

**REVIEW ARTICLE**

# Potential approaches in the development of novel therapeutics for ovarian cancer

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## Abstract

“Ovarian cancer” is not a specific diagnosis; instead, it is a collective term for various cancer types that affect the ovaries, fallopian tubes, and the peritoneum. Over 30 distinct forms of ovarian cancer are estimated to exist, with significant variations in occurrence and prognosis among the various types. Based on GLOBOCAN 2022 estimates, the number of women diagnosed with ovarian cancer is projected to increase by more than 55% by 2050. The annual deaths due to ovarian cancer among women are expected to rise to 350,956, marking an increase of nearly 70% compared to 2022. The incidence of ovarian cancer has been increasing substantially among younger females, probably due to the increasing prevalence of obesity, metabolic syndrome, estrogen exposure, and nulliparity. At present, the primary treatment options for ovarian cancer are based on three pillars: surgical debulking, chemotherapy, and maintenance therapy. However, the long-term survival rate remains low due to the late stages of the disease, with a high recurrence risk. Because treatment still relies heavily on cytotoxic chemotherapy, adverse effects and acquired drug resistance remain common. Therefore, there is a need for new therapeutics that optimize treatment options. In this review, an updated overview of current and future approaches to developing new therapeutics for ovarian cancer is presented.

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## 1. Introduction

Ovarian cancer is the eighth most common cancer and the eighth most common cause of death among women worldwide, according to the World Ovarian Cancer Coalition.<sup>1</sup> According to the World Ovarian Cancer Coalition Atlas 2023, potential risk factors for the development of ovarian cancer include age, specific geographical location, lower socioeconomic status, race/ethnicity, family history, hormonal/reproductive factors, and lifestyle. The mortality rate from ovarian cancer is projected to increase to 350,956, an increase of almost 70% from 2022.<sup>1</sup> Five-year survival for women diagnosed with stage III–IV ovarian cancer is estimated at 22–29%, and is lower in some countries.<sup>2,3</sup> Ovarian

cancer is known as a “silent killer” as it is difficult to detect in the early stages owing to non-specific symptoms, such as bloating, early satiety, changes in bowel habit, and urinary frequency.<sup>4</sup> As a result, there is a growing global need to improve the survival rate of women with ovarian cancer, especially as surgical treatment in International Federation of Gynecology and Obstetrics stage III–IV disease, complete macroscopic cytoreduction (R0) is often not achievable. The primary treatment strategies are the combined platinum–taxane chemotherapy and maintenance therapies. Platinum sensitivity is a key prognostic and treatment-stratifying factor, particularly in the recurrent setting.<sup>5</sup>

The commonly used platinum drug is carboplatin, which undergoes slower aquation due to its bidentate cyclobutane dicarboxylic acid ligands and has a more favorable toxicity profile than cisplatin, with reduced hepatotoxicity, nephrotoxicity, neurotoxicity, and ototoxicity.<sup>6–8</sup> Standard of care for platinum-sensitive recurrent ovarian cancer includes rechallenge with a platinum-based chemotherapy doublet, although most tumors ultimately become platinum resistant. Following the development of platinum resistance, overall survival and progression-free survival (PFS) are short, and maintaining the quality of life becomes crucial.

Once platinum becomes inappropriate, cytotoxic agents, such as paclitaxel, liposomal doxorubicin, gemcitabine, and topotecan, are used for treatment, offering modest response rates and short PFS. However, these drugs are associated with significant toxicity.<sup>9</sup> Studies have shown that weekly paclitaxel can offer a 20–40% response rate in platinum-resistant disease, and the addition of bevacizumab to chemotherapy improves PFS and patient-reported outcomes, although with no significant effect on overall survival.<sup>10</sup> A maintenance treatment that improves PFS and/or overall survival should be considered if toxicity is manageable and health-related quality of life is not significantly affected.

The advent of immune checkpoint inhibitors (ICIs) has significantly improved the effectiveness of immunotherapy for treating ovarian cancer by inhibiting the negative feedback mechanism, allowing T cells to attack cancer cells. Cancer vaccines, antibody–drug conjugates (ADCs), nanoenzymes (nanozymes), and functionalized nanoparticles are being explored to deliver therapeutics and trigger apoptosis in ovarian cancer cells.<sup>11</sup>

The current strategies for developing therapeutics for ovarian cancer are illustrated in [Figure 1](#). In this review, the present novel therapeutic approaches and their mechanisms involved in the treatment of this disease are described.

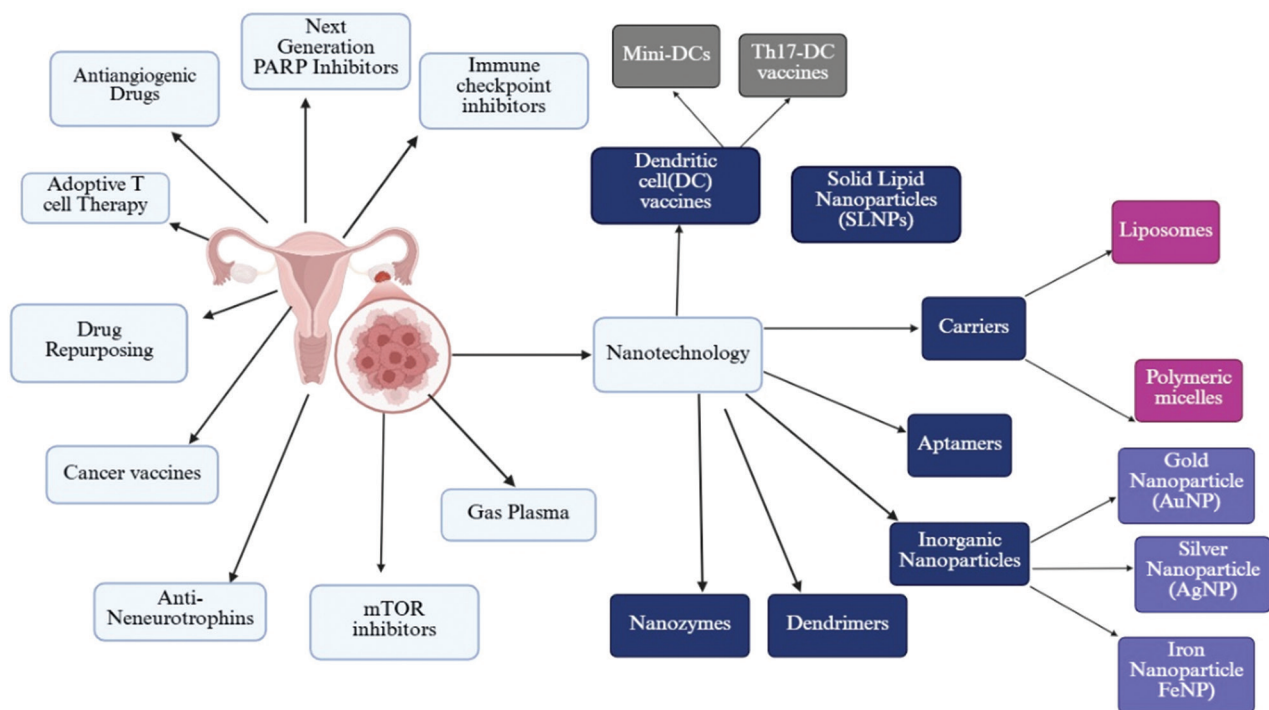
## 2. Maintenance therapy for ovarian cancer

Maintenance therapy is a type of treatment given after the completion of chemotherapy to decrease the chance of cancer recurrence. The choice of maintenance therapy for ovarian cancer depends on factors such as the type of chemotherapy used, response to chemotherapy, number of lines of chemotherapy (first-line, second-line, or third-line), genetic testing for inherited mutations (*BRCA1* or *BRCA2*), and tumor testing. The two agents used for maintenance therapy are Avastin (bevacizumab) and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. The Avastin may be used in the following two ways: (i) As first-line or later-line maintenance therapy (women do not have to undergo any biomarker test to receive Avastin alone), (ii) as first-line therapy in combination with PARP inhibitor, Lynparza (this line of treatment is used for people with *BRCA1* or *BRCA2* inherited tumor or women whose tumor is homologous recombination deficiency [HRD] positive). In contrast, PARP inhibitors are only used in maintenance therapy to treat women with a partial or complete response to their most recent chemotherapy. The three PARP inhibitors that have been approved by the Food and Drug Administration (FDA) for ovarian cancer maintenance therapy are Olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula). For first-line treatment, Lynparza is used alone or in combination with Avastin for women with inherited *BRCA* mutations, tumors with *BRCA* mutations, or HRD-positive tumors. For women regardless of *BRCA* or HRD status, Zejula is used as the maintenance therapy.

## 3. Current and future drugs in treating ovarian cancer and their mechanism of action

### 3.1. PARP inhibitors

PARP are essential enzymes integral to numerous cellular processes, including the response to cellular stress, chromatin remodeling, DNA repair, and apoptosis.<sup>11</sup> PARP inhibitors have been recognized as an innovative therapeutic approach for managing epithelial ovarian cancer (EOC), particularly in patients with deficiencies in the homologous recombination DNA repair pathway, a condition often associated with mutations in the *BRCA1* and *BRCA2* genes.<sup>12</sup> These inhibitors stabilize PARP1, PARP2, and PARP3, thereby preventing the formation of poly(adenosine diphosphate-ribose) polymer and inhibiting nicotinamide adenine dinucleotide from binding to damaged DNA sites, preventing DNA repair and leading to cell death.<sup>13</sup> Although PARP Inhibitors are effective, acquired resistance to these agents has been reported in



**Figure 1.** Schematic representation of current and future strategies in the development of novel therapeutics for ovarian cancer. Created in BioRender. Bahrain team 1, R. (2025) <https://BioRender.com/undefined>.

Abbreviations: mTOR: Mechanistic target of rapamycin; PARP: Poly(adenosine diphosphate-ribose) polymerase.

most tumors, and not all patients with *BRCA1/2* mutations respond to PARP inhibitors.

To overcome resistance, combination therapies using PARP inhibitors with other drugs have been proposed.<sup>11,14</sup> For women with advanced ovarian cancer, the combination of Olaparib with bevacizumab has been approved by the FDA as a maintenance therapy.<sup>15</sup> The next-generation PARP inhibitors focus on selective PARP inhibition to facilitate their combination with other DNA damage repair inhibitors, thereby improving efficacy and safety profiles. Saruparib (AZD5305) is a next-generation PARP1-specific inhibitor, which is effective in tumors that harbor HRD, such as ovarian, prostate, and breast cancers.

Due to its low toxicity, patients can be administered higher doses than those of first-generation PARP inhibitors.<sup>14,15</sup> Some of the risks associated with the use of PARP inhibitors include therapy-related myeloid neoplasia, such as myelodysplastic syndrome and acute myeloid leukemia. When the treatment period exceeds 2 years, patients with platinum exposure and *BRCA* mutations are at increased risk of developing hematopoietic malignancies. Therefore, ongoing surveillance for therapy-related myeloid neoplasia is recommended in the post-treatment period.

### 3.2. DNA replication and repair targets

The major challenge in treating ovarian cancer is resistance to PARP inhibitors, which involves restoring genomic stability by protecting the replication fork. Various novel therapies have been developed to overcome this resistance by alternative mechanisms that preserve the replication fork. The replication fork is the site on DNA where the double helix structure unwinds, promoting the synthesis of a new DNA duplex. The novel therapies that have been developed and those currently under clinical trials are presented in Table 1.

### 3.3. ICIs

ICIs have shown great potential in cancer treatment and are now incorporated in the management of urothelial cancers, triple-negative breast cancer, and microsatellite unstable tumors. ICIs block immune checkpoint pathways, preventing immune response dampening and thereby revitalizing the body's antitumor immune response. Several factors can influence ICI efficacy, including intrinsic factors such as the quantity and activation of immune subsets within the tumor microenvironment (TME), the presence or absence of immune checkpoints, and treatment regimens such as surgery and chemotherapy.<sup>16,17</sup> To date, the results for ICI monotherapy and in combination with

**Table 1. Clinical trials of DNA replication and repair targets for ovarian cancer. Table reproduced from Moufariij *et al.*<sup>11</sup>**

Clinical trial number and phase	Inclusion criteria	Target	Schema
NCT05548296 (Phase 1b/2)	Platinum-resistant, advanced HGSOC/endometrioid ovarian cancer that has progressed on at least one prior regimen; also includes high-grade endometrial carcinoma and urothelial carcinoma	CHK1/2 inhibitor (ACR-368)	Participants with an OncoSignature positive test administered ACR-368 as monotherapy; participants with a negative OncoSignature test administered a combination of ACR-368 and low-dose gemcitabine
NCT02264678 (Phase 1)	Solid tumors, including patients with prior PARP inhibitor use for certain modules, including <i>BRCA</i> mutations or HRD-positive status in certain modules	ATR and RAD-3 inhibitor (ceralasertib)	Ceralasertib+carboplatin versus ceralasertib+olaparib versus ceralasertib+durvalumab
NCT03682289 (Phase 2)	Solid tumors, including renal cell carcinoma, urothelial carcinoma, pancreatic cancers, ovarian (excluding clear cell), and endometrial cancer	ATR and RAD-3 inhibitor (ceralasertib)	Ceralasertib alone versus ceralasertib+olaparib or ceralasertib+durvalumab
NCT04616534 (Phase 1)	Patients with pancreatic and ovarian tumors with measurable disease who progressed on at least one prior line of treatment	ATR inhibitor (elimusertib)	Elimusertib+gemcitabine
NCT04497116 (Phase 1/2a)	Solid tumors resistant or refractory to standard treatment, or patients with solid tumors who cannot tolerate standard therapy. Measurable disease as per RECIST v1.1 needed	ATR inhibitor (camonsertib)	Camonsertib alone versus camonsertib+talazoparib
NCT03462342 (Phase 2)	Recurrent ovarian cancer (platinum-sensitive or platinum-resistant)	ATR inhibitor (AZD6738)	AZD6738+olaparib
NCT04991480 (Phase 1/2)	Advanced disease refractory to standard therapy; at least one radiologically evaluable lesion; estimated life expectancy >12 weeks	Polymerase theta inhibitor (ART4215)	ART4215 as single therapy versus ART4215 with talazoparib, versus ART4215 with niraparib
NCT04826198 (Phase 1b/2)	Life expectancy of at least 3 months; availability of <i>BRCA</i> status; received at least two previous courses of platinum-containing therapy and has platinum-sensitive cancer; received niraparib in maintenance for at least 6 months	DNA repair inhibitor (AsiDNATM)	AsiDNATM in combination with niraparib versus AsiDNATM alone, niraparib alone, olaparib alone, and rucaparib alone
NCT04092270 (Phase 1)	Platinum-resistant or recurrent ovarian cancer	DNA-PK inhibitor (peposertib)	Peposertib with pegylated liposomal doxorubicin

Abbreviations: ATM: Ataxia-telangiectasia mutated; ATR: Ataxia-telangiectasia mutated and RAD-3 related; CHK1: Checkpoint kinase 1; PK: Protein kinase; HGSOC: High-grade serous ovarian cancer; HRD: Homologous recombination deficiency; RECIST: Response Evaluation Criteria in Solid Tumors.

vascular endothelial growth factor (VEGF) inhibitors for ovarian cancer have been disappointing. Therefore, clinical trials have now focused on combining ICIs with other treatments, such as chemotherapy, PARP inhibitors, or other ICIs.<sup>18</sup> Chemotherapy can convert a “cold” TME into a “hot” TME favorable for ICI treatment. In a study, following neoadjuvant chemotherapy, immune checkpoint expression (indoleamine 2,3-dioxygenase, programmed death-ligand 1 [PD-L<sup>1</sup>, lymphocyte activation gene 3, T-cell immunoglobulin and mucin-domain containing-3) was altered in over 70% of EOC samples, where expression either increased or decreased.<sup>19</sup> However, the significant increase in immune checkpoints, including programmed cell death protein 1 (PD-1), PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), could dampen the immune response, or perhaps provide an opportunity for sequential treatment with chemotherapy and ICIs.

In the NRG-GY003 trial, ipilimumab plus nivolumab was associated with a 6-month response rate higher than nivolumab alone in patients with EOC (subtype not specified). Response rates were 31.4% with the combination versus 12.2% with nivolumab monotherapy. A longer, albeit limited, PFS of 3.9 months was observed with the combination treatment compared to 2.0 months for nivolumab alone. Although the combination treatment showed significant improvements, it still provided little benefit for most patients.

The KGOG 3046 trial investigated the use of neoadjuvant chemotherapy in combination with anti-PD-1 (durvalumab) and anti-CTLA-4 (tremelimumab) in the treatment of newly diagnosed advanced-stage high-grade serous ovarian carcinoma (HGSOC). This treatment regimen demonstrated promising results of 12-month, 24-month, and 30-month PFS rates of 63.6%, 45.0%, and 40.0%, respectively. However, this study was limited by a



small sample size of 23 patients and the absence of a control arm. The results from NRG-GY003 and KGOG 3046 trials indicate that additional studies with further combinations are warranted to enhance the durability of the dual regimen. A few clinical trials are ongoing to investigate the combinatorial effect of PARP inhibitors and ICIs, with initial results indicating tolerability, promising antitumor activity, and responses that are better than expected in patients without a *BRCA* mutation. The FDA and European Medicines Agency have approved the use of microsatellite instability, PD-L1 expression, and tumor mutational burden as tissue biomarkers to predict patients' response to ICIs.<sup>20</sup>

### 3.4. Checkpoint kinase inhibitors

Given frequent dysregulation of kinase signaling in EOC and the urgent need for new, effective targeted therapies, single- and multi-kinase inhibitors are being actively investigated, including checkpoint kinase inhibitors. Prexasertib is a checkpoint kinase 1 inhibitor that is currently under investigation as part of a phase 2 trial as a treatment for patients with platinum-resistant ovarian cancer, endometrial adenocarcinoma, and urothelial cancers. The FDA has granted fast-track designation to prexasertib (ACR-368) in two indications, including the treatment of patients with ovarian cancer and endometrial cancer.<sup>21</sup> The first designation supports the investigation of prexasertib as a single-agent treatment option for patients with locally advanced or metastatic recurrent platinum-resistant, high-grade ovarian carcinoma who have received at least 1 prior line of systemic therapy. The second designation supports the investigation of prexasertib as a monotherapy in those with recurrent high-grade endometrial carcinoma previously treated with at least two prior lines of systemic therapy. Investigators are evaluating prexasertib as part of a multi-center, open-label, single-arm phase 2 trial (NCT05548296) in patients with platinum-resistant ovarian cancer, endometrial adenocarcinoma, and urothelial cancers based on sensitivity to prexasertib, as determined with the OncoSignature-predictive test.<sup>21</sup>

Ataxia telangiectasia and RAD3-related inhibitors have also been studied as novel therapeutic agents for patients with HRD tumors. The use of ataxia telangiectasia, ceralasertib (RAD-3 inhibitor), and olaparib resulted in an objective response rate of 8.3% with a 62.5% clinical benefit rate. Polymerase theta inhibitors (ART4215) have been investigated to reduce reversion mutations and overcome PARP-inhibitor resistance. DNA repair inhibitors that mimic the breaking of DNA strands and promote apoptosis have also been assessed in niraparib-treated individuals with platinum-sensitive ovarian cancers. These inhibitors are also known to repair DNA breaks and block protein kinase, thereby promoting apoptosis.

### 3.5. Cell signaling and cell cycle pathway mediators

Another method to overcome PARP resistance is to restore the homologous recombination pathways using cell cycle and cyclin-dependent kinases as mediators. It is known that dysregulation of the phosphoinositide-3-kinase/protein kinase B checkpoint is associated with PARP inhibitor resistance. In combination with paclitaxel, the pan-protein kinase B inhibitor afuresertib is currently being explored as a cell cycle pathway mediator (NCT04374630). AXL is a receptor tyrosine kinase involved in apoptotic cell clearance and epithelial-mesenchymal transition. On binding of the kinase receptor to its ligand, the cell enters the proliferative state and becomes protected from immune system responses. An AXL decoy protein, Batiraxcept, in combination with paclitaxel, showed an objective response rate of 34.8%. However, no significant improvement in PFS was achieved for this combination. Given the high frequency of *TP53* mutations in ovarian cancer, cell-cycle checkpoint inhibitors have also been evaluated as potential therapy. Adavosertib (WEE1 tyrosine kinase inhibitor) has shown several promising initial results, but it was associated with myelosuppression and significant gastrointestinal toxicity. The cell cycle checkpoint inhibitors that are in clinical trials for ovarian cancer are listed in Table 2.

### 3.6. ADCs

ADCs are novel options that can deliver cytotoxic agents directly into ovarian cancer cells by binding to their surface antigens. Several clinical studies have shown that ADCs have a tolerable toxicity profile and notable clinical effectiveness in patients with ovarian cancer. Numerous ADCs have been developed to address different antigens in ovarian cancer therapy, such as folate receptor alpha (FR $\alpha$ ), trophoblast cell surface antigen 2, mesothelin, sodium-dependent phosphate transport protein 2B, human epidermal growth factor receptor 2 (HER2), dipeptidase 3, and tissue factor, and carry different types of cytotoxic payloads to induce cell death on release in tumor cells. Few combinations are currently in clinical trials and are listed in Table 3. Single-agent therapy using anti-PD-1/L1 drugs, such as avelumab and nivolumab, has shown promising responses in clear cell carcinomas but not in recurrent platinum-resistant tumors. Combining these drugs with bevacizumab has shown positive results, but only with a small cohort of platinum-sensitive patients.<sup>21</sup> ICI combination therapies with ADCs, such as mirvetuximab soravtansine (MIRV) and pembrolizumab, have also been studied and shown to have good tolerability. MIRV is a first-in-class ADC targeting FR $\alpha$  and is the only FDA-approved ADC

**Table 2. List of cell cycle checkpoint inhibitors that are in clinical trials for ovarian cancer. Table reproduced from Moufariij *et al.*<sup>11</sup>**

Clinical trial number and phase	Inclusion criteria	Target	Schema
NCT04374630 (Phase 2)	HGSOC, endometrioid ovarian cancer, or ovarian clear cell carcinoma; no previous AKT or PI3K pathway or mTOR inhibitors; disease recurrence between 1 and 6 months after last dose of first-line platinum-based therapy or progression or relapse within 6 months of last dose of platinum-based second- to fifth-line therapies; 1–5 prior chemotherapies	AKT inhibitor (afuresertib)	Paclitaxel and afuresertib compared with paclitaxel
NCT04729608 (Phase 3)	Recurrent ovarian cancer (high-grade serous histology only); platinum-resistant disease; received at least one but no more than four prior therapy regimens	AXL decoy protein (batiraxcept)	Batiraxcept in combination with paclitaxel versus placebo
NCT05198804 (Phase 1/2)	Recurrent high-grade epithelial ovarian cancer with histologic subtypes of serous, clear cell, or endometrial; recurrence within 6 months of platinum therapy	WEE1 inhibitor (ZN-c3)	ZN-c3 administered with niraparib for 30 months
NCT04516447 (Phase 1b)	HGSOC, LVEF≥50%	WEE1 inhibitor (ZN-c3)	ZN-c3 in combination with liposomal doxorubicin, carboplatin, paclitaxel, or gemcitabine
NCT02993705 (Phase 3)	Recurrent platinum-sensitive ovarian cancer with <i>BRCA1/2</i> mutations or <i>BRCA</i> phenotype (patients who received and responded to at least two previous platinum-based treatments)	Alkylating agent (trabectedin)	Trabectedin every 21 days versus the physician's choice chemotherapy (carboplatin, gemcitabine, weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan)

Abbreviations: AKT: Protein kinase B; HGSOC: High-grade serous ovarian cancer; LVEF: left ventricular ejection fraction; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

for ovarian cancer. In the single-group SORAYA trial of MIRV in FR $\alpha$ -positive, bevacizumab-pretreated, platinum-resistant, high-grade serous ovarian cancer, the investigator-assessed objective response was 32.4% (95% confidence interval [CI]: 23.6–42.2), with five complete and 29 partial responses. The median duration of response was 6.9 months (95% CI: 5.6–9.7). The median overall survival in the SORAYA trial was 15.0 months (95% CI: 11.5–18.7); an estimated 37% of patients were alive at year 2. On November 14, 2022, based on the positive results of the pivotal SORAYA trial, the FDA granted accelerated approval to MIRV for adults with FR $\alpha$ -positive, platinum-resistant ovarian cancer (as assessed by an FDA-approved test) who had previously received one to three systemic treatments. Nivolumab in combination with ipilimumab (a human monoclonal antibody targeting CTLA-4) showed promising results in the management of persistent ovarian cancer.<sup>22,23</sup>

Luveltamab tazevibulin (STRO-002-GM1) is an FR $\alpha$ -targeting ADC that uses a stable cleavable linker and an active 3-aminophenyl hemiasterlin, which induces cell death through conjugation at specific tumor sites. In this study, 32.2% of platinum-resistant ovarian cancer patients (10 out of 31) responded positively to this treatment in a phase 1 clinical trial. Based on the ongoing clinical trial (NCT03748186), about 75% of patients achieved disease

control.<sup>25</sup> The monoclonal human antibody, farletuzumab ecteribulin (MORAb-202), is another ADC that targets FR $\alpha$ . Currently, MIRV is the only FR $\alpha$ -targeted ADC approved for FR $\alpha$ -positive platinum-resistant ovarian cancer.

### 3.7. Antiangiogenic drugs

In ovarian cancer, angiogenesis drives ascites formation and extensive metastatic dissemination, thereby accelerating tumor progression and worsening the patient's prognosis. Antiangiogenic agents target various pathways. The primary initial targets are central proangiogenic signaling and VEGF signaling. The combination of anti-VEGF monoclonal antibody bevacizumab with chemotherapy is approved by the FDA for the treatment of platinum-resistant recurrent ovarian cancer.<sup>25,26</sup> The combination of several tyrosine kinase inhibitors is under different phases of clinical trials to evaluate their effectiveness for ovarian cancer either as a stand-alone or in combination with other chemotherapeutic agents.<sup>26</sup>

Tyrosine kinase inhibitors engage multiple targets, such as VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), proto-oncogenes *KIT* and *RET*. Although these inhibitors seem promising, their multi-target mechanism of action can result in variable off-target toxicity and limited

Table 3. Clinical trials with antibody–drug conjugates in ovarian cancer. Reproduced from Revu and Romi<sup>24</sup>

Target	ADC	Clinical trial number and reference number	Phase and study design	Dose and regimen for ADC	ObjectiveZ	Survival outcomes and responses	Adverse effects
FR $\alpha$	MIRV (IMGN853)	NCT01609556; PMID: 28440955 and PMID: 28029313	Phase 1 dose-escalation and expansion study with open-label cohort	6mg/kg; every 3 weeks, administered intravenously	Safety and clinical activity, ORR, PFS, and DOR	(i) For the expansion phase: Median PFS: 4.8 (ii) ORR: 26% (iii) Median DOR: 19.1 weeks	Diarrhea, blurred vision, nausea, and fatigue
		NCT02631876 (FORWARD I trial); PMID: 29424243 and PMID: 33667670	Phase 3, randomized trial. MIRV compared with chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan)	6mg/kg; every 3 weeks, administered intravenously	PFS, ORR, OS, and DOR	Superior outcomes for MIRV over chemotherapy were observed in all secondary endpoints in the FR $\alpha$ high population, including improved ORR (24% vs. 10%)	Nausea, diarrhea, and blurred vision, less myelosuppression, less peripheral neuropathy, and no alopecia
		NCT04296890 (SORAYA trial); PMID: 36716407, PMID: 38858103, and PMID: 37212825	Phase 2, single-arm trial	6mg/kg; every 3 weeks, administered intravenously	ORR, DOR, and TRAE	(i) Median DOR: 6.9 months (ii) Median PFS: 4.3 months (iii) Median OS: 1.5 months (iv) ORR: 32.4%	Blurred vision, keratopathy, and nausea
		NCT04209855 (MIRASOL trial); PMID: 38055253	Open-labeled randomized phase 3 clinical trial comparing MIRV with chemotherapy	6mg/kg; every 3 weeks, administered intravenously	PFS, OS, and objective response	(i) Median OS of 16.46 months with MIRV versus 12.75 months with chemotherapy (ii) Median PFS of 5.62 months with MIRV versus 3.98 months with chemotherapy (iii) ORR of 42.3% with MIRV versus 15.9% with chemotherapy	Blurred vision, keratopathy, abdominal pain, and fatigue in the MIRV-treated group
		NCT02606305 (FORWARD II trial); PMID: 36736157	Multi-arm, phase 1b/2 trial	MIRV-6 mg/kg; every 3 weeks, and bevacizumab (15mg/kg) once every 3 weeks, administered intravenously	Safety and clinical activity of MIRV in combination with bevacizumab	(i) Median PFS was 8.2 months (ii) ORR was 44%, including five CRs Median DOR: 9.7 months	Diarrhea, blurred vision, and nausea
		NCT03748186; PMID: 36459691	Phase 1 dose expansion cohort	4.3mg/kg or 5.2mg/kg once every 3 weeks, administered intravenously	Safety and efficacy	(i) Median DOR was 13 months in the 4.3mg/kg group and 5.4 months in the 5.2mg/kg group (ii) Median PFS was 6.1 months in the 4.3mg/kg group and 6.6 months in the 5.2mg/kg group (iii) ORR was 31.3% in the 4.3mg/kg group and 43.8% in the 5.2mg/kg group	Neutropenia, arthralgia, and anemia
	Luveltamab Tazevibulin (STRO-002-GM1)						(Cont'd...)

Table 3. (Continued)

Target	ADC	Clinical trial number and reference	Phase and study design	Dose and regimen for ADC	ObjectiveZ	Survival outcomes and responses	Adverse effects
	Farletuzumab Ecteribulin (MORab-202)	NCT03386942; PMID: 33926914	Dose escalation phase 1 trial	0.3–1.2mg/kg once every 3 weeks, administered intravenously	Dose-limiting toxicities, safety, tumor responses, pharmacokinetics, and pharmacodynamics	Total: 22 patients; CR was seen in 1; PR was seen in 9; SD was seen in 8	Leukopenia and neutropenia
TROP2	Sacituzumab Govitecan (SG)	NCT01631552; PMID: 33741442	Phase 1/2 IMMU-132-01 basket trial	(8, 10, 12, or 18mg/kg) On days 1 and 8 of 21-day cycles, administered intravenously	ORR, DOR, clinical benefit rate, PFS, and OS	Overall safety population was 1.6% for EOC	Nausea, diarrhea, fatigue, alopecia, and neutropenia
Mesothelin	Anetumab Ravtansine	NCT02751918; PMID: 36564099	Phase 1b clinical trial	6.5mg/kg every 3 weeks, administered intravenously	Safety, pharmacokinetics, and efficacy	(i) ORR: 27.7% (ii) CR: 1 (iii) PR: 17 (iv) Median DOR: 7.6 months	Nausea, decreased appetite, fatigue, diarrhea, and corneal disorder
		NCT03587311	Phase 2 randomized trial	2.2mg/kg weekly on a 28-day cycle, administered intravenously	Safety and efficacy of the combination of AR/ bevacizumab versus weekly paclitaxel/ bevacizumab in PROC	(i) PFS of 5.3 months for the combination of AR and bevacizumab, compared to 9.6 months for bevacizumab and paclitaxel (ii) ORR of 18% for the combination of AR and bevacizumab, compared to 55% for bevacizumab	Thrombocytopenia, fatigue, increased ALT and AST, and peripheral neuropathy
	DMOT4039A	NCT01469793; PMID: 26823490	Phase 1 clinical trials	2.4mg/kg every 3 weeks, administered intravenously	Safety and pharmacokinetics	Total ovarian cancer patients: 31; PR observed in 4 out of 31	Hyperglycemia, hypophosphatemia, gastrointestinal, and constitutional
HER2	Trastuzumab Deruxtecan (T-DXd)	NCT04482309 (DESTINY- PanTumor02 trial); PMID: 37870536	Open-label phase 2 study	5.4mg/kg every three weeks, administered intravenously	ORR, safety, DOR, PFS, and OS	In all patients: (i) ORR: 37.1% (ii) Median DOR: 11.3 months (iii) Median PFS: 6.9 months Median OS: 13.4 months	Grade $\geq 3$ TRAE, drug-related interstitial lung disease, with three deaths
NaPi2B	LIFA	NCT01911598; PMID: 31540980	Phase 1 clinical study	0.2–2.8mg/kg dose on a tri-weekly schedule, administered intravenously	Safety, tolerability, and preliminary antitumor activity	At an active dose $\geq 1.8$ mg/kg, PR was 11/24 (46%)	Fatigue, nausea, decreased appetite, vomiting, and peripheral sensory neuropathy. Most common $\geq 3$ TRAE included neutropenia, anemia, and pneumonia
		NCT01991210; PMID: 29401246	Open-label clinical trial	2.4mg/kg on a tri-weekly schedule, LIFA was administered intravenously or PLD	Comparing ADC with respect to the standard of care	PFS was 5.3 months in LIFA versus 3.1 months in PLD; ORR was 34% in LIFA versus 15% in PLD	Severe toxicities and $\geq 3$ TRAE

(Cont'd...)



Table 3. (Continued)

Target	ADC	Clinical trial number and reference number	Phase and study design	Dose and regimen for ADC	ObjectiveZ	Survival outcomes and responses	Adverse effects
	UpRi; XMT-1536	NCT03319628	Phase 1b/2 clinical trial	36–43mg/m <sup>2</sup> every 4 weeks, injected intravenously	Antitumor activity	ORR of 32% with CR in 2 PROC patients	High ALT, nausea, fatigue, and pyrexia
Dipeptidase 3	Tamrintamab Pamozirine (SC-003)	NCT02539719; PMID: 32513564	Phase 1a/1b clinical study	0.025–0.4mg/kg every three weeks, administered intravenously	Safety, tolerability, pharmacokinetics, and preliminary antitumor activity	ORR: 4%; no durable response	Fatigue, nausea, decreased appetite, pleural effusion, abdominal pain, and peripheral edema
Tissue factor	Tisotumab vedotin	NCT02001623 (innovaTV 201 trial); PMID: 30745090	Phase 1–2, open-label, dose-escalation and dose-expansion study	0.3 and 2.2mg/kg once every 3 weeks, administered intravenously	Safety, tolerability, pharmacokinetic profile, and antitumor activity	ORR: 15.6% across various tumor types	Grade 3 TRAE, including type 2 diabetes mellitus, mucositis, and neutropenic fever; nine deaths were reported

Abbreviations: ADC: Antibody–drug conjugate; ALT: Alanine aminotransferase; AR: Anastrozole; AST: Aspartate aminotransferase; CR: Complete response; DOR: Duration of response; EOC: Epithelial ovarian cancer; FRα: Folate receptor alpha; HER2: Human epidermal growth factor 2; LIFA: Lifastuzumab vedotin; MIRV: Mirvetuximab soravtansine; NaP2B: Sodium-dependent phosphate transporter 2B; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PLD: PEGylated liposomal doxorubicin; PR: Partial response; PROC: Platinum-resistant ovarian cancer; SD: Stable disease; TRAE: Treatment-related adverse event; TROP-2: Trophoblast cell surface antigen 2.

dosing flexibility.<sup>27</sup> Cediranib is an oral tyrosine kinase inhibitor of VEGFR 1–3 and *KIT* receptor tyrosine kinase (c-KIT) that has shown promise in platinum-sensitive recurrent ovarian cancer patients.<sup>28</sup> Lenvatinib is an oral multitargeted inhibitor of VEGFR 1–3, FGFR, PDGFR-β, *RET* receptor tyrosine kinase, and c-KIT. In combination with pembrolizumab, it has been evaluated and approved by the FDA for microsatellite-stable recurrent endometrial cancer.<sup>29</sup>

The angiopoietin–Tie pathways are another target of the antiangiogenic drugs. Trebananib is a recombinant peptide-Fc fusion protein that inhibits tumor angiogenesis by blocking the interaction between Ang1 and Ang2, and their receptor Tie2. In a phase 1 clinical trial of patients with recurrent platinum-resistant ovarian cancer, the combination of drugs demonstrated apparent antitumor effectiveness and tolerable toxicity profiles. In another phase 1 trial on patients undergoing interval or primary debulking surgery, the combination of drugs, such as trebananib with paclitaxel and carboplatin, was found to exhibit antitumor activity and moderate toxicity. However, the results were not reproducible in Phase 3 trials, and the study was terminated.<sup>30</sup>

#### 4. Approved and emerging repurposed drugs for ovarian cancer treatment

Drug repurposing is a novel method to discover new applications for existing drugs and for drugs that are in the developmental stage. The main benefit of this method is the availability of pharmacokinetic and toxicity profiles that allow for advancement into Phase 2 and Phase 3 clinical trials.<sup>31,32</sup> With the advancement in computational science, proteomics, gene sequencing, disease models, etc., this field has received considerable research interest. There are no FDA-approved repurposed drugs for ovarian cancer; however, there is ongoing research to investigate the efficacy of various existing drugs for ovarian cancer.

##### 4.1. Statins

Statins are used to treat hyperlipidemia and have anticancer properties, including suppression of cancer cell proliferation by inhibiting the cancer cell cycle, inducing apoptosis, and autophagy.<sup>33,34</sup> In ovarian cancer, statins demonstrate their antitumor activity by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) within the mevalonate pathway, resulting in the suppression of mitosis in cancer cells *in vitro*, in addition to delaying tumor development. Statins also decrease cell migration *in vitro*, thereby preventing cell metastasis.<sup>35</sup>

The antitumor properties of statins influence the mevalonate pathway by inhibiting HMGCR and may

also affect cell growth, apoptosis, and drug resistance via metabolic reprogramming, modulation of the Bcl-2 family, and other signaling pathways. In addition, statins may have a combined anti-ovarian cancer effect when used alongside various medications. Nevertheless, existing clinical trials primarily focus on the concurrent administration of statins and chemotherapy medications. The use of other drugs in combination is less frequent. A comprehensive understanding of how statins function is expected to enhance the attainment of “precision therapy” through their use alone or in combination, thereby elevating overall clinical effectiveness. Additionally, appropriate tumor markers are crucial and must be explored in future research.<sup>36-39</sup>

#### 4.2. Bisphosphonates

Bisphosphonates are widely used to treat osteoporosis. They reduce the farnesyl pyrophosphate synthase by blocking HMGCR in the mevalonate pathway. In a transgenic ovarian cancer model, bisphosphonate treatment delayed tumor formation and markedly reduced cancer cell proliferation compared to the control group.<sup>39</sup>

#### 4.3. Metformin

Metformin is an antidiabetic drug that exhibits anti-inflammatory properties mediated by nuclear factor- $\kappa$ B. It also exhibits antitumor properties through a non-adenosine monophosphate-activated protein kinase-dependent mechanism that inhibits the mitochondrial respiratory chain and reduces the production of active enzymes. Studies have shown that metformin significantly prolonged overall survival (hazard ratio = 0.61; 95% CI: 0.48–0.77) and reduced the risk of endometrial cancer recurrence. It further amplifies the effects of paclitaxel in endometrial cancers by blocking the mechanistic target of rapamycin (mTOR) signals.<sup>39,40</sup> As these results are based on fundamental studies, it is strongly recommended that clinical studies be conducted in the future to confirm these results in non-diabetic ovarian cancer patients.<sup>40-42</sup>

#### 4.4. Non-steroidal drugs

Non-steroidal anti-inflammatory drugs are widely used to relieve pain and fever, and have also been studied for ovarian cancer despite their contraindications and adverse effects. Non-steroidal anti-inflammatory drug activated gene-1 (NAG-1) is a divergent and unique member of the transforming growth factor- $\beta$  family of proteins. This protein has antitumorigenic properties and promotes apoptosis. The expression of this protein can be upregulated using drugs such as aspirin and ibuprofen in various cancer types.<sup>43,44</sup> Sulindac sulfide is a promising non-steroidal drug that has been shown to upregulate the NAG-1 and

p21 proteins that are involved in the suppression of ovarian tumor growth.<sup>45,46</sup>

#### 4.5. Antiparasitic and antifungal drugs

Antiparasitic and antifungal drugs have also been explored for ovarian cancer treatments. The antiparasitic drug ivermectin (obtained from *Streptomyces avermitilis*) targets the Yes-associated protein 1 (YAP1). Ivermectin has been reported to exhibit antitumor effects against ovarian cancer, in which YAP1 is considered a prognostic marker.<sup>47,48</sup> High karyopherin subunit  $\beta$ 1 (KPNB1) expression is associated with earlier recurrence in EOC. A combination of ivermectin and paclitaxel showed KPNB1-dependent antitumor effects in both *in vitro* and *in vivo* studies.<sup>49</sup> The drug combination suppresses cancer growth by regulating lncRNA-EIF4A3-mRNA axes<sup>50</sup> or by inhibiting p21-activated kinase 1.<sup>49</sup> The antifungal drug itraconazole has also been explored in patients with refractory ovarian cancer.<sup>51,52</sup> In these studies, a combination of itraconazole and paclitaxel on EOC cells (SKOV3ip1 or HeyA8) (orthotopic mouse models) as well as patient-derived xenografts was used. The results of this study showed a significant reduction in tumor weight and the formation of microvessels.

#### 4.6. Antileukemia drug

Teniposide is a chemotherapy medication that is used in combination with other cancer medications to treat children with acute lymphoblastic leukemia. A recent study showed that HGSOC cell lines treated with 10  $\mu$ M teniposide showed a significant cell death and apoptosis. This result was higher and more pronounced than that observed in HGSOC cell lines treated with a clinically relevant dose of carboplatin (30  $\mu$ M), indicating the potential efficacy of this repurposed drug in treating chemo-resistant HGSOC.<sup>53</sup>

#### 4.7. Anti-neurotrophins

The upregulation of neurotrophins, such as nerve growth factor and brain-derived neurotrophic factor, which bind with tropomyosin receptor kinases (TRK), plays an important role in EOC.<sup>54</sup> Neurotrophin dysregulation is found in polycystic ovarian syndrome and EOC. The FDA-approved drugs, entrectinib (Rozlytrek) and larotrectinib (Vitrakvi), are used to treat solid tumors with TRK gene fusions in both pediatric and adult patients.<sup>55,56</sup> The second-generation drug, Loxo-195 (Selitrectinib), overcomes the acquired resistance to the first-generation of TRK inhibitors. Despite the efficacy of these drugs, further molecular and clinical investigations are required to validate the impact of anti-neurotrophins in ovarian cancer.<sup>57-60</sup>

## 5. Cancer vaccines

Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens, prompting the immune system to attack cancer cells bearing these antigens. To date, there are no FDA-approved vaccines for ovarian cancer. A few vaccine targets that are known are (i) FR $\alpha$  (protein commonly overexpressed in cancer),<sup>61-64</sup> (ii) HER2 (pathway that controls cell growth and is commonly overexpressed in cancer),<sup>65</sup> (iii) Mucin (MUC-1; sugar-coated protein that is commonly overexpressed in cancer)<sup>66</sup> (iv) P53 (tumor suppressor protein that is often mutated, non-functional, and overexpressed in cancer), (v) personalized neoantigens (these abnormal proteins arise from mutations and are expressed exclusively by tumor cells),<sup>67</sup> (vi) tumor-associated antigens (proteins often expressed at abnormally high levels on tumor cells and also found on normal cells at lower levels), (vii) Wilms' tumor 1 (protein that is often mutated and abnormally expressed in patients with cancer, especially Wilms' tumor).<sup>68,69</sup>

Despite being easy to produce and safe, nucleic acid vaccines are not currently thought to be an ideal vaccine for ovarian cancer due to various obstacles, such as difficulty in selecting the appropriate therapeutic agents, inadequate immunogenicity, and the immunosuppressive characteristic of ovarian cancer.<sup>70,71</sup> The vaccine called "ovarian vax" is currently in the early developmental stage at Oxford University for ovarian cancer. This vaccine could detect the tumor-associated antigens and provoke an immune response to control the proliferation of cancer cells. The development of a dendritic cell-based vaccine for ovarian cancer is also being conducted by the Mayo Clinic (United States of America). The underlying approach combines vaccines and checkpoint-inhibitor immunotherapy to identify and eliminate the stealth tumors that do not respond to cell therapy.<sup>72</sup>

## 6. Nanotechnology, an innovative approach

Nanotechnology plays a key role in targeted cancer therapy and diagnosis by enabling the direct interaction with cancer cells through binding to complementary surface receptors. This mechanism of action enhances drug accumulation in cancer cells and improves drug solubility, stability, and retention time in the body. For cancer diagnosis, nanoparticles are used to detect cancer biomarkers, including MUC-16, circulating tumor DNA, microRNA, and extracellular vesicles.<sup>73</sup> Nanoparticles with sizes ranging from 1 to 100 nm can be tailored to target specific cells or tissues for treatment purposes. The various types of nanoparticles developed for cancer diagnosis and treatment are illustrated in [Figure 2](#).<sup>74-81</sup>

Drug delivery systems based on nanoparticles have the potential to treat ovarian cancer and overcome drug resistance in tumors by limiting drug concentration in the systemic circulation. Nanoparticles can be modified with ligands to make them suitable for binding with different types of cell surface receptors, such as HER2, folic acid receptors, cluster of differentiation (CD)44 (also referred to as homing cell adhesion molecule), and VEGF, that are overexpressed on ovarian cancer cells, followed by internalization into the cell. The leading nanoparticle-based carriers for ovarian cancer are liposomes and polymeric micelles.

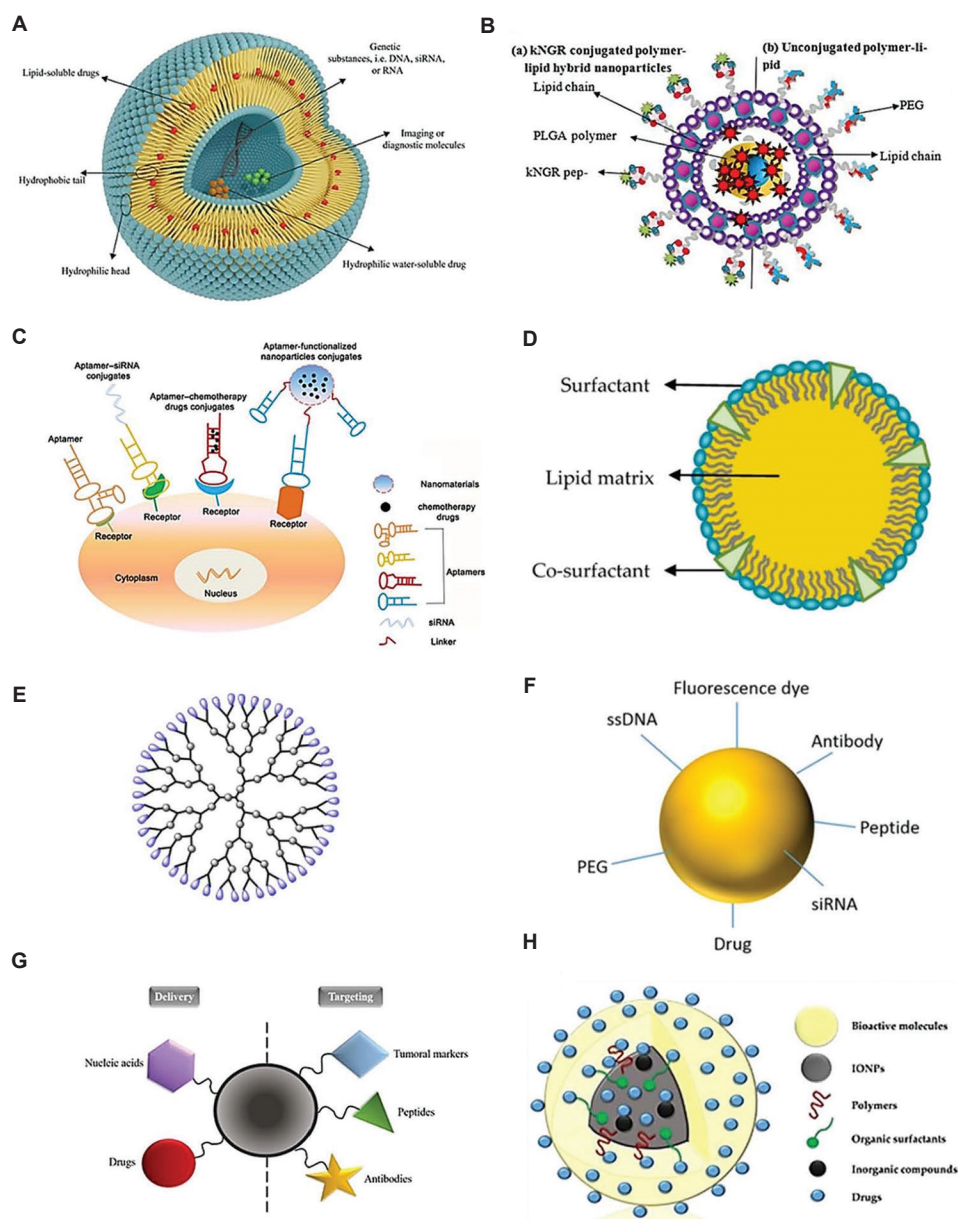
### 6.1. Liposomes

Drugs are loaded into liposomes by incorporating them either into the lipid bilayer or the aqueous core for targeted drug delivery. Polyethylene glycol (PEG)-modified liposomal doxorubicin (Caelyx in Europe and Canada; Doxil in the USA) was the first nanodrug approved by the FDA in 1995 for the treatment of ovarian cancer patients who failed the first-line platinum-based therapy.<sup>82</sup> Liposomes containing niraparib and doxorubicin evaluated in ovarian cancer cell lines (FR $\alpha$ -overexpressing and non-overexpressing) showed improved cellular uptake compared to the unconjugated liposomes. The antagonistic effect was evident in the PEO4 cell line with reverse mutation.<sup>83</sup> Plectin-targeted peptide-conjugated nanoliposomes encapsulating the PARP inhibitor AZ7379 increased inhibition, resulting in slower tumor growth and reduced tumor volumes in mice.<sup>84</sup>

Layer-by-layer polymeric liposomes coated with hyaluronic acid and containing cisplatin and the PARP inhibitor talazoparib (BMN 673) have been studied using female mouse models with ovarian cancer. The formulation targeted the overexpressed CD44 receptors on the surface of ovarian cancer cells, producing a synergistic antagonistic effect. The liposomes exhibited an extended half-life in the bloodstream, with a gradual release of the drugs.<sup>85</sup> PEGylated liposomes containing olaparib and carboplatin exhibited high efficacy and sensitivity on two ovarian cancer cell lines, A2780 (cisplatin-sensitive) and A2780 (acquired resistance to cisplatin).<sup>86,87</sup> Hybrid liposomes consisting of liposomes and exosomes to deliver triptolide and miR497 for cisplatin-resistant ovarian cancer cells were found to increase the tumor apoptosis, increase the production of reactive oxygen species, and upregulate the polarization of macrophages.<sup>88</sup>

### 6.2. Polymeric micelles and solid lipid nanoparticles

Polymeric micelles are nanocarriers with a high loading capacity of therapeutic drugs. Due to their nanoscale structure and surface properties, these materials exhibit



**Figure 2.** Various types of nanoparticles developed for cancer diagnosis and treatment. (A) Liposome. Reprinted from Rommasi and Esfandiari.<sup>74</sup> (B) Polymeric micelle. Reprinted from Gupta *et al.*<sup>75</sup> (C) Aptamer. Reprinted from Han *et al.*<sup>76</sup> (D) Solid lipid nanoparticle. Reprinted from Bayón-Cordero *et al.*<sup>77</sup> (E) Dendrimer. Reprinted with permission from Bhadran *et al.*<sup>78</sup> (F) Gold nanoparticles. Reprinted from Siddique and Chow.<sup>79</sup> (G) Silver nanoparticles. Reprinted from Gomes *et al.*<sup>80</sup> (H) Iron nanoparticles. Reprinted from Arias *et al.*<sup>81</sup> Abbreviations: IONPs: Iron oxide nanoparticles; kNGR: Lysine-asparagine-glycine-arginine peptide; PEG: Polyethylene glycol; PLGA: Poly-lactic-co-glycolic acid.

prolonged circulation in blood plasma, a property widely exploited in targeted drug delivery.<sup>89</sup> Redox-sensitive micelles loaded with paclitaxel and folate-targeted micelles loaded with docetaxel were found to be effective against the ovarian cancer cell line SKOV-3.<sup>90,91</sup> Similarly, micelles loaded with both doxorubicin and irinotecan exhibited significant uptake by ovarian cancer cells followed by

apoptosis.<sup>92</sup> Solid lipid nanoparticles have also been identified and exploited in targeted drug delivery of therapeutics in cancer treatment. These nanoparticles consist of lipids, surfactants, and chemotherapeutic agents. Light-sensitive lipid nanoparticles encapsulated with a clinically approved photosensitizer (verteporfin) were effectively internalized and caused cell death in both *in vivo*



and *in vitro* studies. The *in vivo* studies showed prolonged drug circulation and suppression of tumor growth.<sup>93</sup> Similarly, the lipid nanoparticles containing paclitaxel exhibited a significant increase in cytotoxicity against the SKOV-3 cell line compared to Taxol<sup>®</sup> and increased peritoneal retention in male Wistar rats.<sup>94</sup>

Lipid nanoparticles containing a prodrug doxorubicin showed increased apoptosis in both human ovarian cancer line A2780 wild-type and doxorubicin-resistant cells.<sup>95</sup> The role and potential impact of solid lipid nanoparticles as drug carriers were demonstrated by functionalizing the nanoparticles with platinum-13,5-triaza-7-phosphoadamantane and evaluating their effect on the A2780 cell line.<sup>96</sup> The effective suppression of ovarian cancer cell growth in xenograft mice was demonstrated by delivering a signal-transducer decoy oligodeoxynucleotide using nanoparticles as a drug delivery agent. This oligonucleotide inhibited tumor growth by activating an apoptotic cascade and reversing the epithelial-to-mesenchymal transition.

### 6.3. Aptamers and dendrimers

Aptamers have emerged as a promising theranostic platform for ovarian cancer due to their lower immunogenicity, cell internalization, and rapid tissue penetration features. An aptamer-mediated drug delivery approach was conducted using a highly water-soluble nucleolin aptamer-paclitaxel conjugate. It was found that the aptamer selectively transported and accumulated the drug paclitaxel at the ovarian cancer sites, resulting in increased antitumor activity and reduced toxicity.<sup>97</sup> The effect of the MUC-1 aptamer mir-29b chimera in xenograft tumor models has also been evaluated. The intratumoral injection of chimera significantly inhibited Ovarcar-3 tumor growth by suppressing methylation and downregulating the expression of *PTEN*, *MAPK4*, and *IGF1* genes.<sup>98</sup> The combination of aptamers with first-line treatments for EOC has been explored. The anti-nucleolin aptamer decorated with PEGylated poly(lactic-co-glycolic acid) containing cisplatin was found to bind and deliver the therapeutic to nucleolin-overexpressing ovarian cancer cells.<sup>99</sup>

Dendrimers are branched polymeric structures with tailored properties that have been exploited as targeted drug delivery systems. Dendrimers loaded with cisplatin and paclitaxel have been developed, and their impact on ovarian cancer cell lines (SKOV-3) and xenografts has been evaluated.<sup>100</sup> Fourth-generation polyurea dendrimers containing 1-buthionine sulfoximine have been studied in cancer cell lines. The study showed that the inhibitors were selectively taken up through folate receptor-mediated

mechanisms in both carcinoma-derived and clear cell carcinoma cell lines. Increased cell death was observed due to inhibition of glutathione synthesis and reduction in carboplatin resistance.<sup>101</sup>

### 6.4. Metallic and metal oxide nanoparticles

Numerous types of metallic and metal oxide nanoparticles have been extensively explored for diagnostic and targeted drug delivery applications. The most notable nanoparticles are based on metals such as silver, gold, selenium, platinum, palladium, copper, cobalt, zinc, and titanium.<sup>102,103</sup> Gold nanoparticles functionalized with cationic steroid antibiotic exhibited notable activity against ovarian cancer cells *in vitro* and inhibited the formation of ovarian tumors in mice with minimal cell damage.<sup>104</sup> Gold nanoparticles synthesized using the plant extract from *Satureja rechingeri* showed significant anticancer activity against cisplatin-resistant ovarian cancer cells (A2780CP) due to the synergistic action of the plant extract's various phytochemicals.<sup>105</sup> Composites of gold nanoparticles with docetaxel and a tripeptide exhibited a photothermal synergistic effect on human ovarian cancer cells.<sup>106</sup> Conjugating the gold nanoparticles with luteinizing hormone-releasing hormone showed (*in vitro* and *in vivo*) preferential uptake by ovarian cancer cells.<sup>107</sup> In a study, novel elongated gold nanoparticles in the shape of nanopeanuts exhibited cytotoxicity against the ovarian cancer cell line SKOV-3.<sup>108</sup> Another study by Lee *et al.*<sup>109</sup> has shown hyaluronic acid-modified dendrimer encapsulating gold nanoparticles as active targeted drug delivery nanocarriers for effective treatment of ovarian cancer. The molecular mechanisms underlying the efficacy of gold nanoparticles reveal that they downregulate insulin growth factor binding protein 2 (IGFBP2) by disrupting its autoregulation via the IGFBP2/mTOR/phosphatase and tensin homolog axis.<sup>110</sup>

Silver nanoparticles synthesized using the leaf extract of *Salvia officinalis* showed a dose-dependent cytotoxicity against human ovarian cancer cell lines, with no cytotoxicity against normal cells.<sup>111</sup> Combining silver nanoparticles with gemcitabine was found to inhibit the viability and proliferation of ovarian cancer cells.<sup>112</sup> Silver nanoparticles coated with curcumin and cisplatin exhibited upregulation of the *TP53* gene and downregulation of the *MPP9* gene, thereby promoting sensitivity to cisplatin in the cells.<sup>113,114</sup> The effect of iron nanoparticles containing folic acid, peptide growth factor, chitosan, and superparamagnetic iron oxide nanoparticles on ovarian cancer cells has been explored to investigate the mechanisms involved in internalization, apoptosis, and cellular autophagy.<sup>115-118</sup>



### 6.5. Nanoenzymes

Nanoenzymes (nanozymes) possess intrinsic enzyme-like activities and can overcome the shortcomings of naturally occurring enzymes; however, their clinical translation remains early-stage. Even though nanozymes are based on metal nanoparticles, they have several advantages, including enhanced stability, tunable catalytic activity, multifunctionality, specific enzyme-like properties, and the ability to be remotely controlled using external stimuli like magnetic fields, light, or ultrasound, offering a level of fine-tuning in biological systems that is not achievable with standard metal nanoparticles.<sup>119</sup> The nanozyme system (nanoceria), consisting of cerium oxide nanoparticles, has been shown to significantly inhibit reactive oxygen species production, attenuate growth factor signaling, and mediate cell migration. Reduced tumor growth was also observed in mice with an A2780-generated tumor.<sup>120</sup> The initial studies on conjugated nanoceria with folic acid suggest that these materials have a restorative effect on ovarian cancer cells. Despite their advantages, nanozymes have several issues (Table 4). Clinical translation of nanozymes remains challenging without resolving critical gaps: Standardized assays for reproducibility, biocompatible profiles for long-lasting safety, accurate delivery mechanisms, and synthesis aligned with regulatory requirements. Addressing these gaps will require collaborative efforts across disciplines, integrating computational design with clinical knowledge and incorporating nanozymes into systems guided by feedback.<sup>121</sup>

## 7. Future perspectives of treatment modalities for ovarian cancer

### 7.1. Sonodynamic therapy (SDT)

SDT is a novel anticancer strategy that employs low-intensity ultrasound and a drug (sonosensitizer). The sonosensitizer is activated acoustically, which results in localized cytotoxicity through the production of reactive oxygen species. The use of doxorubicin as a sonosensitizer promoted cell death in both doxorubicin-sensitive and doxorubicin-resistant human ovarian cancer cell lines.<sup>122</sup> Treatment of ovarian cancer with platinum-boron-

phosphorus nanoparticles as sonosensitizers enhanced the decomposition of hydrogen peroxide into molecular oxygen and improved the hypoxic environment of tumor cells. This study, conducted using the BALB/c-nude mouse model of ovarian cancer, showed desired effects on biodistribution, biosafety, and therapeutics.<sup>123</sup> Sonosensitizers based on PEGylated zinc protoporphyrin,<sup>124</sup> graphene nanoribbons functionalized with 4-arm PEG, barium titanate,<sup>125,126</sup> and iron oxide have been developed as potential materials for SDT in ovarian cancer. These materials were well absorbed by metastatic ovarian cancer spheroids and disrupted their adhesion to extracellular proteins and mesothelial cells. The sonodynamic magnetic nanorobot containing iron oxide nanoparticles, when regulated using a magnetic field and low-intensity ultrasound, enabled material navigation to target cells, inducing apoptosis.<sup>127</sup> Despite the advantages, there are translational barriers to SDT. The main barrier is the removal of reactive oxygen species produced by tumor cells' antioxidant systems. Other barriers include the complex TME, such as severe hypoxia and an immunosuppressive microenvironment. The long-term safety and toxicity of SDT-based nanomedicines *in vivo* have consistently been a significant concern in this area. At present, studies on the metabolism and long-term toxicity of these SDT-based nanomedicines are primarily limited to 1 month or less, necessitating additional investigation into their long-term toxicity and metabolic pathways *in vivo*. Consequently, investigating nano sonosensitizers that exhibit excellent biocompatibility, biodegradability, and efficient *in vivo* clearance through advanced nanoengineering methods is highly advantageous for the clinical application of SDT-based therapy.

### 7.2. Gas plasma therapy

The helium gas plasma device (J-Plasma) has recently been introduced in the surgical treatment of patients with advanced ovarian cancer. This technology enables complete or nearly complete cytorreduction rates.<sup>128,129</sup> The effect of plasma radiation on tumor cells has been studied using SKOV-3 cell lines, and morphological changes to the cells have been observed. However, there are several translational barriers to gas plasma therapy. The primary

**Table 4. Current barriers and strategic solutions for translating nanozymes to clinical use. Table reproduced from Austine *et al.*<sup>119</sup>**

Barrier	Challenge	Strategic solution
Lack of standardized assays	Irreproducible catalytic performance metrics	Universal benchmarking protocols (e.g., ISO-like standards)
Long-term biosafety	Poorly characterized toxicity or clearance	Biodegradable carriers, multi-omics toxicity profiling
Scale-up manufacturing	Reproducibility and GMP incompatibility	Modular synthesis routes; cross-lab validation
Regulatory approval	No clear FDA pathways	Precedent from approved nanocarrier: engage with the regulators

Abbreviations: FDA: Food and Drug Administration; GMP: Good manufacturing practice; ISO: International Organization for Standardization.

concern is its delivery modes. Since direct application of gas plasma is effective at short ranges, it may not be helpful when access to tumors is difficult. The use of gas plasma during surgery may face its own limitations, as the necessary duration to deliver an adequate dose could be impractical in the surgical setting. For intraoperative treatments that are clinically compatible and involve a potentially high dose in a single opportunity, gas plasma devices must feature a high dose rate, which may necessitate redesign.

To translate gas plasma medicine into clinical use for cancer treatment, it is essential to develop safe and effective treatment protocols and supporting technologies. For this purpose, scientists and clinicians must work together to design clinical trials with endpoints that can identify and measure the advantages and disadvantages of gas plasma therapies. Although delivering gas plasma therapy to some anatomical sites may initially appear challenging, different clinical scenarios may warrant distinct delivery approaches. For instance, the area where the tumor was removed can be directly treated with cold gas plasma. A benefit of gas plasma in cancer treatment is its ability to be used both directly and through gas plasma-activated solutions.<sup>130</sup>

### 7.3. Adoptive T-cell therapy

Tumor-infiltrating lymphocytes, especially T cells, are associated with improved outcomes in patients with ovarian cancer. Adoptive cell therapy involves the infusion of *ex vivo* expanded or engineered T cells to enhance antitumor immunity and represents a potential treatment option for ovarian cancer. Chimeric antigen receptor therapy targeting mesothelin tumor-associated antigen is currently in Phase 1 and Phase 2 clinical trials.<sup>131</sup> The well-known biomarker of ovarian cancer, CA-125 antigen (MUC-16, a transmembrane glycoprotein), has been considered in cell therapy. The combination of folate receptors and tumor-infiltrating lymphocytes with platinum-based chemotherapy has been reported to be safe and increase PFS.<sup>132</sup> However, more in-depth fundamental research is required to fully evaluate T-cell therapy as a potential treatment for ovarian cancer.

### 7.4. Long non-coding RNAs (lncRNAs)

lncRNAs have emerged as key regulators in cancer biology, influencing cellular processes, such as proliferation, apoptosis, and chemoresistance. The differential expression of lncRNAs in cancer cells compared to normal cells makes them potential biomarkers for ovarian cancer. For example, the lncRNA LOXL1-AS1 shows heightened expression in EOC patients and is associated with poor patient survival, especially in advanced cancer stages. In addition, the overexpression of the lncRNA XIST in 98 EOC patient tissue samples supports its role as a diagnostic biomarker

in ovarian cancer. Furthermore, the pro-tumorigenic role of XIST was validated in the OV90, OVCAR3, SKOV-3, and A2780 ovarian cancer cell lines. In another study, Gene Set Enrichment Analysis data from the GSE10971, GSE29450, and GSE54388 datasets were analyzed, and a panel of four lncRNAs, LINC00511, LINC01132, RP11-83A24.2, and MIR762AG, was found to be highly expressed in ovarian cancer patients and was correlated with low survival using Cox regression analysis. Further intensive study of LINC00511 revealed that it interacts with the enhancer of Zeste homolog 2 and mediates the H3K27me3 modification of the *CDKN1A* promoter, an essential regulator. The exploration of lncRNAs as diagnostic biomarkers is ongoing, with continuous research unraveling new biomarkers and their roles in disease progression. The use of lncRNAs as biomarkers holds great promise for early detection and personalized therapy in ovarian cancer.<sup>133</sup>

### 7.5. Serum trace elements

Monitoring serum levels of elements can be a helpful diagnostic tool in the prevention and early detection of numerous neoplastic diseases. Copper forms complexes with gonadoliberein and increases the secretion of follicle-stimulating hormone and luteinizing hormone, which may contribute to the development of ovarian cancer. Different studies have shown that lower copper and zinc levels in serum are found in ovarian cancer patients compared to healthy individuals. Varied serum levels of microelements, such as magnesium, cadmium, and iron, were observed among ovarian cancer patients at different stages of treatment. Further research and trials are needed to develop these microelements as effective diagnostic tools.<sup>134</sup>

## 8. Conclusion

The treatment modalities of ovarian cancer are rapidly evolving with the new development of various types of inhibitors, bispecific antibodies, and functionalized nanoparticles. The expansion of the therapeutic toolbox for ovarian cancer now encompasses multiple types of functional materials, new diagnostic tools, and therapies targeting unique cancer-associated markers and pathways. This development allows patients to be stratified by tumor profiles and directed toward individualized, targeted therapies. Furthermore, it is crucial to obtain additional data on the impact of combination treatment modalities, as this strategy holds promise for enhancing treatment effectiveness and overcoming drug resistance. The introduction of innovative strategies in drug development and the rapid progress of medical research are expected to lead to improved treatments and survival rates for patients with ovarian cancer.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

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