An Overview about Treatment lines of Ovarian Cancer

Mohammed Abdelgawad Soliman, Lobna Abdelaziz Abdelaziz, Shimaa Shabaan Fathy Mohammed, Doaa Abdelrahman Mandour

Clinical Oncology & Nuclear Medicine Department, Faculty of Medicine - Zagazig University, Egypt

Email: anoshrose743@gmail.com

Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in women, in general. Most women with ovarian cancer are diagnosed in later life, with a median age of diagnosis of 63 years. Most women are symptomatic at disease presentation and have ascites and gastrointestinal dysfunction (for example, constipation and/or bowel obstruction, diarrhoea, nausea, vomiting and gastrointestinal reflux). Specific ovarian carcinoma treatment recommendations are dependent on the stage of the disease and extent of surgical debulking. The long-term OS rate for women with optimally debulked stage III disease is approximately. After surgery, all women should receive at least 6 cycles of platinum-based therapy with either cisplatin or carboplatin in combination with a taxane, usually paclitaxel. If cisplatin is used, patients require careful monitoring of renal function, electrolytes, and neurologic status. Carboplatin and paclitaxel thus have widespread acceptance as initial chemotherapy for ovarian cancer. Women who have residual disease larger than 1 cm after initial debulking surgery have a substantially worse prognosis than those with optimally debulked disease. Nevertheless, a small proportion of these women will have long-term DFS. In contrast, women with disease outside the abdominal cavity or in the liver parenchyma, making them stage IV, have a worse prognosis and rarely have a long-term DFS. In addition to residual tumor volume, other factors associated with a poor prognosis include advanced age, mucinous or clear cell histology, and the presence of ascites. Chemotherapy prolongs survival in women with stage III disease, whether optimally or suboptimally debulked, and possibly in stage IV disease. Although there are many active agents for the treatment of ovarian cancer, the standard of care is combination therapy that includes a taxane and a platinum compound, usually carboplatin and paclitaxel.

Keywords: Treatment lines, Ovarian Cancer

DOI: 10.53555/ecb/2023.12.Si12.347

Surgery is necessary for the diagnosis, staging, and treatment of EOC. Although ovarian cancer can spread hematogenously or via the lymphatic system, the bulk of the tumor will be found on peritoneal surfaces. This peritoneal disease results from shedding of ovarian tumor cells into the peritoneal cavity, circulation of these cells throughout the abdomen and pelvis, and eventual implantation onto peritoneal surfaces. The viability of these cells and successful tumor growth is further dependent upon the development of sufficient neovasculature to support cell survival and tumor growth.

The consistency of the observation of improved outcome with surgical debulking has led to the goal of "optimal" tumor cytoreduction to no macroscopic visible disease with initial diagnostic surgery. The terms "optimal" and "suboptimal" refer to the diameter of the largest residual tumor nodule that remains after debulking surgery: 1 cm or less for optimal, and greater than 1 cm for suboptimal debulking. However, the goal of debulking surgery is to render the patient completely debulked and visibly with no evidence of disease.

Staging laparotomy requires a thorough inspection of the peritoneal cavity, including the paracolic gutters, pelvis, and domes of the diaphragm; total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO); liver palpation and biopsy (if indicated); lymph node sampling; omentectomy; and peritoneal washings. The degree of surgical debulking should be reported, and if incomplete, the surgeon should describe the size, location, and extent of residual disease.

stage II disease is the least commonly diagnosed stage of ovarian cancer. This is likely because there is no anatomic boundary between the pelvis and upper abdomen. If disease has spread outside of the ovary to pelvic structures, it is also likely to spread to the upper abdomen. In the past, trials of the Gynecologic Oncology Group (GOG) have combined stages I and II as a definition of "early" ovarian cancer, with stages III and IV designated as "advanced" ovarian cancer. However, given the observed higher recurrence rate seen for stage II disease, the GOG is now including stage II in the category of advanced disease for trial purposes.

Treatment of Early Stage (Stages I and II)

Specific ovarian carcinoma treatment recommendations are dependent on the stage of the disease and extent of surgical debulking. Approximately 25% of women with ovarian cancer have disease confined to one or both ovaries (FIGO stage I) or to the pelvis (FIGO stage II). Even among this good-prognosis group, the failure rate is high enough to warrant adjuvant chemotherapy in most patients.

The GOG has attempted to precisely define the subgroups of patients with early ovarian cancer that would benefit from adjuvant therapy and determine the optimal form of therapy for these patients. Studies over the past 3 decades have shown that patients with stage IA or IB disease (limited to one or both ovaries with no ascites and negative peritoneal washings) and with well- or moderately differentiated histology have a 5-year disease-free survival (DFS) rate of 91% and a 5-year OS rate of 94% with surgery alone; thus, this subset of patients does well and is generally not treated with adjuvant therapy. It is, however, critical that these patients are fully staged. Studies have documented that almost one-third of apparent early stage patients will have more advanced stage disease when full staging is done. In contrast, chemotherapy improves progression-free survival (PFS) for patients with stage IA or IB poorly differentiated disease, stage IC, or stage II disease, and these patients should receive adjuvant chemotherapy **(1).**

The most recently reported phase 3 study in this population (GOG protocol 157) compared 3 versus 6 cycles of paclitaxel and carboplatin. The 5-year probability of recurrence was 20.1% for 6 cycles versus 25.4% for 3 cycles, a 24% reduction in recurrence risk. However, the OS was similar for both regimens and the decrease in recurrence risk did not reach statistical significance.

while high-grade serous histology had a significantly lower risk of recurrence with 6 compared with 3 cycles. Based on these reports of this study, most recommend a minimum of 3 cycles of paclitaxel and carboplatin for patients with early stage disease who are treated with adjuvant chemotherapy and many recommend 6 cycles for those with high-grade serous cancers **(2).**

Treatment of Advanced Stage (Stages III and IV)

Approximately 75% of women with ovarian carcinoma present with stage III or IV disease. As previously mentioned, prognosis correlates with the extent of residual disease after primary debulking surgery. Although this is best documented in patients with stage III disease, even patients with stage IV disease have an improved prognosis with optimal debulking (no residual implant greater than 1 cm). It is clear that this is a continuum, with those with the least tumor burden after surgery having the best prognosis and with prognosis worsening as the diameter of the smallest residual lesion increases **(3).**

It has been recognized that not all patients can be optimally debulked at initial surgery. This has led to alternate approaches to achieve optimal surgical status. One of these is the administration of chemotherapy before definitive surgery, an approach referred to as neoadjuvant chemotherapy. A recent randomized trial compared primary debulking surgery followed by platinum-based chemotherapy with neoadjuvant platinum-based chemotherapy followed by interval debulking surgery in stage IIIC or IV EOC. **(3).** The findings from this trial were that neoadjuvant chemotherapy was not inferior to primary debulking surgery; however, the median OS of the 2 groups (30 months and 29 months, respectively) is inferior to the findings from GOG trials in this same population. Given the large body of literature demonstrating the survival benefit for cytoreduction, the inability to reliably predict preoperatively which patients will not be able to be

cytoreduced, and the inferior outcome of both arms on this study, neoadjuvant chemotherapy remains controversial.

Treatment of Optimally Debulked Disease

The long-term OS rate for women with optimally debulked stage III disease is approximately 25%; .

After surgery, all women should receive at least 6 cycles of platinum-based therapy with either cisplatin or carboplatin in combination with a taxane, usually paclitaxel. If cisplatin is used, patients require careful monitoring of renal function, electrolytes, and neurologic status. Carboplatin and paclitaxel thus have widespread acceptance as initial chemotherapy for ovarian cancer **(4).**

Treatment of Suboptimally Debulked Stage III and IV Disease

Women who have residual disease larger than 1 cm after initial debulking surgery have a substantially worse prognosis than those with optimally debulked disease. Nevertheless, a small proportion of these women will have long-term DFS. In contrast, women with disease outside the abdominal cavity or in the liver parenchyma, making them stage IV, have a worse prognosis and rarely have a long-term DFS. In addition to residual tumor volume, other factors associated with a poor prognosis include advanced age, mucinous or clear cell histology, and the presence of ascites.

chemotherapy prolongs survival in women with stage III disease, whether optimally or suboptimally debulked, and possibly in stage IV disease. Although there are many active agents for the treatment of ovarian cancer, the standard of care is combination therapy that includes a taxane and a platinum compound, usually carboplatin and paclitaxel.

Primary Adjuvant Chemotherapy for Epithelial Ovarian Cancer

Intravenous regimens	1) Paclitaxel (175 mg/m^2 over 3 h iv) followed by carboplatin (AUC 5-7.5 iv over 1 h) on d 1, every 3 wk for 6 cycles
	2) Docetaxel (60-75 mg/m^2 over 1 h iv) followed by carboplatin (AUC 5-6 iv over 1 h) on d 1, every 3 wk for 6 cycles
	3) Dose-dense paclitaxel (80 mg/m^2 iv over 1 h) on d 1, 8, and 15 plus carboplatin (AUC 6 iv over 1 h) on d 1, every 3 wk for 6 cycles
Intraperitoneal regimens	1) Paclitaxel (135 mg/m^2 iv infusion over 24 h) on d 1, cisplatin (75-100 mg/m^2 ip) on d 2, and paclitaxel (60 mg/m^2 ip) on d 8, every 3 wk for 6 cycles

- iv indicates intravenous; AUC, area under the curve; ip, intraperitoneal

Maintenance Therapy Although achieving a cure for advanced ovarian cancer is extremely rare, the majority of patients do achieve a complete clinical remission after initial cytoreductive surgery and combination chemotherapy. The ability to achieve a complete remission, which is uncommon in other advanced epithelial cancers, provides a unique opportunity to capitalize on this finite period with innovative consolidation and maintenance strategies.

Clinical trials have studied consolidation therapies involving high-dose chemotherapy with stem cell transplantation and ip administration of antibodies conjugated with a variety of radioisotopes, while maintenance therapies have focused on the prolonged use of single-agent chemotherapy, ip chemotherapy, hormonal therapy, and vaccines. Thus far, none of these interventions has shown an improvement in OS **(4).**

Due to the promising results as a second-line treatment strategy coupled with its favorable toxicity profile, the use of bevacizumab has emerged as an attractive choice as a maintenance strategy. Based on the results of prior single-agent phase 2 bevacizumab trials, the GOG performed a randomized, double-blinded, 3-arm phase 3 trial comparing the standard primary chemotherapy regimen of carboplatin/paclitaxel versus carboplatin/paclitaxel plus bevacizumab with chemotherapy versus carboplatin/paclitaxel plus bevacizumab with chemotherapy and bevacizumab continued for 1 year after the completion of chemotherapy. Results were recently presented and demonstrated that chemotherapy plus concurrent and maintenance bevacizumab prolongs PFS however, to date there is no survival difference between the 3 arms **(5).** Duration of Therapy

and Evaluation of the Patient Receiving Therapy Before treatment, levels of the ovarian tumor marker CA 125 should be measured and, if elevated, should be used as adjunctive evidence of response to therapy. Levels should be measured routinely during the course of treatment. A consistent rise in CA 125 can be used as a measure of failure of treatment in the absence of radiographic and clinical changes. Likewise, a linear fall in serum levels of CA 125 can be used as a measure of treatment success. Levels of carcinoembryonic antigen and CA 19-9 may be elevated in women with mucinous carcinomas and may be potentially useful in following the course of the disease.

Treatment should consist of 6 to 8 cycles of chemotherapy. Residual disease should be measured before beginning therapy by visual inspection at the time of surgery, by computed tomography (CT) scan if bulk disease remains, or by physical examination when appropriate.

Recurrent EOC may be suspected by the development of new symptoms, the radiographic detection of an asymptomatic disease recurrence by CT scans, or a rising serum concentration of CA 125, which may predate radiographic disease progression by many months. Timing of second-line therapy is controversial. Immediate institution of therapy is indicated for symptomatic women, with the specific goal being symptom palliation. In contrast, the optimal timing of second-line therapy for an asymptomatic woman with recurrent disease (typically detected because of an asymptomatic rise in the serum level of CA 125) has been controversial.

Treatment of Recurrent EOC The goals of treatment of recurrent ovarian cancer are thus to prolong survival, to delay time to progression, to control disease-related symptoms, to minimize treatment-related symptoms, and to maintain or improve quality of life.

Recurrent ovarian cancer (potential platinum-sensitive) is defined as the recurrence of active disease in a patient who has achieved a documented response to initial platinum-based treatment and has been off therapy for an extended period of time **(6).**

Resistant ovarian cancer is defined as disease that has responded to initial chemotherapy but demonstrates recurrence within a relatively short period of time following the completion of treatment. Again, GOG has decided that patients with documented recurrence within six months of completing initial therapy should be considered "platinum-resistant."

Refractory ovarian cancer occurs in patients who have failed to achieve at least a partial response to therapy. This includes patients with either stable disease or actual disease progression during primary therapy, which occurs in approximately 20% of cases. As might be expected, this group has the lowest response rate to second-line therapy.

Treatment of Platinum-Sensitive Recurrent EOC

Treatment Recommendations for Patients With Platinum-Sensitive Ovarian Cancer

Consider secondary cytoreductive surgery for appropriate patients
Platinum retreatment is the standard of care
Platinum-based combinations improve PFS and, in some cases, overall survival compared with platinum alone
Prior and persistent toxicities should be considered when choosing therapy

Treatment of Recurrent Platinum-Resistant EOC Most patients with recurrent ovarian cancer will eventually develop platinum-resistant disease. In general, platinum-resistant patients will be treated with sequential single agents rather than combination therapy.

Common Chemotherapy Regimens in Recurrent Platinum-Resistant Ovarian Cancer

Topotecan daily × 5 d, every 3 wk
Topotecan wkly on d 1, 8, and 15, every 4 wk
Pegylated liposomal doxorubicin every 4 wk

Gemcitabine on d 1 and 8 every 3 wk OR d 1, 8, and 15 every 4 wk

Etoposide orally 14/21 d or 14-21/28 d

Paclitaxel wkly on d 1, 8, and 15 every 4 wk OR d 1, 8, 15, and 21 every 4 wk

Docetaxel every 3 wk

Targeted Therapies Targeted agents that are documented to be effective in recurrent disease will then be candidates for study in front-line therapy. Although several families of agents have been studied in recurrent ovarian cancer, the greatest success to date has been with the use of agents that target the vascular endothelial growth factor (VEGF) pathway.

Bevacizumab is an anti-VEGF monoclonal antibody that inhibits activation of VEGF receptors (VEGF-R) through binding of their ligands. Angiogenesis, which is controlled by a myriad of proangiogenic factors, including VEGF, plays a central role in the physiologic function of the healthy ovary as well the malignant ovarian cancer cells **(5).**

Aflibercept (VEGF Trap) is a fusion protein that binds with high affinity to VEGF and functions as a soluble VEGF-R. Early results of a randomized phase 2 trial of 2 doses of aflibercept (2 or 4 mg/kg) administered iv every 2 weeks in patients with recurrent ovarian cancer were reported in 2007. Of 45 patients, 5 had partial responses (11% response rate) **(7).**

Sorafenib an oral tyrosine kinase inhibitor that targets Raf and other receptor kinases (eg, VEGF-R, platelet-derived growth factor receptor [PDGFR], fms-related tyrosine kinase 3 [FLT3], and c-Kit) and may have antiangiogenic activity through inhibition of VEGF-R.

Sorafenib is also being tested in combination with chemotherapy, both in recurrent disease and as initial therapy in newly diagnosed patients **(8).**

Sunitinib multitargeted receptor tyrosine kinase inhibitor with activity against a number of targets, including VEGF-R and PDGFR.

Cediranib (AZD2171) is a selective oral tyrosine kinase inhibitor of VEGF-R1, VEGF-R2, VEGF-R3, and c-Kit.

Targeting Folate Receptor Alpha Another potential target in ovarian cancer is the folate receptor alpha (FRA). FRA is overexpressed in the majority of EOCs but is largely absent from normal tissue. MORAb-003 is a humanized monoclonal antibody to FRA. Binding of MORAb-003 to FRA blocks phosphorylation by Lyn kinase and produces cytotoxicity via antibody-dependent cellular cytotoxicity.

An alternate means of targeting FRA is through the use of folate-linked cytotoxic therapy. EC145 is a conjugate of folate and the vinca alkaloid desacetylvinblastine monohydrazide (DAVLBH). EC145 binds to the folate receptor, delivering DAVLBH into the cell via endocytosis **(9).**

Anti-Epidermal Growth Factor Receptor Agents family is commonly overexpressed in ovarian cancer and has been associated with a negative prognosis, efforts to target the EGFR pathway have as yet not proven useful as therapy for ovarian cancer **(10).**

Poly (ADP-Ribose) Polymerase (PARP) is another target for developing agents in ovarian cancer. Repair of DNA damage is essential for the maintenance of genomic integrity. Distinct pathways exist for repair of single-strand and double-strand DNA breaks.

The protein products of the *BRCA1* and *BRCA2* genes are critical cofactors in the repair of double-strand DNA breaks. Because loss of function of BRCA genes is common in ovarian cancer, these cells are more dependent upon single-strand DNA repair processes. Because PARP is critical to the process of single-strand DNA repair, PARP inhibitors could prevent cells with aberrant BRCA function from repairing chemotherapy-induced DNA damage, thus increasing cytotoxicity **(11).**

Hormonal Therapies tamoxifen, aromatase inhibitors (eg, letrozole), or fulvestrant is associated with low objective response rates (10%); however, occasional patients experience a dramatic tumor marker response, and some women have prolonged periods of stable disease **(12).**

Advance in ovarian cancer treatment

Exosomes A potential tool for immunotherapy of ovarian cancer

Exosomes have great potential in the field of ovarian cancer immunotherapy as potential therapeutic markers for cancer, or as a more effective, rapid, and safe vehicle for the delivery of antitumor drugs. Exosome-based immunotherapy can activate the immune system and eliminate tumor cells **(13).**

Exosomes have immunogenicity and molecular transfer ability and most can participate in the immune response.Indeed, exosomes derived from CD8+ T cells and CD4+ T cells have antigen-specific functions, which affect immune cells. The essence of the effect of exosomes in different body fluids is different.

Exosomes in ascites contain miR-6780b-5p **(14).,**those in serum contain EpCAM, Claudin4**,**and those in urine contain microRNA-30a-5p **(15).**

In other words, a variety of exosome-based approaches can be employed to treat ovarian cancer. Exosomes are not only derived from different body fluids, but also from different cells in the tumor microenvironment (TME), which have different effects on the immune response. Some cells may promote and enhance the occurrence of immune response, while others may inhibit and weaken the strength of immune response. Exosomes can form a pre-metastatic niche by acting on immune cells, and their transfer of miR-21 can change the malignant phenotype of ovarian cancer cells, which is a potential treatment for metastatic ovarian cancer **(15).**

However, exosomes derived from ovarian cancer induce T-cell arrest, which allows cancer cells to achieve immune escape **(16).**

Meanwhile, cancer cells may produce more exosomes than normal cells, and the amount of exosomes produced by different cancer cells is also different

Treatment of GCT

early stages

*Most GCT will be diagnosed at early stages and FSS is the main treatment option, especially as the patients affected are children or young women**.** This includes unilateral salpingo-oophorectomy (USO) with the unaffected ovary and uterus left in place—biopsy of the second ovary is only performed if there is obvious abnormality to reduce the risk of adhesions or ovarian failure* **(17).**

advanced stages

advanced disease is present, debulking surgery is performed instead to try and remove as much cancer as possible and second-look surgery may be an option if the cancer is not resected completely **(18).**

Depending on the histology, staging and molecular features of the GCT, surgery will be followed by active surveillance or adjuvant chemotherapy, which has revolutionised GCT treatment in the last 40 years **(18).**

Currently, dysgerminomas confined to the ovary and grade I immature teratoma are managed with surveillance post-operatively **(17).**

Otherwise, platinum-based chemotherapy is used, and the standard regime consists of bleomycin, etoposide and cisplatin (BEP) for four to six cycles **(17).**

A subset of GCT can acquire KRAS-activating mutations and other genetic alterations, such as BRCA1/2, KIT, and MAPK; nevertheless, the efficacy of targeted therapy and genomic features contributing to chemoresistance still remain to be elucidated. Finally, programmed death-ligand 1 (PD-L1) overexpression in testicular GCT has been recently described **(17).**

Recurrences usually occur within two years of initial diagnosis and typically relapse in the peritoneal cavity and retroperitoneal lymph nodes. The response rate to salvage chemotherapy in patients with GCT is approximately 50%, and recommended regimens include vinblastine, ifosfamide, and cisplatin; etoposide,

ifosfamide, and cisplatin; and paclitaxel, ifosfamide, and cisplatin. Secondary cytoreductive surgery could be performed in selected patients with recurrent disease **(19).**

Treatment of SCST

can involve surgery, chemotherapy, radiotherapy and targeted therapy. Cytoreductive debulking surgery is the standard management, which may be followed by adjuvant platinum-based chemotherapy.

In advanced disease, if there is tumour recurrence, cytoreductive surgery can be used. Complete resection of the tumour during the initial surgery is important, as it has been shown in that for those patients who had residual tumours and underwent cytoreductive surgery, they all developed tumour recurrence.

The differential diagnosis for SCST can include such diverse entities as carcinoma, sarcoma, GCT, melanoma, peritoneal carcinomatosis and malignant peritoneal mesothelioma **(19).**

Treatment of Ovarian GrCT

Patients who present in their reproductive years are managed with a USO.

For patients who are postmenopausal or have no desire of childbearing, they are treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) **(20).**

For patients with stage IA GrCT, surgery alone provides an excellent prognosis, with no adjuvant therapies used. Around 97% of GrCT are unilateral **(20).**

For stage IB, i.e., involving both ovaries, a total abdominal hysterectomy with BSO is used.

For stage IC, surgery alongside adjuvant platinum-based chemotherapy is used.

For advanced or metastatic disease, cytoreductive surgery is the most effective treatment. Additional chemotherapy courses can be used in these patients, as the prognosis is poor, with a high recurrence rate **(21).**

Hormone therapy has been shown to have a role in GrCT which express steroid hormone receptors. No corroboration between hormonal therapy and hormone receptor expression has been established. Aromatase inhibitors have been found to be the most responsive hormone therapy, though data is limited **(21).**

Treatment Sertoli-Leydig Cell Tumours

For young patients who have stage IA SLCT and are of reproductive age, FSS is offered. Those with poorly differentiated malignancy are offered adjuvant chemotherapy.

Patients who have no desire of childbearing are offered a total abdominal hysterectomy and BSO.

For SLCT staging greater than IA, surgery and adjuvant chemotherapy are offered irrespective of tumour differentiation. The chemotherapy regimens are platinum-based **(21).**

Treatment Small Cell Ovarian Carcinomas

Conventional surgical treatment includes radical surgery (hysterectomy and BSO), followed by adjuvant platinum-etoposide chemotherapy.

The evidence for the potential role of the immunotherapy is extrapolated from the small-cell lung cancers. It seems that there is a promising activity of the anti-PD1 antibodies in this context **(21).**

Emerging prognostic biomarkers in ovarian cancer and novel technologies.

Biomarker/ Drug/ Inhibitor	Treatment Strategies/ Components	Therapeutic Response	Features/ Properties/ Nature	Detection Level	Supported Technologies	Refs.
PARP inhibitor	Extended PFS	OC, phase 3 trial	Personalized medicine	HRD-positive tumors		**(González-Martín et al., 2019)**

Biomarker/ Drug/ Inhibitor	Treatment Strategies/ Components	Therapeutic Response	Features/ Properties/ Nature	Detection Level	Supported Technologies	Refs.
PARP inhibitor, bevacizumab	PFS benefit, anti-VEGF	OC, phase 3 trial	Antiangiogenic	HRD-positive tumors, BRCA mutation		**(Ray-Coquard et al ., 2019)**
Combination of PARP and ATR inhibitor	Overcomes PARPi and platinum resistance	OC, PDX models	Stabilize stressed replication fork and apoptosis	DNA, protein	Western blot, IHC, NGS, RPPA	**(Kim et al., 2020)**
ARNTL	Epi-biomarker by reducing promoter methylation	OC	Circadian and tumor-suppressor gene	DNA	CpG island microarray, COBRA, ChIP-PCR	**(Swiatly et al., 2018)**
RUNX3/CAMK2N1	Epigenetic prognostic marker	EOC	Hypermethylation of CpG island reduces PFS	DNA	GWA and targeted NGBS confirming array	**(Feliu et al., 2020)**]
Fkbp1/Pax9	Epi-biomarker for platinum-resistant therapeutic target	OC	PAX9 hypermethylation causes a poor prognosis for OS	DNA, RNA	Sanger sequencing, RT-PCR	**(Soto et al., 2021)]**
COL11A1	Promotes tumor progression through TGF-β1–MMP3 axis and predicts poor prognosis	OC	Disease-progression-associated gene	mRNA	Microarray, RT-PCR, casein zymography, and ChIP assay	**(Wu et al., 2014)]**
circCELSR1	Increases paclitaxel resistance and poor prognosis	OC	Circular RNA	miRNA	Microarray analysis and RT-qPCR	**[(Zhao et al., 2019)**
microRNA-137	Promotes apoptosis; represses mRNA translation	Improves drug resistance	Regulating RNA	Short non-coding RNA	Dual-luciferase reporter assay	**(Liu et al., 2012)**
FOXM1	Prognostic and chemoresistant therapeutic target	Non-serous EOC	Oncogene	mRNA, protein	Microarray, RT-qPCR, and IHC	**(Tassi et al., 2017)**

Biomarker/ Drug/ Inhibitor	Treatment Strategies/ Components	Therapeutic Response	Features/ Properties/ Nature	Detection Level	Supported Technologies	Refs.
RBP4	Diagnostic or prognostic biomarker	Ovarian endometrioma	Adipokine RBP4 involved in the pathogenesis of endometriosis	Protein	Human XL proteome profile assay, IHC, cell viability, and invasiveness assay	**(Lee et al., 2021)**]
AAT, NFKB, PMVK, VAP1, FABP4, and PF4	Predicts prognosis	HGSOC	Differentially expressed proteins	Protein	Hierarchical clustering, bioinformatics, LC-MS, and IHC	**(Kim et al., 2020)**]
Serotransferrin, amyloid A1, hemopexin, C-reactive protein, albumin	Multimarker test specific for screening and detection of OC	OC	Molecular signaling pathways of OC	Protein	ITRAQ-tagging coupled with mass spectrometry	**(Swiatly et al., 2018)]**
PDGFR-beta and VEGFR-2	Predictive biomarker for treatment response	OC	Angiogenesis-related growth factor receptors	mRNA Protein	Quantitative RPPA, bioinformatic analysis	**(Avril et al., 2017)]**
Circulatory protein	Personalized therapy for early diagnosis and prediction of drug resistance	OC	Proteomic landscape	Protein	Proteomic	(**Mukherjee** et al., 2021)]
2-piperidinone and 1-heptadecanoylglycerophosphoethanolamine	Clinical diagnosis and treatment	OC	Candidate biomarker	Metabolites	UPLC/Q-TOF MS	] **(Yang et al., 2020)**

References

1. Young, R. C., Walton, L. A., Ellenberg, S. S., Homesley, H. D., Wilbanks, G. D., Decker, D. G., ... & Major Jr, F. (2006). Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. New England Journal of Medicine, 322(15), 1021-1027.

2. Brady, M. F., Young, R. C., Lage, J., Walker, J. L., Look, K. Y., ... & Spirtos, N. M. (2010). Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. Gynecologic oncolo

3. Bristow, R. E., Tomacruz, R. S., Armstrong, D. K., Trimble, E. L., & Montz, F. J. (2014). Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. In Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. Centre for Reviews and Dissemination (UK).gy, 102(3),

432-439.

4. Ozols, R. F., Bundy, B. N., Greer, B. E., Fowler, J. M., Clarke-Pearson, D., Burger, R. A., ... & Baergen, R. (2013). Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. Journal of Clinica

5. Burger, R. A., Brady, M. F., Bookman, M. A., Walker, J. L., Homesley, H. D., Fowler, J., ... & Liang, S. X. (2015). Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. Journal of Clinical Oncology, 28(18_suppl), LBA1-LBA1.l Oncology, 21(17), 3194-3200.

6. Thigpen, J. T., Blessing, J. A., Ball, H., Hummel, S. J., & Barrett, R. J. (2000). Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. Journal of clinical oncology, 12(9), 1748-1753.

7. Tew, W. P., Colombo, N., Ray-Coquard, I., Oza, A., Del Campo, J., Scambia, G., & Spriggs, D. (2007). VEGF-Trap for patients (pts) with recurrent platinum-resistant epithelial ovarian cancer (EOC): preliminary results of a randomized, multicenter phase II study. Journal of Clinical Oncology, 25(18_suppl), 5508-5508.

8. Matei, D., Sill, M. W., Lankes, H. A., DeGeest, K., Bristow, R. E., Mutch, D., ... & Birrer, M. J. (2011). Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. Journal of Clinical Oncology, 29(1), 69-75.

9. Naumann, R. W., Coleman, R. L., Burger, R. A., Sausville, E. A., Kutarska, E., Ghamande, S. A., ... & Messmann, R. A. (2015). PRECEDENT: a randomized phase II trial comparing vintafolide (EC145) and pegylated liposomal doxorubicin (PLD) in combination versus PLD alone in patients with platinum-resistant ovarian cancer. J Clin Oncol, 31(35), 4400-4406.

10. Gordon, A. N., Finkler, N., Edwards, R. P., Garcia, A. A., Crozier, M., Irwin, D. H., & Barrett, E. (2005). Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. International Journal of Gynecologic Cancer, 15(5).

11. Ashworth, A. (2008). A synthetic lethal therapeutic approach: poly (ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. Journal of Clinical Oncology, 26(22), 3785-3790.

12. Argenta, P. A., Thomas, S. G., Judson, P. L., Downs Jr, L. S., Geller, M. A., Carson, L. F., ... & Ghebre, R. (2009). A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. Gynecologic oncology, 113(2), 205-209.

13. Whiteside, T. L. (2016). Tumor-derived exosomes and their role in cancer progression. Advances in clinical chemistry, 74, 103-141.

14. Cai, J., Gong, L., Li, G., Guo, J., Yi, X., & Wang, Z. (2021). Exosomes in ovarian cancer ascites promote epithelial–mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell Death & Disease, 12(2), 210.

15. Ye, M., Wang, J., Pan, S., Zheng, L., Wang, Z. W., & Zhu, X. (2022). Nucleic acids and proteins carried by exosomes of different origins as potential biomarkers for gynecologic cancers. Molecular Therapy-Oncolytics, 24, 101-113.

16. Zhao, L., Hu, C., Zhang, P., Jiang, H., & Chen, J. (2019). Genetic communication by extracellular vesicles is an important mechanism underlying stem cell-based therapy-mediated protection against acute kidney injury. Stem Cell Research & Therapy, 10(1), 1-9.

17. Shaaban, A. M., Rezvani, M., Elsayes, K. M., Baskin Jr, H., Mourad, A., Foster, B. R., ... & Menias, C. O. (2014). Ovarian malignant germ cell tumors: cellular classification and clinical and imaging features. Radiographics, 34(3), 777-801.

18. Kaur, B. (2020). Pathology of malignant ovarian germ cell tumours. Diagnostic Histopathology, 26(6), 289-297.

19. Mikropoulos, C., Samartzis, E., Karihtala, P., Moschetta, M., Sheriff, M., ... & Pavlidis, N. (2020). Wise management of ovarian cancer: on the cutting edge. Journal of personalized medicine, 10(2), 41.

20. Khosla, D., Dimri, K., Pandey, A. K., Mahajan, R., & Trehan, R. (2014). Ovarian granulosa cell tumor: clinical features, treatment, outcome, and prognostic factors. North American journal of medical sciences, 6(3), 133.

21. Ray-Coquard, I., Pautier, P., Pignata, S., Pérol, D., González-Martín, A., Berger, R., ... & Harter, P. (2019). Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. New England Journal of Medicine, 381(25), 2416-2428.