JAMA Oncology | Review

Advances in Ovarian Cancer Care and Unmet Treatment Needs for Patients With Platinum Resistance
A Narrative Review

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IMPORTANCE Platinum-based chemotherapy has been the standard of care for ovarian cancer for the past 3 decades. Although most patients respond to platinum-based treatment, emergence of platinum resistance in recurrent ovarian cancer is inevitable during the disease course. Outcomes for patients with platinum-resistant ovarian cancer are poor, and options remain limited, highlighting a substantial unmet need for new treatment options.

OBSERVATIONS This review summarizes the current and evolving treatment landscape for platinum-resistant ovarian cancer with a focus on the development of novel compounds. Biologic and targeted therapies such as bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors—originally approved in the platinum-resistant setting but since withdrawn—are now used in the up-front or platinum-sensitive setting, prolonging the duration of platinum sensitivity and delaying the use of nonplatinum options. The greater use of maintenance therapy and the emphasis on using platinum beyond first-line treatment has most likely been associated with a greater number of lines of platinum therapy before a patient is designated as having platinum-resistant ovarian cancer. In this contemporary setting, recent trials in platinum-resistant ovarian cancer have mostly had negative outcomes, with none having a clinically significant effect on progression-free or overall survival since the approval of bevacizumab in combination with chemotherapy. Nonetheless, a multitude of new therapies are under evaluation; preliminary results are encouraging. A focus on biomarker-directed treatment and patient selection may provide greater success in identifying novel therapies for treating platinum-resistant ovarian cancer.

CONCLUSIONS AND RELEVANCE Although many clinical trials in platinum-resistant ovarian cancer have had negative outcomes, these failures provide insights into how clinical trial design, biomarker-directed therapy, and patient selection could facilitate future successes in platinum-resistant ovarian cancer treatment.

JAMA Oncol. doi:10.1001/jamaoncol.2023.0197
Published online April 20, 2023.

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Ovarian cancer is the third most common and the most lethal gynecologic malignant neoplasm worldwide, with 313 959 new diagnoses and 207 252 deaths globally in 2020 and an estimated 19 880 new diagnoses and 12 810 deaths in the US in 2022.[1-3] Epithelial ovarian cancer is the most common subtype of ovarian cancer, which can be divided into high grade-serous ovarian cancer (HGSOC), endometrioid carcinomas, clear-cell carcinomas, mucinous carcinomas, and low-grade serous carcinomas. Of these, HGSOC is the most common and has been shown to be associated with 70% to 80% of deaths among patients with ovarian cancer[4,5] with an average 5-year survival of less than 50% and a median overall survival (OS) of 40.7 months (mo).[3,6,7]

During the past decade, both the incidence of new diagnoses and the death rate for ovarian cancer have steadily declined and the prevalence of patients living with the disease has increased.[3] The backbone of first-line treatment has changed little in the past 3 decades, with the use of platinum-based chemotherapy plus paclitaxel being the primary treatment option for HGSOC since the mid-1990s. However, recent guidance on maintenance therapy has evolved to include poly (ADP-ribose) polymerase (PARP) inhibitors and/or the antiangiogenic agent, bevacizumab.[8] Use of maintenance therapy in the platinum-sensitive setting has been steadily increasing in the US and Europe[9,10]; it has likely positively affected survival outcomes for patients with platinum-sensitive ovarian cancer[11,12] and possibly contributed to the steady decline in the annual death rate. These increases in prevalence and survival require adjustments to the treatment strategy for long-term care, especially when the ovarian cancer becomes platinum resistant.

Ovarian cancer has a reported response rate of 75% to 80% with frontline therapy.[13] However, 70% of tumors will recur and eventually become platinum resistant, typically defined as disease relapse within 6 mo after the last dose of a platinum-based therapy.[14] Moreover, approximately 20% of patients have no response to frontline platinum-based treatment and are considered primary platinum refractory, defined as progression within 4 weeks of the last dose of platinum-based chemotherapy.[8,15]

Unfortunately, the determination of platinum resistance still relies on a progression-free interval following platinum-based therapy. Although a validated method for predicting platinum resistance is still lacking, several disease features have been associated with platinum resistance or platinum-free interval (PFI), including higher functional score for homologous recombination repair, lack of *BRCA 1/2* variation, amplification of *CCEN1* gene, higher rate of CA-125 elimination, higher number of circulating tumor cells, lower number of tumor-infiltrating lymphocytes, and defined gene signatures (detailed by You and colleagues[16]). Several mechanisms of platinum resistance have been proposed, including alteration of drug efflux, sequestration of platinum by intracellular proteins, repair of platinum-induced DNA damage, and alterations in expression of survival proteins.[17-19] Ultimately, mechanisms of platinum resistance are heterogenous and unclear. Resistance to platinum-based therapy remains the leading cause of mortality in advanced ovarian cancer, with limited treatment options and a lack of guidance on treatment sequencing in the platinum-resistant setting.[14]

Currently, the standard treatment for platinum-resistant ovarian cancer (PROC) is sequential single-agent nonplatinum chemotherapy or enrollment in a clinical trial. Nonplatinum chemotherapy has been associated with low objective response rates (ORRs, <12%), short progression-free survival (PFS, <4 mo) and OS (<12 mo),[8,20-22] and significant adverse effects such as neutropenia, alopecia, neuropathy, and palmar-plantar erythrodysesthesia, which can impair quality of life (QOL).[8,23]

Considering that the currently available therapies have limited efficacy and substantially affect QOL, an important need exists for new treatment options for patients with PROC. The purpose of this review was to discuss the current treatment landscape of ovarian cancer and promising therapeutic options for addressing the imperative and unmet needs of patients with PROC.

Evolution of PROC Treatment and Recent Developments

The antiangiogenic agent bevacizumab was approved in the US and Europe in 2014 as the first noncytotoxic therapy for PROC. The pivotal AURELIA[20] trial evaluated bevacizumab with vs without single-agent chemotherapy in patients with PROC. Notably, AURELIA excluded patients who had received more than 2 systemic therapies. Most patients (58%) in the trial received 1 prior line of therapy, which aligned with clinical practice at the time that the study was conducted, and only 7% to 8% of enrolled patients received prior antiangiogenic therapy (**Table 1**).[20] After a median follow-up of approximately 14 mo, bevacizumab plus chemotherapy was associated with an ORR of 30.9% (vs 12.6% with chemotherapy) and met its primary end point with a median PFS of 6.7 mo (vs 3.4 mo).

Although the findings of the primary analysis did not demonstrate improved OS with the addition of bevacizumab, a post hoc analysis of AURELIA suggested that survival assessments were confounded by postprogression crossover use of bevacizumab among patients in the chemotherapy group. This study revealed a 32% to 40% decrease in the risk of death associated with receiving bevacizumab plus chemotherapy or bevacizumab following progression vs never receiving bevacizumab.[27] An additional post hoc analysis suggested that weekly paclitaxel with bevacizumab was associated with improved PFS and ORR vs weekly topotecan or pegylated liposomal doxorubicin (PLD) with bevacizumab.[28] Treatment effect on OS in the paclitaxel cohort was also more pronounced (unadjusted hazard ratio, 0.65; 95% CI, 0.42-1.02; median 22.4 vs 13.2 mo).

Despite this success, bevacizumab has been associated with treatment-related adverse events, including hypertension, proteinuria, hemorrhage, thrombosis, and bowel perforation, which preclude its use in some patients.[29] Bevacizumab-induced bowel perforation can occur in 9% to 11% of patients with recurrent ovarian cancer.[29,30] Moreover, because bevacizumab is recommended in frontline induction and maintenance in platinum-sensitive ovarian cancer,[8] most patients will have already received bevacizumab by the time they develop PROC.[10] Evidence to date indicates that previous bevacizumab treatment is unlikely to influence outcomes with subsequent treatment, suggesting that bevacizumab retreatment likely remains an option in patients with PROC.[11,31]

Initially, PARP inhibitors were approved for use in PROC based on acceptable response rates (33%-41%),[32-35] primarily in subsets of patients with *BRCA* variation and/or homologous recombination deficiency. However, recent post hoc analyses (with clear limitations) suggested a potential OS detriment in patients with recurrent ovarian cancer who received PARP inhibitor monotherapy vs chemotherapy based on the SOLO3[36] (median OS, 29.9 vs 39.4 mo in patients with ≥3 prior lines of therapy) and ARIEL4[37] (median OS, 19.4 vs 25.4 mo in patients with ≥2 prior lines of therapy) studies. This prompted voluntary withdrawals of olaparib, rucaparib, and niraparib monotherapy treatment indications for recurrent ovarian cancer beyond second line.[38,39] In all, the recent withdrawals of PARP inhibitors treatment indications in the recurrent setting as well as the greater success and incorporation of PARP inhibitors into frontline maintenance treatment further limits options for patients with PROC and underscores the high unmet medical need in this setting.

Cytoreductive surgery is often included in frontline treatment of ovarian cancer and has been associated with significant survival benefit,[40] particularly in patients with primary platinum resistance who may derive less benefit from platinum-based chemotherapy.[16] Secondary cytoreductive surgery (SCS) in the recurrent setting has only been prospectively evaluated in platinum-sensitive ovarian cancer, where clear criteria have been developed.[41] However, in patients with PROC, SCS has not been well-studied; to our knowledge, there are no available prospective trials and few retrospective studies. A prospective phase 3 trial of SCS in PROC was planned and ultimately withdrawn owing to poor patient accrual. However, HIPOVA-01, a prospective phase 3 trial to evaluate SCS with intraperitoneal hyperthermic chemotherapy is underway in patients with PROC (National Clinical Trial [NCT] Identifier, NCT03220932). Considering the lack of prospective evidence, SCS is currently recommended only in patients with platinum-sensitive ovarian cancer.[41]

Unsuccessful Trials in PROC

Unfortunately, many subsequent novel therapies have not been associated with improved clinical outcomes in PROC (Table 1).[20-22,24-26] Despite the success of bevacizumab, alternate antiangiogenic therapies (eg, cediranib, ofranergene obadenovec [ofra-vec]) have either failed to improve outcomes or have been withdrawn from de-

Table 1. Recent Phase 3 Randomized Clinical Trials (RCTs) by Mechanism of Action in Platinum-Resistant Ovarian Cancer, 2009 to 2018

Trial details	Mechanism	Patient characteristics	Efficacy outcome
AURELIA,[20] bevacizumab (Bev) plus chemotherapy vs chemotherapy alone (Pac/Topo/PLD)			
361 Patients enrolled in October 2009-April 2011	Antiangiogenesis	Median (range) age, y: 61 (25-84) vs 62 (25-80) 2 prior lines of chemotherapy: 43% vs 40% Prior antiangiogenic therapy: 8% vs 7% PFI <3 mo: 25% vs 28%	Median follow-up, mo: 13.0 vs 13.9 ORR, 30.9% vs 12.6% Chemotherapy subgroup ORRs: Bev-Pac vs Pac: 53.3% vs 30.2%; Bev-Topo vs Topo: 17.0% vs 0%; Bev-PLD vs PLD: 13.7% vs 7.8% mPFS (95% CI), mo: 6.7 (5.7-7.9) vs 3.4 (2.2-3.7) mOS (95% CI), mo: 16.6 (13.7-19.0) vs 13.3 (11.9-16.4)
JAVELIN Ovarian 200,[24] avelumab alone vs avelumab with chemotherapy (PLD) vs chemotherapy alone			
566 Patients enrolled in January 2016-May 2017	Immunotherapy	Median (IQR), age y: 60 (53-67) vs 60 (53-69) vs 61 (53-70) Prior lines of anticancer therapy: 1, 48% vs 48% vs 48%; 2-3, 52% vs 52% vs 52% Prior Bev: 26% vs 28% vs 34%	Median follow-up, mo: 18.4 vs 17.4 vs 18.2 ORR, 13% vs 4% vs 4% mPFS (95% CI), mo: 3.7 (3.3-5.1) vs 3.5 (2.1-4.0) vs 1.9 (1.8-1.9) mOS (95% CI), mo: 15.7 (12.7-18.7) vs 13.1 (11.8-15.5) vs 11.8 (8.9-14.1)
NINJA,[25] nivolumab vs gemcitabine (Gem) or PLD			
316 Patients enrolled in October 2015-July 2016, and March 2017-December 2017	Immunotherapy	Median (range) age, y: 58 (29-84) vs 60 (34-80) Prior lines of chemotherapy: 1, 24% vs 20%; 2, 42% vs 41%; 3, 19% vs 22%; ≥4, 15% vs 17% 1 prior chemotherapy regimen after platinum resistance diagnosis: 28.0% vs 34.6%	Median follow-up: not reported ORR, 7.6% vs 13.2% mPFS (95% CI), mo: 2.0 (1.9-2.2) vs 3.8 (3.6-4.2) mOS (95% CI), mo: 10.1 (8.3-14.1) vs 12.1 (9.3-15.3)
FORWARD-1,[22] mirvetuximab soravtansine (MS) vs chemotherapy (PLD/Pac/Topo)			
366 Patients enrolled in January 2017 and April 2018	ADC	Median (range) age, y: 64 (34-89) vs 64 (31-86) Prior lines of systemic therapy: 1-2, 64% vs 63%; 3, 35% vs 36% Prior Bev: 49% vs 47% Prior PARPi: 18% vs 16%	Median follow-up, mo: 12.5 vs 12.5 ORR, 22% vs 12% mPFS, mo: 4.1 vs 4.4 mOS, mo: 17.3 vs 12.0
PENELOPE,[26] pertuzumab plus chemotherapy vs chemotherapy (Gem/Pac/Topo)			
156 Patients enrolled in October 2013-September 2014	ERBB2 (HER2) receptor inhibitor	Median (range) age, y: 65 (32-79) vs 64 (26-80) Prior lines of chemotherapy: 2, 49% vs 62%; 3, 3% vs 0%; 4, 1% vs 0% Prior Bev: 24% vs 29% PFI <3: 24% vs 27%; 3-6, 76% vs 73%	Median follow-up, mo: 10.3 vs 10.1 ORR, 13.1% vs 8.7% Chemotherapy subgroup ORRs: pertuzumab-Gem vs Gem: 5.3% vs 0%; pertuzumab-Topo vs Topo: 4.5% vs 0%; pertuzumab-Pac vs Pac: 30.0% vs 24.0% mPFS (95% CI), mo: 4.3 (3.7-6.0) vs 2.6 (2.1-4.3) mOS (95% CI), mo: 10.3 (6.7-NR) vs 7.9 (6.1-12.0)
CORAIL,[21] lurbinectedin vs PLD/Topo			
442 Patients enrolled in June 2015-October 2018	DNA RNA synthesis binder	Median (range) age, y: 63 (25-85) vs 59 (28-87) Prior lines of chemotherapy: 1-2, 77% vs 76%; 3, 23% vs 24% Prior Bev: 40% vs 46% Prior PARPi: 5% vs 4%	Median follow-up, mo: 25.6 overall ORR, 15% vs 13% Chemotherapy subgroup ORRs: lurbinectedin vs PLD: 14.5% vs 14.2%; lurbinectedin vs Topo: 14.5% vs 10.6% mPFS (95% CI), mo: 3.5 (2.1-3.7) vs 3.6 (2.7-3.8) mOS (95% CI), mo: 11.4 (9.0-14.2) vs 10.9 (9.3-12.5)

Abbreviations: ADC, antibody-drug conjugate; Bev, bevacizumab; ERBB2, erb-b2 receptor tyrosine kinase 2 (formerly HER2); Gem, gemcitabine; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; Pac, paclitaxel; PARPi, poly (ADP ribose) polymerase inhibitor; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

velopment. Ofra-vec, an antiangiogenic and antitumor response gene therapeutic agent, was assessed in combination with weekly paclitaxel in the phase 3 OVAL trial[42] and did not show any significant improvement in PFS (5.3 vs 5.4 mo) or OS (13.4 vs 13.1 mo) vs weekly paclitaxel. Although these results were preliminarily shared, the formal presentation of the trial data will help clarify the efficacy signal seen in the weekly paclitaxel control group.

Lurbinectedin, a DNA RNA synthesis binder, also did not have a clinical advantage vs chemotherapy in a randomized clinical trial (RCT). Lurbinectedin inhibits oncogenic transcription, and its activity is enhanced in cancer cells that are proficient in nucleotide excision repair, which are typically more resistant to platinum.[43,44] The phase 3 CORAIL trial[21] was conducted on the basis of promising preclinical evidence and encouraging efficacy findings with lurbinectedin vs topotecan in a phase 2 RCT.[45] Unfortunately, neither median PFS (3.5 vs 3.6 mo) nor median OS (11.4 vs 10.9 mo) showed improvement with lurbinectedin vs topotecan or PLD.[21] Compared with the more successful phase 2 RCT[45] on which it was based, the CORAIL patient population was older, more heavily pretreated, and had a higher proportion of patients who did not experience a response or whose cancer progressed shortly after prior platinum-based therapy.[21]

Immunotherapies, although efficacious in treatment of many other solid malignant neoplasms, have shown less promise in ovarian cancer to date. The JAVELIN Ovarian 200 RCT[24] evaluated the pro-

grammed cell death-ligand 1 (PD-L1) inhibitor, avelumab, either as a monotherapy or in combination with PLD in patients with platinum-resistant or platinum-refractory ovarian cancer and did not demonstrate improved PFS when avelumab was combined with PLD (median 3.7 vs 3.5 mo) or OS (median 15.7 vs 13.1 mo) vs PLD alone. Avelumab monotherapy led to poorer PFS (median 1.9 mo) and OS (median 11.8 mo) vs either of the PLD-receiving groups.[24] The programmed cell death protein 1 inhibitor, nivolumab, had similarly disappointing results when tested as a monotherapy, with no improvement in PFS (median 2.0 vs 3.8 mo) or OS (median 10.1 vs 12.1 mo) vs gemcitabine or PLD in the NINJA trial.[25] The NRG GY009 trial (NCT02839707) is currently evaluating PLD with atezolizumab and/or bevacizumab in patients with PROC, with results expected in 2023.

Evolving Definition of Platinum Resistance

The classic definition of platinum resistance, *disease progression within 6 months of completing a platinum-based regimen*, is commonly used as an enrollment criterion for clinical trials and regulatory approvals. However, it is difficult to adapt this dichotomous definition to clinical practice because platinum-based combinations have shown modest response rates in patients who were considered to be platinum resistant per this definition. In a phase 2 RCT,[46] the ORR for cisplatin plus gemcitabine in patients with PROC was 57%, with 3 of 14 patients reaching a complete response. Accordingly, the European Society for Medical Oncology guidelines[8] now recommend the use of platinum-based therapies until platinum is no longer appropriate. Additionally, during the past decade, the Gynecologic Cancer InterGroup[47] has recommended replacing the binary terminology for platinum-resistant and platinum-sensitive ovarian cancer with PFI, defined as the time since the last dosage of platinum-based therapy. Longer PFI has been associated with increased response to platinum-based therapy, although PFI has been shown to decrease with each line of therapy.[8] Further categorization of time following previous therapy as treatment-free intervals (TFI) has been suggested, including TFI from last platinum-based therapy, TFI from last nonplatinum-based therapy, and TFI from last biologic agent[15] Ultimately, the use of maintenance treatments, which prolong clinical benefit to platinum-based lines of therapy, and the evolving definition of platinum resistance has shifted the characteristics of patients with PROC toward a population that is later in the disease course and more heavily pretreated. Additionally, in this contemporary treatment landscape, prior exposure to PARP inhibitor maintenance therapy may compromise responses to subsequent platinum-based treatment strategies and may affect disease biology in a manner that is, to date, not clearly understood.[48] Unfortunately, clear evaluation of characteristics defining patients with PROC, as well as epidemiologic trends in PROC over time, represent a current knowledge gap that requires assessment.

Many of the recent trials of PROC[20-22,24-26] included patients with up to 3 prior lines of therapy, and most patients in these trials received 1 to 2 prior lines of therapy (Table 1). In the chemotherapy control groups of these trials, response rates ranged from 4% to 13%, and median PFS ranged from 3.4 to 4.1 mo. Considering these poor outcomes, it is critical to develop novel therapeutic options and identify biomarker-directed strategies to personalize treatment for patients who are most likely to benefit.

Future Therapeutic Strategies in PROC

Novel regimens with a multitude of mechanisms of action are currently being assessed as possible therapeutic options for PROC. There are several notable trials under way (**Table 2**).

Antibody Drug Conjugates

Antibody drug conjugates (ADCs) are an emerging class of drugs for treatment of ovarian cancer that are of particular interest because of the ability to identify biomarker-defined patient subgroups that have a higher probability of treatment response. Given that ADCs use monoclonal antibodies coupled to a payload, they deliver a potent cytotoxic agent specifically to tumor cells. This optimized targeted delivery could result in an expanded therapeutic index compared with conventional chemotherapeutics.[49] Moreover, the structure of ADCs, containing an antibody, linker, and drug portion, offers opportunities to innovate by optimizing each component to enhance efficacy while reducing toxic effects.[50]

Several ADCs targeting various biomarkers are being assessed for patients with PROC. In November 2022, mirvetuximab soravtansine, an ADC that targets folate receptor α (FRα), was approved by the US Food and Drug Administration for use in patients with PROC who are FRα-positive and have received 1 to 3 prior therapies. Mirvetuximab soravtansine comprises an anti-FRα antibody joined to the microtubule toxin DM4 via a cleavable linker.[22] Owing to its differential expression on ovarian cancer cells vs healthy tissue, FRα represents a promising therapeutic target.[51] The phase 3 FORWARD-1 RCT evaluated mirvetuximab soravtansine vs chemotherapy in patients with FRα-positive PROC.[22] Median PFS was not improved with mirvetuximab soravtansine vs chemotherapy (4.1 vs 4.4 mo) in all patients; however, a trend was observed toward increased PFS with mirvetuximab soravtansine vs chemotherapy in patients defined as having high expression of FRα (4.8 vs 3.3 mo). Hazard ratios for efficacy outcomes consistently favored mirvetuximab soravtansine in those with high FRα expression.[22] The lack of statistical significance in patients with high FRα was posited to be associated with unreliable methods of determining FRα status; ie, the study methods allowed for patients with lower-than-expected levels of FRα to be included in the high FRα group.[22]

The approval of mirvetuximab soravtansine was based on the single-group phase 3 SORAYA RCT[52] in patients with PROC with high expression of FRα (immunohistochemical proportion score ≥2). In SORAYA, mirvetuximab soravtansine achieved an ORR of 32% (5% complete response rate) and PFS of 4.3 mo. Adverse effects (all grades) included blurred vision (41%), keratopathy (29%), diarrhea (22%), neutropenia (13%), and peripheral neuropathy (12%). The most common treatment-related adverse effects of grade 3 or higher included keratopathy (9%), blurred vision (6%), dry eye (2%), and diarrhea (2%). The MIRASOL confirmatory phase 3 RCT (NCT04209855) is currently under way to evaluate mirvetuximab soravtansine in patients with high FRα-expressing PROC. Two other FRα-targeting ADCs are also currently being explored for PROC: STRO-002 (NCT03748186) and MORAb-202 (NCT03386942).

Another ADC being developed for PROC treatment is upifitamab rilsodotin (UpRi), an ADC that targets the sodium-dependent transporter NaPi2b, which is broadly expressed in ovarian cancer and limited in healthy tissue. Immunohistochemical analysis has esti-

Table 2. Key Ongoing Trials of Therapeutic Agents and Mechanism of Action for Platinum-Resistant Ovarian Cancer, 2023

Therapeutic agent	Mechanism	Registration identifier	Phase	Description
Anetumab ravtansine	ADC	NCT03587311	2	Anetumab ravtansine + bevacizumab vs paclitaxel + bevacizumab
Mirvetuximab soravtansine	ADC	NCT04209855	3	MIRASOL: MS vs investigator's choice chemotherapy in patients with high FRα
Mirvetuximab soravtansine	ADC	NCT02606305	1/2	MS + bevacizumab vs MS + carboplatin vs MS + PLD vs MS + pembrolizumab vs MS + bevacizumab + carboplatin
Upifitamab rilsodotin	ADC	NCT03319628	1/2	UPLIFT: upifitamab rilsodotin dose escalation, dose expansion, and pivotal cohort
Afuresertib	AKT inhibitor	NCT04374630	2	PROFECTA-II: afuresertib + paclitaxel vs afuresertib + carboplatin
BD0801	Antiangiogenic	NCT04908787	3	BD0801 + chemotherapy vs chemotherapy
Bevacizumab	Antiangiogenic	NCT03632798	3	Bevacizumab + chemotherapy ± chemosensitivity testing
Bevacizumab	Antiangiogenic	jRCTs031180244	2	JGOG3023: SOC ± bevacizumab
Chiauranib	Antiangiogenic	NCT04921527	3	CHIPRO: chiauranib + weekly paclitaxel vs weekly paclitaxel
Relacorilant	Antiglucocorticoid	NCT05257408	3	ROSELLA: relacorilant ± nab-paclitaxel
Adavosertib	ATR/WEE1 inhibitor, PARPi	NCT03579316	2	Adavosertib ± olaparib
ZN-c3	ATR/WEE1 inhibitor, PARPi	NCT05198804	1/2	ZN-c3 + niraparib
Batiraxcept	AXL inhibitor	NCT04729608	2/3	AXLerate-OC: batiraxcept + paclitaxel vs paclitaxel
Decitabine	Chemotherapy	NCT03467178	2	Decitabine + carboplatin vs physician's choice chemotherapy
APX005M	Immunotherapy	NCT05201001	2	APX005M ± radiation therapy in *BRCA*wt vs SOC
Doxorubicin	Immunotherapy	NCT02839707	2/3	PLD + atezolizumab and/or bevacizumab
Nemvaleukin alfa	Immunotherapy	NCT05092360	3	ARTISTRY-7: nemvaleukin α + pembrolizumab vs investigator's choice chemotherapy
Pembrolizumab	Immunotherapy	NCT05116189	3	KEYNOTE-B96: (pembrolizumab + paclitaxel vs paclitaxel) ± bevacizumab
TQB2450	Immunotherapy	NCT05145218	3	TQB2450 + anlotinib vs paclitaxel
VTX-2337	Immunotherapy	NCT01666444	2	VTX-2337 + PLD vs PLD
Durvalumab, olaparib, and cediranib	Immunotherapy, antiangiogenic, PARPi	NCT04739800	2	Paclitaxel + doxorubicin + topotecan vs durvalumab + cediranib + olaparib vs durvalumab + cediranib vs cediranib + olaparib
Cediranib, olaparib	PARPi	NCT02502266	2/3	Cediranib + olaparib vs cediranib vs olaparib vs chemotherapy
Fluzuloparib	PARPi	NCT05170594	2	Fluzuloparib + bevacizumab + chemotherapy vs fluzuloparib
Niraparib-TSR 042 (dostarlimab)	PARPi, immunotherapy	NCT04679064	3	Niraparib-TSR 042 vs TSR 042 vs physician's choice chemotherapy
Copanlisib	PARPi, PI3Ki	NCT05295589	2	Copanlisib + olaparib vs standard chemotherapy
Alpelisib	PI3Ki	NCT04729387	3	EPIK-O: alpelisib + olaparib vs single-agent chemo in *BRCA*wt
Tumor treatment field	Tumor treatment field	NCT03940196	3	INNOVATE-3: tumor treatment fields + weekly paclitaxel vs SOC
MC1365	Vaccine	NCT02364713	2	MC1365 vs physician's choice chemotherapy
Olvimulogene nanivacirepvec	Vaccine	NCT05281471	3	Olvi-vec followed by platinum-doublet + bevacizumab vs chemotherapy + bevacizumab

Abbreviations: ADC, antibody drug conjugate; ATR, ataxia telangiectasia and Rad3-related; *BRCA*wt, breast cancer susceptibility gene–wild type; FRα, folate receptor α; MS, mirvetuximab soravtansine; olvi-vec, olvimulogene nanivacirepvec; PARPi, poly (ADP ribose) polymerase inhibitor; PI3Ki, phosphatidylinositol-3-kinase inhibitor; PLD, pegylated liposomal doxorubicin; SOC, standard of care.

mated that approximately two-thirds of patients with HGSOC have high expression of NaPi2b.[53] A phase 1b RCT[54] evaluated UpRi in patients with HGSOC and either 1 to 3 prior lines of therapy in the platinum-resistant setting or up to 4 prior lines of therapy regardless of platinum status. The interim analysis of the expansion cohort found that UpRi was associated with an ORR of 34% and a duration of response of 5 mo in patients who were NaPi2b-positive—defined as having a tumor proportion score of 75 or greater. The most common adverse effects (all grades) included fatigue (79%), nausea (59%), increased transient aspartate aminotransferase (AST; 38%), and pyrexia (34%). The most common adverse effects of grade 3 or higher included transient AST increase (21%), transient thrombocytopenia (14%), and fatigue (10%) and did not include ocular toxic effects, neutropenia, or peripheral neuropathy. An ongoing phase 2 registrational trial, UPLIFT, is evaluating UpRi monotherapy in patients with PROC who have had up to 4 prior lines of therapy (NCT03319628).

Replication Stress Inhibitors

Replication stress is a targetable vulnerability in cancer cells owing to their mitotic rate as well as the loss of normal machinery to repair or prevent errors in DNA replication.[55] Ataxia telangiectasia and Rad3-related protein (ATR) and WEE1 are major regulators of the cellular DNA damage response and are commonly upregulated by cancer cells to increase tolerance for replication stress.[56] Small-molecule inhibition of ATR or WEE1 sensitizes cells to chemotherapeutic agents, which increase replication stress.[56] Berzosertib, a first-in-class ATR inhibitor, was recently tested with vs without gemcitabine in an open-label phase 2 RCT[57] in patients with PROC and showed a significant increase in PFS (27.7 vs 9.0 weeks) and OS (84.4 vs 40.4 weeks) in patients with a PFI of less than 3 mo. In a phase 2 RCT,[58] the WEE1 inhibitor adavosertib plus carboplatin resulted in an ORR of 67% with a 100% disease control rate, although hematologic toxic effects were a concern. In a second phase 2 RCT,[59] adavosertib plus gemcitabine prolonged PFS

(median 4.6 vs 3.0 mo) and OS (median 11.4 vs 7.2 mo) vs gemcitabine in patients with PROC. Despite these promising preliminary results, the development of adavosertib has recently been discontinued. However, WEE1 inhibition is still being evaluated for patients with PROC. Another inhibitor, ZN-c3, demonstrated a disease control rate of 80% in an ongoing phase 1 study with a tolerable safety profile.[60] Ultimately, identifying biologically effective doses with acceptable safety has been difficult and will be critical in using WEE1 inhibitors.

Immunotherapies

Although checkpoint inhibitors have had limited success in improving outcomes for patients with PROC, some biomarker-based strategies in patient subgroups defined by PD-L1 and CD8 expression are being explored. A positive trend in ORR was reported for patients with high expression of PD-L1 and/or CD8 who received avelumab in JAVELIN Ovarian 200[24] or pembrolizumab in KEYNOTE-100[61]; however, a similar trend was not observed in patients with higher PD-L1 expression who were treated with nivolumab in NINJA.[25] Notably, the diagnostic assay used to determine PD-L1 positivity was inconsistent between these studies, and further assessments are warranted to determine the feasibility of this biomarker strategy and the relevance of PD-L1 expression in ovarian cancer. Thus far, immunotherapeutic monotherapies have disappointed; however, combination regimens continue to be an active area of study. Dual checkpoint inhibition with nivolumab and ipilimumab has shown promise with a greater response rate (31% vs 12%) vs nivolumab alone. Moreover, although OS did not show improvement, the median PFS with nivolumab plus ipilimumab was 3.9 mo vs 2.0 mo with nivolumab alone.[62]

There are at least 18 ongoing trials testing immunotherapies, with a multitude of immune-therapeutic targets for PROC. Nemvaleukin alfa is an engineered cytokine that selectively binds to IL-R2 to activate $CD8^+$ T cells and natural killer cells, demonstrating an ORR of 28.6% and disease control rate of 71.4% in a recent trial.[63] A phase 3 RCT, ARTISTRY-7, of nemvaleukin alfa plus pembrolizumab in patients with PROC is currently under way (NCT05092360).

Other Therapeutic Strategies

Other targeted therapies are under exploration in PROC, including phosphatidylinositol-3-kinase inhibitors (copanlisib, alpelisib), AKT inhibitors (afuresertib), antiglucocorticoids (relacorilant), antiangiogenic therapies (BD0801, chiauranib), and new combinations with vascular endothelial growth factor inhibitors (fluzuloparib plus bevacizumab, bevacizumab plus anetumab ravtansine or weekly paclitaxel). Furthermore, alternate novel therapies build on a backbone of weekly paclitaxel,[64] and include tumor-treating fields, an electrical field therapy to disrupt mitosis (INNOVATE study, NCT03940196),[64,65] and batiraxcept, which targets the receptor tyrosine kinase Axl and growth arrest specific protein 6 (NCT04729608).

Future Directions and Additional Considerations

Despite the difficulties in identifying new treatment options for PROC, substantial optimism remains that novel targeted treatments may result in clinically meaningful benefit. Cell-based immunotherapies, including chimeric antigen receptor and T-cell receptor therapies, comprise an active field of research in solid tumors, including ovarian cancer.[66] Additionally, the p53 protein–reactivating drug, eprenetapopt (APR-246), has been shown to resensitize PROC cells to platinum treatment in culture,[67,68] and early phase clinical studies for PROC treatment are under way.

Strategies to improve patient selection and personalize treatment are an important area of focus and will depend on the identification of effective biomarkers that are differentially expressed on ovarian cancer vs normal tissues. As discussed, there are several biomarker-directed ADCs under investigation with encouraging results in defined subgroups of patients with PROC. The identification of additional biomarkers and development of optimized diagnostic assays for biomarker testing is an important focus of future research in PROC.

Conclusions

Ovarian cancer treatment is currently at an inflection point. New maintenance strategies that prolong PFI and the changing treatment paradigm of using platinum therapy until it is no longer appropriate have given rise to a population of more heavily pretreated patients with PROC. The effects of heavier pretreatment on disease biology demand more thoughtful implementation and design of clinical trials. Ultimately, effective treatment must provide clinically meaningful improvements in PFS without compromising QOL. The accumulation of negative findings from clinical trials during the past several years underscores the need for additional therapeutic options for PROC, with improved trial designs to adequately capture contemporary patient characteristics, appropriately perform patient selection, and increase the granularity of molecular characterization of PROC. Nevertheless, the numerous ongoing RCTs and planned studies reflect the continued excitement and preserved momentum of the effort to improve cancer outcomes for patients with PROC.

ARTICLE INFORMATION

Accepted for Publication: December 13, 2022.

Published Online: April 20, 2023. doi:10.1001/jamaoncol.2023.0197

Conflict of Interest Disclosures: Dr Richardson reported consultancy/advisory fees from Mersana, AstraZeneca, Genentech, GlaxoSmithKline, Immunogen, and Deciphera; institutional research support from GlaxoSmithKline, Celsion, Roche, Aravive, Shattuck, Mersana, Syros, Arch Oncology, Harpoon, Hookipa, Clovis, and Karyopharm, all outside the submitted work. Dr Eskander reported consulting and advisory fees from AstraZeneca, Clovis Oncology, Myriad, Eisai, Elevar Therapeutics, Genentech/Roche, Mersana, GSK/Tesaro, Cardiff Oncology, Merck, and Immunogen; institutional research support from AstraZeneca, NovoCure, Merck, Eisai, and Clovis Oncology; speakers' bureau fees for AstraZeneca and Eisai, all outside the submitted work. Dr O'Malley reported consulting and advisory fees from AbbVie, Adaptimmune, Agenus, Arquer Diagnostics, Arcus Biosciences, AstraZeneca, Atossa Therapeutics, Boston Biomedical, Cardiff Oncology, Celcuity, Clovis Oncology, Corcept Therapeutics, Duality Bio, Eisai, Elevar, Exelixis, Genentech, Genelux, GlaxoSmithKline, GOG Foundation, Hoffmann-La Roche, ImmunoGen, Imvax, InterVenn Biosciences, INXMED, IOVANCE Biotherapeutics, Janssen, Jazz Pharmaceuticals, Laekna, Leap Therapeutics, Luzsana Biotechnology, Merck, Merck Sharp & Dohme, Mersana Therapeutics, Myriad, Novartis, NovoCure, OncoC4, Onconova, Regeneron, Replimune, R Pharm, Roche Diagnostics, Seagen, Sorrento, Sutro Biopharma, Tarveda Therapeutics, Toray, Trillium, Umoja, Verastem, VBL Therapeutics, Vencerx Pharma, Xencor, and Zentalis; institutional research funding from AbbVie, Advaxis, Agenus, Alkermes, Aravive, Arcus Biosciences, AstraZeneca, BeiGene, Boston Biomedical, Bristol Myers Squibb,

Clovis Oncology, Deciphera Pharma, Eisai, EMD Serono, Exelixis, Genentech, Genmab, GlaxoSmithKline, GOG Foundation, Hoffmann-La Roche, ImmunoGen, Incyte, IOVANCE Biotherapeutics, Karyopharm Therapeutics, Leap Therapeutics, Ludwig Institute for Ca, Merck, Merck Sharp & Dohme, Mersana, US National Cancer Institute, Novartis, NovoCure, NRG Oncology, OncoC4, OncoQuest, Pfizer, Precision Therapeutics, Prelude Therapeutics, Regeneron Pharmaceuticals, Radiation Therapy Oncology Group, Rubius Therapeutics, Seagen, Sutro Biopharma, SWOG, Tesaro, and Verastem, outside the submitted work. No other disclosures were reported.

Funding/Support: This review was supported by Mersana Therapeutics.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Medical writing support was provided by Jerylin Gan, PhD, and Allison Cherry, PhD (Bio Connections, Chicago, Illinois); these contributors were compensated by Mersana.

REFERENCES

1. Huang J, Chan WC, Ngai CH, et al; on behalf of NCD Global Health Research Group of Association of Pacific Rim Universities Apru. Worldwide burden, risk factors, and temporal trends of ovarian cancer: a global study. *Cancers (Basel)*. 2022;14(9):2230. doi:10.3390/cancers14092230

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708

3. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: ovarian cancer. Accessed July 14, 2022. https://seer.cancer.gov/statfacts/html/ovary.html

4. Bowtell DD, Böhm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat Rev Cancer*. 2015;15(11):668-679. doi:10.1038/nrc4019

5. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers*. 2016;2:16061. doi:10.1038/nrdp.2016.61

6. Peres LC, Cushing-Haugen KL, Köbel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst*. 2019;111(1):60-68. doi:10.1093/jnci/djy071

7. Gockley A, Melamed A, Bregar AJ, et al. Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstet Gynecol*. 2017;129(3):439-447. doi:10.1097/AOG.0000000000001867

8. Colombo N, Sessa C, du Bois A, et al; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30(5):672-705. doi:10.1093/annonc/mdz062

9. Moss HA, Perhanidis JA, Havrilesky LJ, Secord AA. Real-world treatment patterns of maintenance therapy in platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol*. 2021;163(1):50-56. doi:10.1016/j.ygyno.2021.07.026

10. Kathleen N, Moore MRM, Gourley C, et al. Evolution of the ovarian cancer treatment paradigm, including maintenance treatment, in the US and Europe: a real-world chart review analysis (2017–2020). Presented at: Society of Gynecologic Oncology; September 29-October 1, 2022; New York City, New York.

11. Haunschild CE, Tewari KS. Bevacizumab use in the frontline, maintenance and recurrent settings for ovarian cancer. *Future Oncol*. 2020;16(7):225-246. doi:10.2217/fon-2019-0042

12. Matulonis UA, Mansoor RM, Malinowska IA, Perhanidis JA, Woodward T, Kalilani L. Real-world clinical outcomes with poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors as second-line maintenance therapy in patients with recurrent ovarian cancer in the United States. Presented at: the Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, Arizona.

13. van Zyl B, Tang D, Bowden NA. Biomarkers of platinum resistance in ovarian cancer: what can we use to improve treatment. *Endocr Relat Cancer*. 2018;25(5):R303-R318. doi:10.1530/ERC-17-0336

14. Yang L, Xie HJ, Li YY, Wang X, Liu XX, Mai J. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer. *Oncol Rep*. 2022;47(4):82. doi:10.3892/or.2022.8293

15. Pujade-Lauraine E, Banerjee S, Pignata S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. *J Clin Oncol*. 2019;37(27):2437-2448. doi:10.1200/JCO.19.00194

16. You B, Freyer G, Gonzalez-Martin A, et al. The role of the tumor primary chemosensitivity relative to the success of the medical-surgical management in patients with advanced ovarian carcinomas. *Cancer Treat Rev*. 2021;100:102294. doi:10.1016/j.ctrv.2021.102294

17. Damia G, Broggini M. Platinum resistance in ovarian cancer: role of DNA repair. *Cancers (Basel)*. 2019;11(1):119. doi:10.3390/cancers11010119

18. Cooke SL, Brenton JD. Evolution of platinum resistance in high-grade serous ovarian cancer. *Lancet Oncol*. 2011;12(12):1169-1174. doi:10.1016/S1470-2045(11)70123-1

19. Ortiz M, Wabel E, Mitchell K, Horibata S. Mechanisms of chemotherapy resistance in ovarian cancer. *Cancer Drug Resist*. 2022;5(2):304-316. doi:10.20517/cdr.2021.147

20. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308. doi:10.1200/JCO.2013.51.4489

21. Gaillard S, Oaknin A, Ray-Coquard I, et al. Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: a multicenter, randomized, controlled, open-label phase 3 study (CORAIL). *Gynecol Oncol*. 2021;163(2):237-245. doi:10.1016/j.ygyno.2021.08.032

22. Moore KN, Oza AM, Colombo N, et al. Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. *Ann Oncol*. 2021;32(6):757-765. doi:10.1016/j.annonc.2021.02.017

23. Lindemann K, Gibbs E, Åvall-Lundqvist E, et al. Chemotherapy vs tamoxifen in platinum-resistant ovarian cancer: a phase III, randomised, multicentre trial (Ovaresist). *Br J Cancer*. 2017;116(4):455-463. doi:10.1038/bjc.2016.435

24. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol*. 2021;22(7):1034-1046. doi:10.1016/S1470-2045(21)00216-3

25. Hamanishi J, Takeshima N, Katsumata N, et al. Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). *J Clin Oncol*. 2021;39(33):3671-3681. doi:10.1200/JCO.21.00334

26. Kurzeder C, Bover I, Marmé F, et al. Double-blind, placebo-controlled, randomized phase iii trial evaluating pertuzumab combined with chemotherapy for low tumor human epidermal growth factor receptor 3 mRNA-expressing platinum-resistant ovarian cancer (PENELOPE). *J Clin Oncol*. 2016;34(21):2516-2525. doi:10.1200/JCO.2015.66.0787

27. Bamias A, Gibbs E, Khoon Lee C, et al. Bevacizumab with or after chemotherapy for platinum-resistant recurrent ovarian cancer: exploratory analyses of the AURELIA trial. *Ann Oncol*. 2017;28(8):1842-1848. doi:10.1093/annonc/mdx228

28. Poveda AM, Selle F, Hilpert F, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial. *J Clin Oncol*. 2015;33(32):3836-3838. doi:10.1200/JCO.2015.63.1408

29. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007;25(33):5180-5186. doi:10.1200/JCO.2007.12.0782

30. Richardson DL, Backes FJ, Hurt JD, et al. Which factors predict bowel complications in patients with recurrent epithelial ovarian cancer being treated with bevacizumab? *Gynecol Oncol*. 2010;118(1):47-51. doi:10.1016/j.ygyno.2010.01.011

31. Pignata S, Lorusso D, Joly F, et al; MITO16b/MANGO–OV2/ENGOT–ov17 Investigators. Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial. *Lancet Oncol*. 2021;22(2):267-276. doi:10.1016/S1470-2045(20)30637-9

32. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852-861. doi:10.1016/S1470-2045(11)70214-5

33. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*. 2010;28(15):2512-2519. doi:10.1200/JCO.2009.26.9589

34. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in *BRCA* mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol*. 2013;14(9):882-892. doi:10.1016/S1470-2045(13)70240-7

35. Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus standard-of-care chemotherapy

in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(4):465-478. doi:10.1016/S1470-2045(22)00122-X

36. Penson R, Valencia RV, Colombo N, et al. Final overall survival results from SOLO3: Phase III trial assessing olaparib monotherapy versus non-platinum chemotherapy in heavily pretreated patients with germline BRCA1- and/or BRCA2-mutated platinum-sensitive relapsed ovarian cancer (026). *Gynecol Oncol*. 2022;166:S19-S20. doi:10.1016/S0090-8258(22)01244-6

37. Oza A, Lisyanskaya A, Fedenko A, et al. 518O Overall survival results from ARIEL4: a phase III study assessing rucaparib vs chemotherapy in patients with advanced, relapsed ovarian carcinoma and a deleterious BRCA1/2 mutation. *Ann Oncol*. 2022;33:S780. doi:10.1016/j.annonc.2022.07.646

38. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):636-648. doi:10.1016/S1470-2045(19)30029-4

39. Tew WP, Lacchetti C, Kohn EC. Panel PIitMoOCGE. Poly(ADP-Ribose) polymerase inhibitors in the management of ovarian cancer: ASCO Guideline rapid recommendation update. *J Clin Oncol*. 2022:40(33):3878-3881. doi:10.1200/JCO.22.01934

40. de Bree E, Michelakis D, Anagnostopoulou E. The current role of secondary cytoreductive surgery for recurrent ovarian cancer. *Front Oncol*. 2022;12:1029976. doi:10.3389/fonc.2022.1029976

41. Krause D, Richardson DL. Is there a role for secondary debulking in ovarian cancer? a review of the current literature. *Curr Opin Obstet Gynecol*. 2023;35(1):1-5. doi:10.1097/GCO.0000000000000831

42. VBL Therapeutics. VBL announces top-line data from phase 3 OVAL trial of Ofra-Vec in patients with platinum-resistant ovarian cancer. Accessed August 1, 2022. https://ir.vblrx.com/news-releases/news-release-details/vbl-therapeutics-announces-top-line-data-phase-3-oval-trial-ofra

43. Soares DG, Machado MS, Rocca CJ, et al. Trabectedin and its C subunit modified analogue PM01183 attenuate nucleotide excision repair and show activity toward platinum-resistant cells. *Mol Cancer Ther*. 2011;10(8):1481-1489. doi:10.1158/1535-7163.MCT-11-0252

44. Vidal A, Muñoz C, Guillén MJ, et al. Lurbinectedin (PM01183), a new DNA minor groove binder, inhibits growth of orthotopic primary graft of cisplatin-resistant epithelial ovarian cancer. *Clin Cancer Res*. 2012;18(19):5399-5411. doi:10.1158/1078-0432.CCR-12-1513

45. Poveda A, Del Campo JM, Ray-Coquard I, et al. Phase II randomized study of PM01183 versus topotecan in patients with platinum-resistant/refractory advanced ovarian cancer. *Ann Oncol*. 2017;28(6):1280-1287. doi:10.1093/annonc/mdx111

46. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol*. 2003;88(1):35-39. doi:10.1006/gyno.2002.6855

47. Wilson MK, Pujade-Lauraine E, Aoki D, et al; on behalf of the participants of the Fifth Ovarian Cancer Consensus Conference. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol*. 2017;28(4):727-732. doi:10.1093/annonc/mdw663

48. Park J, Kim SI, Jeong SY, et al. Second-line olaparib maintenance therapy is associated with poor response to subsequent chemotherapy in BRCA1/2-mutated epithelial ovarian cancer: a multicentre retrospective study. *Gynecol Oncol*. 2022;165(1):97-104. doi:10.1016/j.ygyno.2022.02.002

49. Tolcher AW. The evolution of antibody-drug conjugates: a positive inflexion point. *Am Soc Clin Oncol Educ Book*. 2020;40:1-8. doi:10.1200/EDBK_281103

50. Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody-drug conjugates: a comprehensive review. *Mol Cancer Res*. 2020;18(1):3-19. doi:10.1158/1541-7786.MCR-19-0582

51. Vergote IB, Marth C, Coleman RL. Role of the folate receptor in ovarian cancer treatment: evidence, mechanism, and clinical implications. *Cancer Metastasis Rev*. 2015;34(1):41-52. doi:10.1007/s10555-014-9539-8

52. Matulonis UA, Oaknin A, Pignata S, et al. Mirvetuximab soravtansine (MIRV) in patients with platinum-resistant ovarian cancer with high folate receptor alpha (FRα) expression: characterization of antitumor activity in the SORAYA study. *J Clin Oncol*. 2022;40(16)(suppl):5512. doi:10.1200/JCO.2022.40.16_suppl.5512

53. Richardson DL, Barve MA, Strauss JF, et al. Phase 1 expansion study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC): preliminary efficacy, safety, and biomarker results in patients with previously treated metastatic ovarian cancer (OC) or non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2020;38:3549. doi:10.1200/JCO.2020.38.15_suppl.3549

54. Richardson DL, Hamilton EP, Barve M, et al. Updated results from the phase 1b expansion study of upifitamab rilsodotin (UpRi; MT-1536), a NaPi2b-directed dolaflexin antibody drug conjugate in ovarian cancer. Presented at: the Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, Arizona.

55. Nickoloff JA. Targeting replication stress response pathways to enhance genotoxic chemo- and radiotherapy. *Molecules*. 2022;27(15):4736. doi:10.3390/molecules27154736

56. Gorecki L, Andrs M, Korabecny J. Clinical candidates targeting the ATR-CHK1-WEE1 axis in cancer. *Cancers (Basel)*. 2021;13(4):795. doi:10.3390/cancers13040795

57. Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(7):957-968. doi:10.1016/S1470-2045(20)30180-7

58. Moore KN, Chambers SK, Hamilton EP, et al. Adavosertib with chemotherapy in patients with primary platinum-resistant ovarian, fallopian tube, or peritoneal cancer: an open-label, four-arm, phase II study. *Clin Cancer Res*. 2022;28(1):36-44. doi:10.1158/1078-0432.CCR-21-0158

59. Lheureux S, Cristea MC, Bruce JP, et al. Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2021;397(10271):281-292. doi:10.1016/S0140-6736(20)32554-X

60. Pasic A, Richardson G, Vranjes Z, et al. Abstract CT148: a phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer. *Cancer Res*. 2022;82:CT148. doi:10.1158/1538-7445.AM2022-CT148

61. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol*. 2019;30(7):1080-1087. doi:10.1093/annonc/mdz135

62. Zamarin D, Burger RA, Sill MW, et al. Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study. *J Clin Oncol*. 2020;38(16):1814-1823. doi:10.1200/JCO.19.02059

63. Vaishampayan UN, Tomczak P, Muzaffar J, et al. Nemvaleukin alfa monotherapy and in combination with pembrolizumab in patients (pts) with advanced solid tumors: ARTISTRY-1. *J Clin Oncol*. 2022;40(16)(suppl):2500. doi:10.1200/JCO.2022.40.16_suppl.2500

64. Lee MX, Tan DS. Weekly versus 3-weekly paclitaxel in combination with carboplatin in advanced ovarian cancer: which is the optimal adjuvant chemotherapy regimen? *J Gynecol Oncol*. 2018;29(6):e96. doi:10.3802/jgo.2018.29.e96

65. Jones TH, Song JW, Abushahin L. Tumor treating fields: an emerging treatment modality for thoracic and abdominal cavity cancers. *Transl Oncol*. 2022;15(1):101296. doi:10.1016/j.tranon.2021.101296

66. Wu JWY, Dand S, Doig L, et al. T-cell receptor therapy in the treatment of ovarian cancer: a mini review. *Front Immunol*. 2021;12:672502. doi:10.3389/fimmu.2021.672502

67. Fransson Å, Glaessgen D, Alfredsson J, Wiman KG, Bajalica-Lagercrantz S, Mohell N. Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant high-grade serous ovarian cancer. *J Ovarian Res*. 2016;9(1):27. doi:10.1186/s13048-016-0239-6

68. Mohell N, Alfredsson J, Fransson Å, et al. APR-246 overcomes resistance to cisplatin and doxorubicin in ovarian cancer cells. *Cell Death Dis*. 2015;6(6):e1794. doi:10.1038/cddis.2015.143