing higher responses (ORR, 45%; DCR, 73%). In platinum-sensitive recurrent ovarian cancer, adding atezolizumab to carboplatin and niraparib maintenance does not improve PFS, regardless of BRCA status or PD-L1 expression (171). The DUO-O trial (NCT03737643) demonstrated that triplet therapy (Durvalumab with chemotherapy and Bevacizumab, followed by maintenance Durvalumab, Bevacizumab and Olaparib) extended the median PFS by 5 months overall and 14.3 months in HRD-positive patients compared with bevacizumab alone, offering notable benefits for non-BRCAm ovarian cancer (172). Furthermore, ICIs have been studied with antibody-drug conjugates in the FORWARD II trial (NCT02606305). MIRV combined with pembrolizumab had promising efficacy in 14 patients with FRα-platinum-resistant recurrent ovarian cancer, achieving a 43% ORR, a median duration of response of 6.9 months and a median PFS of 5.2 months, with no severe adverse events (145).

The FDA has approved olaparib in combination with bevacizumab as a maintenance treatment for patients with advanced ovarian cancer who show improvement after receiving first-line platinum-based chemotherapy and whose tumors are positive for HRD (173). The primary endpoint of investigator-assessed PFS was markedly longer with olaparib + bevacizumab compared with the placebo + bevacizumab after a median follow-up of 22.9 months. The combination of olaparib and bevacizumab resulted in a markedly improved PFS for patients with BRCAm tumors and tumors positive for HRD compared with bevacizumab alone. The combined group receiving olaparib and bevacizumab had a median OS of 56.5 months, while the placebo + bevacizumab group had a median OS of 51.6 months, according to a randomized controlled trial (174). Patients whose tumors were positive for HRD or for BRCAm had the longest median PFS and the highest rates of PFS at 18 months (175,176). Furthermore, OVARIO (phase II), has examined the use of niraparib with bevacizumab as a first-line maintenance regimen for patients with recently diagnosed advanced ovarian cancer demonstrated

promising progression-free survival (PFS) outcomes. The safety profile was consistent with the established adverse effect patterns of niraparib and bevacizumab when administered as monotherapies. In the triplet combination of niraparib, dostarlimab and bevacizumab, the OPAL-A trial (NCT03574779) observed limited ORR in patients with platinum-resistant ovarian cancer, although the median PFS of 7.9 months and OS of 22.1 months were favorable compared with historical data. Notably, the majority of responders (85.7%) were bevacizumab-naïve. Exploratory biomarker analysis from paired pre- and post-treatment samples indicated immune activation, warranting further investigation into whether these biomarkers predict the clinical efficacy of triplet therapy (177).

Combining therapeutic modalities can improve the efficacy of ovarian cancer treatment, but it also makes treatment more complicated and raises the possibility of adverse effects, such as immunological, hematological and gastrointestinal toxicity (178).

Nanoparticles. The domain of cancer nanomedicine is experiencing notable growth, with a range of nanoparticle systems investigated through various targeting strategies, suggesting potential for reshaping cancer therapeutics (179,180). Nanomedicine may confer notable advantages over traditional chemotherapeutic agents (181). Nanotechnology-based therapeutics are associated with improved efficacy, decreased toxicity experienced by healthy tissues and improved patient adherence (182). Furthermore, the encapsulation of drugs within nanocarriers offers control over pharmacokinetic properties, including drug release kinetics, prolonged circulation half-life and interaction with healthy tissues (58,180). As such, numerous materials, including carbon- and metal-based nanomaterials, liposomal formulations, cubosomes, lipid and polymeric nanoparticles, micelles (179,182), as well as viral and cell membrane-coated nanoconstructs (179), have been investigated.

Notably, investigations have examined the application of nanomaterials in the encapsulation and concurrent delivery of not only pharmaceutical agents but also imaging agents and genetic material, as well as in the recognition of neoplastic cells through receptor-specific binding mechanisms (179,183). Additionally, these nanostructures yield synergistic effects by amalgamating imaging techniques, such as Ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), fluorescence Imaging, and photoacoustic Imaging, with one or multiple therapeutic approaches, such as chemotherapy, photodynamic and photothermal therapy, radiotherapy, and immunotherapy (179).

Two principal tumor targeting strategies, passive and active targeting, have been investigated (180,182). The aberrant vascular architecture resulting from rapid tumor vascularization, coupled with inadequate lymphatic drainage, facilitates the enhanced permeability and retention (EPR) effect, which is key for the enrichment of proliferating malignant tumors (180-182). Nevertheless, passive targeting is associated with non-discriminatory accumulation in both healthy and diseased tissue, akin to conventional chemotherapeutic regimens (181). Additionally, the EPR effect presents challenges, as macromolecules or nanoparticles must evade reticuloendothelial system clearance and renal filtration to infiltrate tumor tissue (184). Furthermore, to exploit the EPR effect, a drug must remain in circulation for ≥6 h to accumulate in neoplastic tissues (180). By contrast, active targeting strategies leverage the strong binding affinity of targeting ligands or agents to tumor cell surfaces, facilitating receptor-mediated endocytosis (180,181). Targeted nanocarriers offer advantages over non-targeted counterparts by enhancing efficacy at the delivery site while mitigating potential adverse effects (181). Several active targeting ligands, including folate receptors, monoclonal antibodies, nucleic acids and polypeptides, have been employed to modify nanocarriers, thereby promoting cell uptake (185).

Patients with ovarian cancer often initially respond favorably to conventional therapeutic approaches, but develop resistance over time (182,186). An avenue to enhance the effectiveness and specificity of chemotherapeutic agents involves nanotechnology-based formulations, encompassing encapsulated, conjugated or entrapped/loaded forms within nanocarriers or drug delivery vectors (58,182). The integration of nanotechnology in ovarian cancer management has garnered increasing attention due to its promising attributes in molecular imaging, tumor targeting and drug delivery (187,188). Furthermore, the use of nanotechnology in ovarian cancer extends beyond the delivery of therapeutic agents, including the incorporation of imaging and diagnostic materials (189), rendering such systems 'theranostic' nanotechnology (190,191). Various types of nanoparticles have been employed in ovarian cancer therapeutics to facilitate the delivery of drugs, including liposomes, nanoparticles, micelles, dendrimers and polymers (187,189). Notably, certain formulations loaded with chemotherapeutic agents have gained approval from the FDA for ovarian cancer treatment (58). Examples of approved nanoparticles include Doxil®, Genexol-PM® (192) and Abraxane® (190).

Several clinical studies have incorporated drugs into nanoparticles for the treatment of ovarian cancer. Although the majority of studies focused on applying nanoparticles with chemotherapeutic agents, primarily paclitaxel (trial nos. NCT03304210, NCT00499252, NCT00825201, NCT00666991 and NCT00989131), docetaxel (trial no. NCT03742713) and doxorubicin (trial no. NCT01489371), other clinical studies demonstrated the effectiveness of applying nanoparticles with other treatment options such as PARP inhibitors [olaparib (trial no. NCT04669002)] or angiogenesis inhibitors [bevacizumab (trial no. NCT01652079)]. Furthermore, the application of nanoparticles in ovarian cancer extends to studies of the application of combination therapy with nanoparticles such as irinotecan with bevacizumab (trial no. NCT04753216), sargramostim with paclitaxel (trial no. NCT00466960) (193), apatinib and paclitaxel (trial no. NCT03942068), and lapatinib and paclitaxel (trial no. NCT00313599) (186).

Although nanoparticles have potential, there are drawbacks, including toxicity, issues with biocompatibility and immunological reactions that can cause accumulation in organs (194). Concerns regarding scalability, quality control and environmental effects are associated with the complicated and expensive production process (195). Numerous types of treatment based on nanoparticles are in the experimental stage and have had minimal clinical success despite continuous research (196,197).

Genetic testing and gene therapy. HRR pathway germline or somatic mutations are responsible for 20-30% of ovarian cancer cases (198). BRCA1/2, RAD51C, RAD51D, BRIP1, PALB2 and BRCA1 associated RING domain 1 are key proteins in the HRR pathway. According to recommendations by National Comprehensive Cancer Network (NCCN) (9,199,200), American Society of Clinical Oncology and Society of Gynecologic Oncology, genetic testing is recommended for all newly diagnosed cases of EOC (200). Furthermore, BRCA1/2 mutation testing is crucial because it can inform the potential efficacy of PARP inhibitors (9,200). Despite the clinical advantages of genetic testing in ovarian cancer treatment, such as detection of hereditary cancer syndromes, guiding treatment decisions, facilitating risk assessment, early intervention and preventive measures for patients and their family members, it remains underused due to insufficient awareness among clinicians and patients, financial and insurance-related barriers, and limited availability of genetic counseling resources (9). Genetic testing for hereditary ovarian cancer includes whole-exome/genome sequencing, multigene panels or single-gene tests, with next-generation sequencing enabling high-throughput analysis (201). Variant interpretation follows American College of Medical Genetics and Genomics guidelines, with *in silico* tools, databases such as ClinVar and tumor testing used to differentiate germline from somatic mutations (202). A key part of the genetic testing process is genetic counseling, particularly for individuals with hereditary cancer syndrome. Professional genetic counselors or adequately qualified oncologists should provide counseling, in accordance with regional regulatory requirements (9).

The process of correcting a mutated gene to treat an underlying disorder is known as gene therapy (203). Several gene therapy approaches have been investigated in preclinical studies focused on the management of ovarian cancer (96,204): These strategies include the replacement of tumor suppressor genes to reestablish cellular regulation (such as TP53), oncogene inhibition (such as EGFR), suicide gene therapy involving the introduction of toxin-encoding genes (such as herpes simplex virus thymidine kinase), genetic immunopotentiation to enhance the immune response against tumor cells (such as IL-12A/B), antiangiogenic gene therapy (such as collagen type XVIII α1 chain), methods to restore pharmacological sensitivity (such as survivin) and cancer virotherapy (such as vesicular stomatitis virus). Notably, several of these approaches have been tested in clinical trials; although they showed promising results, most of them are in phase I (96,204).

Hormone receptor modulators. It is well established that estrogen stimulates the proliferation of ovarian cancer cells (205-207). Estrogen signaling, which is mediated by estrogen receptor (ER)α and ERβ and their various isoforms, is further amplified by G protein-coupled ER 1 (208). Both *in vitro* and *in vivo* studies have demonstrated that estrogen, through its interaction with ERα, influences cell motility and survival by promoting ovarian cancer cell proliferation and migration and triggering epithelial-mesenchymal transition (205,209,210). Several clinical studies have demonstrated that EOCs, which express ERα, respond well to hormonal therapy such as tamoxifen and aromatase inhibitors (such as letrozole) (211-213). When binding to ER, tamoxifen competes with estrogen, but aromatase inhibitors work by preventing the synthesis of estrogen (96).

Patients with platinum-resistant and recurrent ovarian cancer may consider hormonal therapy as an alternative treatment option according to the 2019 guidelines from the European Society for Medical Oncology-European Society of Gynecological Oncology (214) and the 2021 guidelines from NCCN (version 2.2021) (215). To the best of our knowledge, the clinical effectiveness of hormonal therapy in the treatment of ovarian cancer has not been systematically evaluated in large-scale clinical trials, in spite of these recommendations. Notable trials have assessed fulvestrant, an ER degrader (trial no. NCT00617188), tamoxifen (trial nos. NCT02728622 and NCT00041080), arzoxifene, an ER modulator (trial no. NCT00003670) and mifepristone, a progesterone receptor modulator (trial nos. NCT00459290 and NCT02046421) (96).

Hyperthermic intraperitoneal chemotherapy (HIPEC). For patients undergoing surgery, adjuvant treatment options such as intraperitoneal and HIPEC therapy should be considered (216). Following cytoreductive surgery, HIPEC is the administration of chemotherapeutic agents directly into the peritoneal cavity to improve patient outcomes through more efficient removal of residual disease. The sensitivity of the tumor to treatment is increased by the hyperthermic environment, which also improves chemotherapeutic drug penetration at the peritoneal surface (96). Notably, when several ovarian cancer treatments, such as carboplatin, paclitaxel and docetaxel, are administered intraperitoneally compared with intravenously, their effective drug concentration in the abdominal cavity is increased several fold and their clearance from the peritoneal cavity is notably slower (34). Although intraperitoneal therapy has been demonstrated to markedly improve the OS (216), other studies have found that paclitaxel and cisplatin intraperitoneal therapy do not extend OS or PFS in patients with stage III ovarian cancer (217,218).

HIPEC is effective in treating gastric and colorectal cancer and primary peritoneal carcinomatosis (92). Uncertainties exist regarding patient selection, drug delivery protocol, treatment timing, chemotherapeutic regimen and possibility of complications (96). The current NCCN guidelines state that patients with ovarian cancer with peritoneal carcinomatosis (FIGO stage III) who show improvement or stable disease following neoadjuvant chemotherapy should be considered for HIPEC (96). Additionally, intraperitoneal injection application has extended to include the administration of low-dose bevacizumab after the drainage of malignant ascites and has shown efficacy and a tolerable safety profile, especially in symptomatic patients with chemotherapy-resistant ovarian, fallopian tube or primary peritoneal cancer (219).

FRα-targeting drugs. The metabolism of folate is key for cellular functions such as DNA synthesis, methylation and repair (220). Folate and its derivatives enter cells via endocytosis, which is aided by the transmembrane glycoprotein FRα (221). In most cases, FRα expression is limited to specific tissue, such as the kidney, retina, lung, choroid plexus and placenta. FRα is markedly upregulated in several types of cancer, such as those that impact the ovaries, breast, lung and

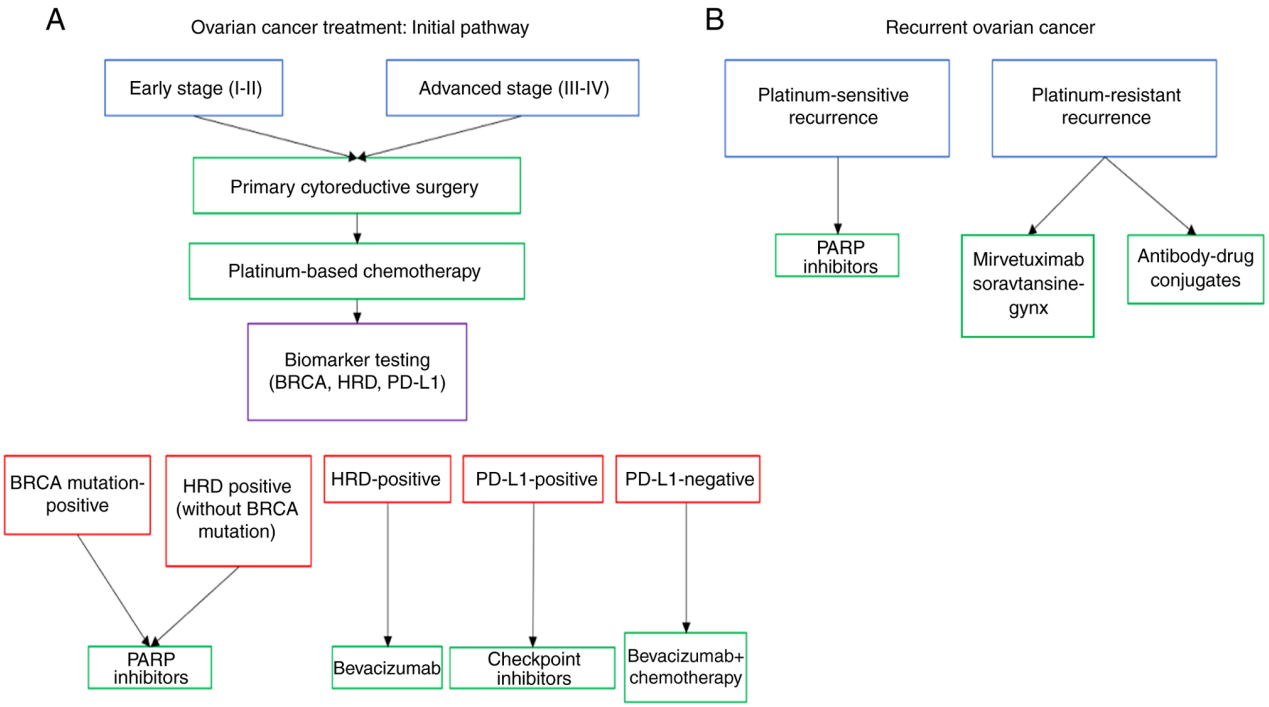

Figure 1. Ovarian cancer treatment flow chart. Treatment for (A) initial and (B) recurrent ovarian cancer. HRD, homologous recombination deficiency; PD-L1, programmed death ligand 1; PARP, poly(ADP-ribose) polymerase.

endometrium (222,223). Due to the capacity to enter the cell post-ligand binding and its selective upregulation, FRα is a desirable target for cancer drug delivery schemes (96). FRα is typically upregulated in ovarian carcinoma, while this receptor is absent in normal ovarian epithelium. Notably, the levels of soluble FRα (sFRα) in circulation are associated with tumor FRα expression, disease progression and treatment outcomes in patients with EOC. As a result, sFRα shows improved diagnostic accuracy compared with serum CA-125 levels, suggesting it may be a useful biomarker for early EOC detection (224).

Approaches that target FRα have become increasingly attractive in the treatment for ovarian cancer (96,225,226). Antibody-drug conjugates are a specialized class of drugs to deliver chemotherapeutics to tumor sites in a targeted and selective manner. A common antibody-drug conjugate that targets FRα, MIRV, combines an anti-FRα antibody with DM4, a strong tubulin-targeting agent. This compound functions by binding FRα and allowing for the targeted delivery of DM4 to tumor cells, which optimizes the balance of beneficial to side effects (225). Treatment of platinum-resistant EOC using MIRV has been evaluated (225). Following encouraging results from the phase III trial SORAYA (trial no. NCT04296890), the FDA granted accelerated approval in 2022 for use in patients with FRα-positive, platinum-resistant EOC who have previously received systemic anticancer therapy (225,227). The humanized monoclonal antibody farletuzumab is another treatment strategy involving FRα. Preclinical research has demonstrated that farletuzumab may hinder FRα-expressing ovarian cancer cell proliferation (228,229). However, clinical trials evaluating farletuzumab in combination with other therapies for platinum-sensitive EOC (trial nos. NCT00318370 and NCT02289950) have yielded conflicting outcomes (96,226).

STRO-002 is an innovative antibody-drug conjugate targeting FRα, currently under clinical investigation for ovarian and endometrial cancer . Preclinical studies have demonstrated that a single dose of STRO-002 markedly inhibited tumor growth in FRα-expressing xenograft and patient-derived models, with enhanced efficacy when combined with carboplatin or bevacizumab (230,231). These findings underscore its potential as a promising therapeutic option for FRα-expressing cancer, including ovarian, endometrial and non-small cell lung cancer (226).

Treatment options for ovarian cancer either in the initial stages or if recurrence occurs are presented in Fig. 1.

Drug repurposing. Drug repurposing is the process of finding novel therapeutic uses for approved medications outside of their initial indications (Table IV) (232). For example, vitamin D and its analogs, are being studied for the treatment of ovarian cancer (233-237). These steroid-like compounds have demonstrated antitumor activity in preclinical models, in addition to their typical physiological roles. In particular, they suppress cell proliferation and the potential for metastasis while causing tumor cell differentiation and apoptosis (238). As a result, synthetic vitamin D analogs, designed to mitigate the risk of hypercalcemia, have been developed for targeting malignant disease, such as breast, colorectal and prostate cancer. By contrast, the effect of vitamin D and its analogs on ovarian cancer remains unclear (96,239). Vitamin D-based treatment may improve the effectiveness of PARP inhibitors and chemotherapeutics (240). The active form of vitamin D, calcitriol, has been shown to inhibit PARP1 activity in both cell-free and cellular assays. This suggests that vitamin D supplementation may enhance the efficacy of pharmacologic PARP1 inhibitors through a synergistic inhibitory effect (240). Furthermore,

Table IV. Repurposing drugs that have been studied in the treatment of ovarian cancer.

Repurposed drug	Initial indication	First author/s, year	(Refs.)
Arsenic trioxide	Leukemia	Sambasivan, 2022	(9)
β-blockers	Hypertension	Tavares V. *et al*, 2024	(96)
Bisphosphonates	Osteoporosis	Sambasivan S., 2022	(9)
Disulfiram	Alcoholism	Sambasivan S., 2022	(9)
Hydroxychloroquine	Rheumatoid arthritis, malaria and lupus erythematosus	Sambasivan S., 2022; Tavares V. *et al*, 2024	(9,96)
Ivermectin	Parasitic infection	Sambasivan S., 2022	(9)
Metformin	Type 2 diabetes mellitus	Sambasivan S., 2022; Tavares V. *et al*, 2024	(9,96)
NSAIDs	Inflammation	Sambasivan S., 2022	(9)
Sodium valproate	Bipolar disorder and epilepsy	Tavares V. *et al*, 2024	(96)
Statins	Hypercholesterolemia	Sambasivan, 2022; Tavares V. *et al*, 2024	(9,96)
Vitamin D	Vitamin D deficiency	Srivastava *et al*, 2018; Dovnik A and Fokter Dovnik N., 2020; Kuittinen *et al*, 2020; Wang *et al*, 2020; Kim *et al*, 2021	(233-237)

NSAID, non-steroidal anti-inflammatory drug.

combining vitamin D with immunotherapy may be advantageous due to its immunomodulatory effects (241,242). To the best of our knowledge, there are few clinical studies that have evaluated the effectiveness of vitamin D-based treatment for ovarian cancer (96,239).

Coagulation-targeting approaches. Venous thromboembolism (VTE), which has an incidence rate of 10-30%, is a common diagnosis in patients with ovarian tumors (243). For patients with cancer, this thrombotic event is the second most common cause of mortality. Notably, most patients with cancer show signs of hypercoagulability even in the absence of VTE (244). Within the tumor microenvironment, cancer cells produce tissue factor (TF) independently and promote TF production by normal cells. The pro-tumorigenic functions of TF include tumor cell proliferation, maintenance of cancer stemness, angiogenesis, immune evasion and metastasis through both clotting-dependent and -independent mechanisms (245-247). In several tumor types, including ovarian cancer, upregulation of TF is associated with a poor prognosis (96).

The FDA recently approved tisotumab vedotin (Tivdak™), a human antibody-drug conjugate specific to TF and associated with the tubulin-targeting agent monomethyl auristatin E, for the treatment of recurrent or metastatic cervical cancer (248). In patients with platinum-resistant ovarian cancer, the drug exhibits a favorable safety profile and notable antitumor activity, according to the phase I/II innovaTV-201 trial (trial no. NCT02001623) (249). These findings support the continued investigation of tisotumab vedotin in this patient cohort.

Key clinical trials for ovarian cancer treatment are listed in Table V.

4. Future perspective and directions

Despite notable advancements in targeted therapy, ICIs and biomarker-driven treatment, several gaps remain in the treatment of ovarian cancer. These gaps include underserved patient populations, the role of precision medicine and the integration of comprehensive molecular profiling in clinical decision-making.

Underserved patient populations. While biomarker-driven treatment strategies have improved outcomes for certain groups, disparities persist, particularly for ethnic minorities, elderly patients and those with rare ovarian cancer subtypes. Clinical trials have predominantly included Caucasian populations, leading to limited data on Black, Hispanic and Asian patients (102,113). Studies have indicated that African American and Hispanic patients experience higher mortality rates and lower enrollment in clinical trials (250), which may limit access to novel therapies such as PARP inhibitors and immunotherapy (251). Additionally, several clinical trials exclude older patients (aged ≥70 years) or those with multiple comorbidities, despite the fact that ovarian cancer predominantly affects postmenopausal patients (252-254). Accordingly, trial findings may not be generalizable to the broader patient population. This is revealed by the limited number of trials, such as ROSiA, ENGOT-OV16/NOVA, and GOG-182 trials, that were conducted on patients aged 70 or more (252-254). The impact of aggressive treatments, such as PARP inhibitors, ICIs and combination regimens, on older or frail patients requires further investigation.

Another underserved subgroup is patients with rare ovarian cancer subtypes, such as LGSOC, clear cell and mucinous ovarian cancer. Most phase III clinical trials focus on HGSOC, which represents the majority of cases, while rarer subtypes exhibit distinct molecular alterations that may render standard therapies less effective (46,113,126,255,256). For example, LGSOC often harbors KRAS or BRAF mutations, suggesting that MEK inhibitors may be a more effective approach compared with traditional platinum-based chemotherapy (134). However, these alternatives remain

Table V. Key clinical trials for ovarian cancer treatment (306).

Trial (registration number)	Phase	Therapy	Findings and impact on clinical practice
SOLO1 (NCT01844986)	III	Olaparib (PARP inhibitor) in patients with BRCA mutation	Marked improvement in PFS, which led to FDA approval of olaparib as a first-line maintenance therapy
PRIMA (NCT02655016)	III	Niraparib (PARP inhibitor) in newly diagnosed advanced ovarian cancer	Longer PFS, regardless of HRD status; supports broader PARP inhibitor use
ATHENA-MONO (NCT03522246)	III	Rucaparib (PARP inhibitor) for maintenance therapy	Improved PFS in both HRD-positive and -negative patients, supporting its use as a maintenance strategy
PAOLA-1 (NCT02477644)	III	Olaparib + bevacizumab	Longest median PFS (56.5 months) in patients with HRD-positive tumors, supporting combination therapy in maintenance settings
ICON7 (NCT00483782) and GOG218 (NCT00262847)	III	Bevacizumab (VEGF inhibitor) in primary treatment and maintenance	Increased PFS with bevacizumab maintenance therapy, leading to standard-of-care adoption
JAVELIN OVARIAN PARP100 (NCT03642132)	III	Avelumab + chemotherapy followed by maintenance	Phase I trials showed promising PFS improvement, leading to phase III trials, but combination strategies remain under evaluation
KEYNOTE-028 (NCT02054806)	Ib	Pembrolizumab (PD-1 inhibitor) in PROC	Modest response rate (11.5%), with 23% achieving stable disease; pembrolizumab is not widely adopted for ovarian cancer
IMagyn050 (NCT03038100)	III	Atezolizumab + chemotherapy/ bevacizumab	Ongoing trial evaluating OS and PFS as co-primary endpoints in advanced ovarian cancer
SORAYA (NCT04296890)	III	Mirvetuximab soravtansine (FRα-targeted ADC) in PROC	Led to FDA accelerated approval (2022) for FRα-positive, platinum-resistant EOC
innovaTV-201 (NCT02001623)	I/II	Tisotumab vedotin (ADC) in platinum-resistant ovarian cancer	Favorable safety profile and marked antitumor activity, supporting continued investigation
NCT02289950	II	Farletuzumab in combination with carboplatin + paclitaxel or PLD	Adding farletuzumab to standard chemotherapy did not improve PFS in patients with platinum-sensitive ovarian cancer at first relapse who have low CA-125 levels.
NCT00318370	II	Farletuzumab + carboplatin and taxane	Neither dose of farletuzumab achieved the primary PFS endpoint; pre-specified subgroup analyses revealed that patients with CA-125 level ≤3 times the ULN and those with higher farletuzumab exposure exhibited improved PFS and OS compared with the placebo group
NCT02046421	I	Carboplatin, gemcitabine hydrochloride and mifepristone in patients with advanced breast cancer or recurrent or persistent ovarian epithelial, fallopian tube or primary peritoneal cancer	No results reported
NCT00459290	II	Mifepristone in patients with recurrent or persistent ovarian epithelial, primary peritoneal or fallopian tube cancer	Mifepristone was not effective in the treatment of patients with recurrent or persistent ovarian, peritoneal and fallopian tube cancer
NCT00003670	II	Hormone therapy with arzoxifene hydrochloride in patients with metastatic refractory ovarian or primary peritoneal cancer	No results reported
NCT00041080	III	Tamoxifen compared with thalidomide in patients with ovarian epithelial, fallopian tube or primary peritoneal cancer	Thalidomide was not more effective than tamoxifen in delaying recurrence or mortality and was more toxic

Table V. Continued.

Trial (registration number)	Phase	Therapy	Findings and impact on clinical practice
NCT02728622	III	Chemotherapy vs. hormonal treatment in PROC resistant or refractory to platinum and taxane	No results reported
NCT00617188	II	Fulvestrant in patients with recurrent ovarian epithelial cancer	Fulvestrant was well-tolerated and efficacious; ORR was low, but disease stabilization was common
NCT00313599	I	Lapatinib and paclitaxel in patients with advanced solid tumors	No results reported
NCT03942068	II	Apatinib with albumin-bound paclitaxel in patients with recurrent PROC	No results reported
NCT00466960	II	Sargramostim and paclitaxel albumin-stabilized nanoparticle formulation in patients with advanced ovarian, fallopian tube or primary peritoneal cancer that did not respond to previous chemotherapy	Nab-paclitaxel combined with GM-CSF demonstrated biochemical responses in a majority of patients, although responses were not sustained; this combination did not demonstrate an advantage in OS over nab-paclitaxel monotherapy; agents that modulate MDSC should be studied as potential adjuvants; strategies to expand T-cell recognition of tumor-associated antigens in ovarian cancer should be investigated
NCT04753216	II	Irinotecan liposome and bevacizumab for platinum-resistant, recurrent or refractory ovarian, fallopian tube or primary peritoneal cancer	This combination showed a partial ORR of 100% but no complete ORR
NCT01652079	II	CRLX101 in combination with bevacizumab for recurrent ovarian/tubal/peritoneal cancer	No results reported
NCT04669002	II	EP0057 in combination with olaparib in advanced ovarian cancer	No results reported
NCT01489371	I	EGEN-001 and PLD in patients with recurrent or persistent ovarian epithelial, fallopian tube or primary peritoneal cancer	No results reported
NCT03742713	II	Efficacy study of CPC634 (CriPecÂ® docetaxel) in PROC	No results reported
NCT00989131	III	Paclitaxel in patients with ovarian cancer	No results reported
NCT00666991	I	Pharmacokinetic, safety and efficacy of nanoparticle paclitaxel in patients with peritoneal cancer	No results reported
NCT00825201	I	Intraperitoneal paclitaxel albumin-stabilized nanoparticle formulation in patients with advanced cancer of the peritoneal cavity	No results reported
NCT00499252	II	Paclitaxel albumin-stabilized nanoparticle formulation in patients with recurrent or persistent ovarian epithelial, fallopian tube or primary peritoneal cancer	Nab-paclitaxel had noteworthy single-agent activity and was tolerable in patients with refractory ovarian cancer previously treated with paclitaxel

Table V. Continued.

Trial (registration number)	Phase	Therapy	Findings and impact on clinical practice
NCT03304210	I	PIPAC nab-paclitaxel for stomach, pancreas, breast and ovarian cancer	Albumin-bound paclitaxel has promise for intraperitoneal aerosol delivery
NCT01191216	I	1-Methyl-D-tryptophan and docetaxel in patients with metastatic solid tumors	No results reported
NCT01611558	II	Ipilimumab monotherapy in recurrent platinum-sensitive ovarian cancer	ORR was 10.3%, and 50% of patients reported grade 3 adverse events; this high rate of toxicity, potentially associated with the high dose of ipilimumab, discouraged pursuing anti-CTLA-4 in recurrent ovarian cancer
NCT00729664	I	Multiple ascending doses of MDX1105-01	No results reported
PRIME trial (NCT03709316)	III	Efficacy and safety of niraparib using an individualized starting dose as a maintenance treatment following CR/PR to 1L CT in patients with advanced ovarian cancer	Patients who received niraparib had a marked clinical improvement in PFS compared with those who received placebo, regardless of biomarker status; niraparib was well tolerated and no new safety concerns were observed.
AURELIA trial (NCT00976911)	III	Bevacizumab combined with chemotherapy for recurrent PROC	Adding bevacizumab to chemotherapy markedly improved PFS and ORR; OS was not markedly different; no new safety signals were observed
GOG-281 trial (NCT02101788)	II/III	Trametinib vs. standard of care in patients with recurrent low-grade serous ovarian cancer	Trametinib should be considered a standard-of-care option for patients with progressive or relapsed low-grade serous carcinoma
UMIN000005714	II	Antitumor effect of nivolumab on subsequent chemotherapy for PROC	10% of patients had a sustained CR using nivolumab
ATALANTE trial (NCT02891824)	III	Atezolizumab vs. placebo in late relapse ovarian cancer treated with chemotherapy + bevacizumab	No results reported
TOPACIO/ KEYNOTE-162 trial (NCT02657889)	I/II	Niraparib combined with pembrolizumab in patients with recurrent ovarian carcinoma	Combination of niraparib and pembrolizumab was well tolerated and showed promising antitumor activity in patients with ovarian carcinoma who had limited treatment options, irrespective of platinum sensitivity, biomarker status, or prior bevacizumab use. Patients without tumor BRCA mutations or those with non-homologous recombination deficient (non-HRD) tumors exhibited higher response rates than typically seen with either monotherapy.
DUO-O trial (NCT03737643)	III	Durvalumab treatment in combination with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab and olaparib treatment in patients with advanced ovarian cancer	Compared with that in the control group, the median PFS in the triple therapy group was extended by ~5 months, with a 38% decrease in the risk of mortality; in patients with HRD, the median PFS in the triple therapy group was extended by 14.3 months compared with that of the chemotherapy and bevacizumab monotherapy group
FORWARD II trial (NCT02606305)	II	Mirvetuximab soravtansine combined with pembrolizumab in patients with high FRα expression and PROC	Promising clinical efficacy, with an ORR of 43%, a median DOR of 6.9 months, a median PFS of 5.2 months and no severe adverse events

Table V. Continued.

Trial (registration number)	Phase	Therapy	Findings and impact on clinical practice
OPAL-A trial (NCT03574779)	II	Triplet combination of niraparib, dostarlimab and bevacizumab	Limited ORR in patients with PROC, although the median PFS of 7.9 months and OS of 22.1 months were favorable compared with historical data; notably, the majority of responders (85.7%) were bevacizumab-naïve

PFS, progression-free survival; OS, overall survival; HRD, homologous recombination deficiency; PD-1, programmed cell death protein; ADC, antibody-drug conjugate; FRα, folate receptor α; FDA, Food and Drug Administration; PARP, poly(ADP-ribose) polymerase; EOC, epithelial ovarian cancer; CA-125, cancer antigen-125; ULN, upper limit of normal; GM-CSF, granulocyte-macrophage colony-stimulating factor; MDSC, myeloid-derived suppressor cell; ORR, overall response rate; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PROC, platinum-resistant ovarian cancer; DOR, duration of response; PLD, pegylated liposomal doxorubicin; CR, complete response; PR, partial response; PIPAC, pressurized intraperitoneal aerosol chemotherapy; nab, albumin; 1l CT, first-line platinum-based chemotherapy.

underexplored, emphasizing the need for histology-specific clinical trials.

Role of precision medicine. While precision medicine has transformed ovarian cancer treatment, current biomarker-based strategies remain incomplete. Presently, treatment decisions are primarily guided by BRCAm status and HRD testing, but these biomarkers do not fully capture the complexity of ovarian cancer biology. A large proportion of HRD-negative tumors respond to PARP inhibitors, suggesting that improved stratification tools are needed to identify the true PARP-sensitive patient population. Additionally, certain HRD-positive tumors exhibit intrinsic resistance to PARP inhibitors, highlighting the limitations of genomic testing alone (257).

Beyond HRD testing, the role of other emerging biomarkers, such as tumor mutation burden (TMB), microsatellite instability (MSI) and PD-L1 expression, is uncertain in ovarian cancer. While high TMB and MSI are used as predictive biomarkers for checkpoint inhibitor therapy in several types of cancer, their utility in ovarian cancer has not been well established (258,259). Similarly, PD-L1 expression, a key biomarker for ICIs in lung and breast cancer, has shown limited predictive value in ovarian cancer trials (260-262). The lack of validated predictive biomarkers for immunotherapy is a major limitation, contributing to the low success of ICIs in ovarian cancer compared with other solid tumors.

Another gap in precision medicine is the reliance on genomic HRD assays, which assess DNA repair deficiencies at a static point in time, but may not accurately predict treatment response. Some researchers argue that functional HRD testing, which directly measures the ability of a tumor to repair DNA damage, may be a more reliable biomarker for PARP inhibitor sensitivity (263,264). As some HRD-negative tumors benefit from PARP inhibitors, the development of more comprehensive functional assays may improve patient selection and maximize treatment efficacy (265).

Tailoring treatment using comprehensive molecular profiling. The integration of genomic, transcriptomic and proteomic data may transform ovarian cancer treatment by identifying novel drug targets and guiding therapy selection (266). However, challenges remain in implementing comprehensive molecular profiling in routine clinical practice. A notable limitation is the lack of real-time, actionable molecular data. Most genomic profiling methods provide retrospective insight, but real-time molecular testing is necessary to dynamically adjust treatment based on tumor evolution (267). The integration of liquid biopsy, which analyzes ctDNA or circulating tumor cells, may offer a minimally invasive way to track treatment response and resistance mechanisms in real-time (268).

Another challenge is the integration of multi-omic data to create a holistic view of tumor biology. Several targeted therapies focus on a single pathway, yet ovarian cancer is heterogeneous, and adaptive resistance mechanisms often emerge. For example, while PARP inhibitors target DNA repair defects, resistance can develop through secondary BRCA reversion mutation or upregulation of drug efflux transporters. The ability to combine genomic, epigenomic, transcriptomic and proteomic insight may facilitate more precise, patient-specific treatment strategies (269). Additionally, targetable mutations in TP53, cyclin E1, KRAS and PI3K/AKT pathways remain underexplored in ovarian cancer, highlighting the need for novel drug development beyond BRCA/PARP inhibitors.

5. Conclusion

Targeted therapies have replaced surgery and chemotherapy as the mainstays of ovarian cancer treatment, notably improving patient outcomes. However, optimal patient selection, resistance mechanisms and the long-term effectiveness of these medicines are key concerns. Although targeted treatments provide improved control of ovarian cancer, issues with cost-effectiveness, accessibility and treatment-associated toxicity exist in practical application. Furthermore, due to the possibility of medication resistance and secondary malignancy, it is still unclear how long the response lasts and how it affects long-term survival. Future studies should concentrate on improving biomarker-driven strategies for treatment, identifying combination treatments to overcome resistance and developing affordable models for greater accessibility globally.

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KA designed and performed the narrative review, and drafted and proofread the article critically. AZA helped in writing the section on poly(ADP-ribose) polymerase inhibitors, immunotherapy, angiogenesis inhibitors and targeted therapy, and critically revised the manuscript. GBH helped in writing the combination therapy, MEK inhibitors and microRNAs sections, and revised the article critically for intellectual content. AFA contributed to writing of the section on hyperthermic intraperitoneal chemotherapy. OSG, AA, SM and MJA revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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