Chemotherapy-free treatment of recurrent advanced ovarian cancer: myth or reality?

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ABSTRACT

Advanced ovarian cancer remains a leading cause of death from gynecologic malignancy. Surgery and, in most cases, platinum-based chemotherapy with or without maintenance with bevacizumab and/or poly-ADP ribose polymerase inhibitors (PARPi) represent the mainstay of treatment, but the disease typically recurs. The treatment of these patients represents a clinical challenge because sequential chemotherapy regimens are often used, with suboptimal outcomes and cumulative toxicity. Chemotherapy-free regimens, based on combinations of PARPi, vascular endothelial growth factor receptor inhibitors, anti-programmed cell death protein-1/programmed death-ligand 1, and anti-cytotoxic T-lymphocyte-associated protein-4 antibodies, among others, represent a valid option, with manageable toxicity profile and ease of administration. This review addresses this new strategy in the management of recurrent ovarian cancer and discusses its feasibility in the treatment landscape of the disease.

INTRODUCTION

Ovarian cancer is a leading cause of death from gynecologic malignancy.[1] Due to absence of specific clinical symptoms and lack of early screening programs, most patients present in advanced disease stages, with dismal prognosis.[2]

Cytoreductive surgery and platinum-based chemotherapy with or without maintenance therapy (bevacizumab and/or poly-ADP ribose polymerase (PARP) inhibitors) represent the mainstay of treatment.[3] However, despite a generally favorable response to first-line chemotherapy, the disease frequently recurs.[4] Due to limited therapeutic options, sequential chemotherapy regimens are often used based on platinum sensitivity (determined by the platinum-free interval), residual toxicities, general condition/performance status, and co-morbidities, with suboptimal outcomes and cumulative toxicity.[4 5] Treatment effectiveness decreases over time, with resistance to platinum drugs precluding diminished survival and quality of life.[6 7]

Chemotherapy-free regimens, based on various combinations of PARP inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, anti-programmed cell death protein-1 (PD-1) and its ligand (programmed death-ligand 1, PD-L1) antibodies, and anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibodies, among others, have shown a strong rationale to be valid therapeutic options in the platinum-resistant setting of ovarian cancer (Table 1), with potentially comparable or greater efficacy than chemotherapy, and are actively being pursued in this setting. Research is also ongoing in platinum-sensitive disease, although the use of chemotherapy-free regimens seems to be more challenging in this setting.

This review outlines chemotherapy-sparing strategies for the treatment of patients with recurrent ovarian cancer.

MONOTHERAPY

PARP inhibitors

PARP inhibitors revolutionized the treatment paradigm of ovarian cancer and became a mainstay in patients' treatment.[8] Olaparib, rucaparib, and niraparib are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of epithelial ovarian cancer as maintenance treatment. As an alternative to chemotherapy, the FDA approved olaparib, rucaparib, and niraparib only in patients with BRCA mutation in latter lines. Rucaparib is the only PARP inhibitor approved by EMA for patients with BRCA mutation who are unable to tolerate further platinum-based chemotherapy.

Study 42 was a large multi-tumor phase II trial including 193 patients with ovarian cancer and germline BRCA mutations ineligible for platinum who were treated with olaparib. Most (80%) had received at least three prior lines of therapy, achieving an objective response rate of 34% and a median duration of response of 7.9 months with olaparib[9] (Table 2). The duration of response was similar for platinum-sensitive and platinum-resistant disease. In addition, despite the very small patient number, some responses were observed in platinum-refractory disease (objective response rate 14%).[10]

In the phase III SOLO3 trial, treatment with olaparib improved clinical outcomes versus non-platinum chemotherapy in women with platinum-sensitive disease.[11] Results showed superior objective response rate (72.2% vs 51.4%, OR 2.53, 95% CI 1.40 to 4.58; p=0.002) and progression-free survival (median 13.4 vs 9.2 months, HR 0.62, 95% CI 0.43 to 0.91; p=0.013) for the PARP inhibitor, with no significant overall survival difference between treatments.[12]

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Table 1 Rationale underlying chemotherapy-sparing options in the treatment of recurrent ovarian cancer

Therapeutic strategy	Rationale
Monotherapy	
PARP inhibitors	PARPs are a large family of 17 nucleoproteins with diverse functions, including in DNA repair, spurring the development of PARP inhibitors as cancer therapies.[8 9] The inhibition of PARP enzymes causes single-strand breaks to persist and subsequent double-strand breaks to accumulate. While normal cells are able to repair double-strand breaks via homologous recombination repair, cancer cells with homologous recombination deficiency (such as loss-of-function BRCA mutations) are unable to repair double-strand breaks, resulting in the accumulation of DNA damage and cell death.[10 11] Other mechanisms of PARP inhibitor activity have been described, such as PARP1 trapping, impaired BRCA1 recruitment, and activation of non-homologous end joining.[12 13]
Immunotherapy	The presence of TIL in the tumor microenvironment, detected in around 50% of ovarian cancers, has been associated with a survival benefit, regardless of tumor grade, stage, or histologic subtype.[31 32] However, several factors in the tumor microenvironment counteract the activity of TIL, generating immune escape mechanisms that enable cancer progression.[33–38] Blocking these inhibitory signals with checkpoint inhibitors allows restoration of the anti-tumor activity of effector T-cells and mediates tumor regression.[39]
Dual combination therapy	
PARP inhibitors with anti-angiogenic agents	PARP inhibition decreases angiogenesis and may prevent accumulation of HIF1, which is involved in the acquisition of resistance to angiogenesis inhibitors.[57] Additionally, VEGFR inhibition can affect homologous recombination DNA repair, by downregulating BRCA1/2 and RAD51, and simultaneously suppress angiogenesis, increasing the anti-tumor activity of PARP inhibitors.[58]
PARP inhibitors with immunotherapy	Homologous recombination-deficient cells have error-prone DNA repair mechanisms, leading to somatic mutations that can result in neoantigen formation and immune system activation.[49] On the other hand, BRCA-mutated and homologous recombination-deficient ovarian cancers also have increased CD3+and CD8+ immune cell infiltration compared with homologous recombination-proficient tumors.[50] Another mechanism by which defective DNA repair can lead to immune activation is by release of damaged DNA resulting in activation of the innate immune system. The cGAS-STING pathway is a major mechanism of the innate immune system, which protects cells from cytosolic DNA derived from any source, including viruses and tumor cells. The anti-tumor efficacy of PARP inhibition is dependent on STING pathway activation. In mouse models, PARP inhibition with olaparib triggered robust anti-tumor activity that was diminished by loss of cytotoxic T-cells or loss of STING pathway signaling in BRCA-deficient[51] as well as BRCA-wild type models.[52] This body of evidence suggested that, by interfering with homologous recombination repair, PARP inhibitors could increase neoantigen production and stimulate the tumor immune microenvironment to synergize with checkpoint inhibitors.
Anti-angiogenic agents with immunotherapy	Angiogenic factors like VEGF are key regulators of physiological and pathological angiogenesis and play a major role in tumorigenesis.[58] VEGF is highly expressed in the tumor microenvironment of ovarian cancer,[59] promoting tumor angiogenesis, favoring peritoneal dissemination of ovarian cancer through malignant ascites formation, and enhancing vascular permeability.[60] In addition, VEGF creates an immunosuppressive environment through release of inhibitory cytokines and recruitment of immunosuppressive cells.[61] This provided the rationale for the combined targeting of angiogenesis and immune checkpoints as a way of reversing immunosuppression mediated by VEGF and thus increasing the efficacy of checkpoint inhibitors in ovarian cancer.

BRCA, BReast CAncer gene; CD, cluster of differentiation; DNA, deoxyribonucleic acid; HIF1, hypoxia inducible factor 1 alpha; PARP, poly-ADP ribose polymerase; cGAS-STING pathway, cyclic GMP-AMP synthase-stimulator of interferon genes pathway; TIL, tumor-infiltrating lymphocyte; VEGFR, vascular endothelial growth factor receptor.

Not having a platinum agent in the comparator arm was a study limitation.

The phase II Study 12/ICEBERG 3 evaluated olaparib versus pegylated liposomal doxorubicin as recurrent treatment in BRCA-mutated ovarian cancer.[13] No progression-free survival (HR 0.88, 95% CI 0.51 to 1.56; p=0.66) or objective response rate benefit was found. Olaparib anti-tumor activity was higher in patients with partially sensitive disease, confirming platinum sensitivity as a predictor of response to PARP inhibitors. Although the use of a platinum-free comparator was pointed out as a study limitation, platinum-free chemotherapy is an option in multi-treated patients, given that platinum has not shown an overall survival benefit after second line.[11]

The phase II CLIO study randomized patients with platinum-resistant ovarian cancer irrespective of BRCA status to olaparib or chemotherapy.[14] Patients had a median of three prior lines of

Table 2 Monotherapy with PARP inhibitors for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Objective response rate (%)	Progression-free survival (median months)	Overall survival (median months)
Study 42 (Domchek et al. 2016)[9]	II	Olaparib	Platinum-resistant/ refractory or platinum-sensitive germline BRCA1/2-mutated ovarian cancer	193	34%	6.7	Not reported
SOLO3 (Penson et al. 2020; Penson et al. 2022)[11 12]	III	Olaparib vs non-platinum chemotherapy	Platinum-sensitive recurrent germline BCRA-mutated ovarian cancer	266	72.2% vs 51.4%	13.4 vs 9.2	34.9 vs 32.9
Study 12/ICEBERG 3 (Kaye et al. 2012)[13]	II	Plaparib 200 mg vs olaparib 400 mg vs liposomal doxorubicin	Platinum-sensitive/resistant recurrent germline BRCA-mutated ovarian cancer	97	25% vs 31% vs 18%	6.5 vs 8.8 vs 7.1	Not reported
CLIO (Vanderstichele et al. 2019)[14]	II	Olaparib vs physician's choice chemotherapy	Platinum-resistant ovarian cancer	100	18% vs 6%	2.9 vs 3.4	Not reported
LIGHT (Cadoo et al. 2020 & 2021; Mathews et al. 2021)[15 16 59]	II	Olaparib	Platinum-sensitive recurrent, high-grade serous/endometrioid epithelial ovarian cancer	271	37%	7.4	Not reported
ARIEL 4 (Kristeleit et al. 2021)[20]	III	Rucaparib vs standard-of-care chemotherapy	Platinum-sensitive/resistant, high-grade germline BRCA/ somatic-mutated recurrent ovarian cancer	349	40.3% vs 32.3%	7.4 vs 5.7	Not reported
QUADRA (Moore et al. 2019)[21]	II	Niraparib	Relapsed, high-grade serous (grade 2 or 3) ovarian cancer	461	28%	5.5	17.2
Coleman et al. 2015[22]	II	Veliparib	Primary BRCA-mutated/ germline BRCA ovarian cancer	50	26%	8.11	19.7
Steffensen et al 2017[23]	I/II	Veliparib	Platinum-resistant or intermediate sensitive relapsed ovarian cancer	45	44%	5.6	13.7

BRCA, BReast CAncer gene; PARP, poly-ADP ribose polymerase.

treatment and achieved an objective response rate of 18% with olaparib and 6% with chemotherapy. The objective response rate with olaparib was 38% in BRCA-mutated and 13% in BRCA-wild type subgroup. The median duration of response was similar between treatment arms (5.4 vs 4.5 months), as was the median progression-free survival (2.9 vs 3.4 months). These results suggested that olaparib monotherapy had a favorable response rate compared with chemotherapy in platinum-resistant disease also in the BRCA-wild type phenotype.

The phase II LIGHT study was the first prospective study evaluating olaparib in patients with platinum-sensitive ovarian cancer according to BRCA and homologous recombination deficiency status.[15 16] A total of 271 patients distributed across four cohorts were treated: germline BRCA mutations; somatic BRCA mutations; homologous recombination deficiency positive (non-BRCA-mutated); and homologous recombination deficiency negative. Olaparib showed activity across all cohorts, with similar efficacy in germline and somatic BRCA groups. The objective response rate was 37% (95% CI 32% to 44%) in the overall population and 69% (95% CI 58% to 80%), 64% (95% CI 43% to 82%), 29% (95% CI 19% to 42%), and 10% (95% CI 8% to 18%) in each of the four cohorts, respectively.[15] In non-BRCA-mutated patients, longer median progression-free survival and higher objective response rate were observed in the homologous recombination deficiency positive subgroup.[15] In the final survival analysis, the 18 month overall survival ranged from 60% to 88% across cohorts, with higher benefit in BRCA-mutated subgroups (86.4% and 88.0% in patients with germline and somatic BRCA mutations, respectively).[16] Among patients without BRCA mutations, 18 month overall survival was highest in the homologous recombination deficiency positive cohort (78.6% vs 59.6% in the homologous recombination deficiency negative cohort).[16]

Single-agent rucaparib was approved for the treatment of patients with platinum-sensitive or platinum-resistant BRCA-mutated recurrent ovarian cancer with at least two previous lines of platinum-based chemotherapy based on data from phase I/II Study 10[17] and ARIEL2.[18 19] Study 10 established rucaparib 600 mg twice daily as the recommended dose and provided initial evidence of its anti-tumor activity in patients with germline BRCA-mutated tumors.[17] In ARIEL2 Part 1, progression-free survival was significantly longer in BRCA-mutant (HR 0.27, 95% CI 0.16 to 0.44; p<0.0001) and BRCA-wild type/genomic loss of heterozygosity-high (HR 0.62, 95% CI 0.42 to 0.90; p=0.011) subgroups compared with BRCA-wild type/ loss of heterozygosity-low, suggesting the potential benefit of this agent and PARP inhibitor in general in the treatment of ovarian cancer beyond BRCA mutations.[19] The confirmatory ARIEL4 phase III trial enrolled 349 patients with high-grade ovarian cancer and germline BRCA (84%) or somatic (16%) mutations with at least two prior chemotherapy regimens, 51% of whom were platinum resistant, 28% partially platinum sensitive, and 21% fully platinum

sensitive.[20] The progression-free survival was significantly longer (median 7.4 vs 5.7 months, HR 0.64; p=0.001), objective response rate was similar (40.3% vs 32.3%; p=0.13), and the duration of response was also longer (median 9.4 vs 7.2 months, HR 0.59) with rucaparib versus chemotherapy.

Niraparib was approved in patients with ovarian cancer with at least three prior chemotherapy regimens and homologous recombination deficiency positive tumors based on results of the phase II QUADRA trial.[21] The study included 463 patients and demonstrated activity in the primary efficacy population, with an objective response rate of 28% (95% CI 15.6% to 42.6%; one-sided p=0.00053) in patients sensitive to the most recent platinum-based therapy and a median duration of response of 9.2 months (95% CI 5.9 to not estimable). No new safety signals were identified.

Veliparib achieved similar objective response rate results to other PARP inhibitors in patients who were highly pre-treated. In a phase II trial, the objective response rate was 26% in 50 patients with germline BRCA-mutated ovarian cancer, 60% of whom were platinum resistant and 72% had two to three prior lines of therapy, and 20% in patients who were platinum resistant and 35% in those who were platinum sensitive.[22] More recently, a phase I/II trial explored the benefit of veliparib in 45 patients with germline BRCA-mutated platinum partially sensitive or resistant ovarian cancer with a median of four prior lines of therapy.[23] Study results showed an objective response rate of 44% and a median duration of response of 7.6 months. The median progression-free survival was 5.6 months (95% CI 5.2 to 7.3) and the median ovarian cancer was 13.7 months (95% CI 10.2 to 17.3), and both were significantly longer in partially sensitive patients.

IMMUNOTHERAPY

Immunotherapy in the form of immune checkpoint blockade revolutionized the treatment paradigm of several tumors. In ovarian cancer, the value of immune checkpoint inhibitors remains controversial, but the results obtained so far with these agents in monotherapy or combination with standard chemotherapy have been disappointing compared with other tumors.

Several checkpoint inhibitors have been investigated as single agents in recurrent ovarian cancer, including anti-PD-1, anti-PD-L1, and anti-CTLA-4, with limited benefit.

The first evidence of a potential benefit of this approach came from a phase I trial evaluating the anti-PD-L1 BMS-936559 in patients with several solid tumors, including 17 patients with recurrent ovarian cancer[24] (Table 3). One patient (6%) had a partial response and three (18%) had stable disease lasting at least 24 weeks.

The anti-PD-1 pembrolizumab was first investigated in the phase Ib KEYNOTE-028 trial.[25] A multi-treated PD-L1-positive population (n=26) was studied, with 85% of patients previously treated for recurrent disease and 38.5% with at least five prior lines of therapy. An objective response rate of 11.5% and disease control rate of 34.6% were achieved with pembrolizumab. The median progression-free survival was 1.9 months (95% CI 1.8 to 3.5) and the median overall survival was 13.8 months (95% CI 6.7 to 18.8). Subsequently, the phase 2 KEYNOTE-100 trial assessed pembrolizumab in two cohorts of patients with recurrent disease, one (cohort A; n=285) with up to three prior lines of therapy and a treatment-free interval of 3–12 months, and another (cohort B; n=91 patients) with four to six prior lines of therapy and a treatment-free interval of at least three months.[26 27] Objective response rates were modest (8.1% for cohort A and 9.9% for cohort B), with a median duration of response of 8.3 and 23.6 months and disease control rate of 22.1% and 22.0%, respectively. The median progression-free survival was 2.1 months in both cohorts (95% CI 2.1 to 2.2 for cohort A; 95% CI 2.1 to 2.6 for cohort B) and the median overall survival was 18.7 months for cohort A (95% CI 17.0 to 22.5) and 17.6 months for cohort B (95% CI 13.3 to 24.4). A trend was observed towards longer overall survival with higher PD-L1 expression in both cohorts.[26 28]

The efficacy of pembrolizumab in patients with non-colorectal, microsatellite instability-high/mismatch repair-deficient cancer was assessed in the non-randomized phase II KEYNOTE-158 study.[29] In five patients with ovarian cancer, the objective response rate was 33.3% (including three complete responses), the median progression-free survival was 2.3 months, and the median duration of response (range 4.2—20.7+months) and overall survival (95% CI 3.8 months to not reached) had not been reached. The FDA approved pembrolizumab for the treatment of solid microsatellite instability-high/mismatch repair-deficient cancers in May 2017.

Nivolumab, another anti-PD-1, showed promising results in an initial phase II trial investigating two drug schedules in platinum-resistant ovarian cancer.[30] An objective response rate of 15%, disease control rate of 45%, median progression-free survival of 3.5 months (95% CI 1.7 to 3.9), and median overall survival of 20.0 months (95% CI 7.0 to not reached) were reported. Encouraged by these results, the subsequent randomized phase III NINJA trial compared outcomes with the anti-PD-1 and chemotherapy in the same platinum-resistant setting.[31] However, nivolumab failed to demonstrate a survival advantage over chemotherapy (HR 1.03, 95% CI 0.80 to 1.32; p=0.808). The HR for overall survival was consistent across PD-L1 status (positive vs negative). A numerically longer overall survival with nivolumab was observed in the subgroup of patients with clear-cell carcinoma (HR 0.8, 95% CI 0.5 to 1.3). Both progression-free survival (HR 1.46, 95% CI 1.15 to 1.85; p=0.002) and objective response rate (8% vs 13%, OR 0.6, 95% CI 1.02 to 1.3; p=0.191) favored chemotherapy. Importantly, among patients who responded to treatment, the median duration of response was longer in the nivolumab vs chemotherapy group (18.7 vs 7.4 months, respectively).

The activity of the anti-PD-L1 atezolizumab in recurrent ovarian cancer was explored in a phase Ia dose-escalation/expansion study enrolling 12 patients.[32] Among nine patients with evaluable response, two (22%) had partial response. The duration of response in these responders was 8.1 and 16.6 months, respectively. Nine of 10 patients evaluable for progression-free survival/overall survival had a PD-L1 score on immune cells of 2/3 and achieved a median progression-free survival of 2.9 months (95% CI 1.3 to 5.5), with a median overall survival of 11.3 months (95% CI 5.5 to 27.7) and 17.4 months (95% CI 5.9 to 27.7) for immune cell score of 2 and 3, respectively.

Another anti-PD-L1, avelumab, was also investigated in recurrent ovarian cancer in the JAVELIN clinical development program. In JAVELIN phase Ib trial, avelumab was associated with an objective response rate of 9.6% (95% CI 5.1% to 16.2%), a median progression-free survival of 2.6 months (95% CI 1.4 to 2.8), and

Table 3 Immunotherapy in monotherapy for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Follow-up (median months)	Objective response rate (%)	Progression-free survival (median months)	Overall survival (median months)
Brahmer et al. 2012 [24]	I	BMS-936559	Recurrent ovarian cancer	17	Not reported	6%	Not reported	Not reported
KEYNOTE-028 (Varga et al. 2019[25]	Ib	Pembrolizumab	PD-L1+recurrent ovarian cancer	26	15.4	11.5%	1.9	13.8
KEYNOTE-100 (Matulonis et al. 2019; Matulonis et al. 2020)[26 27]	II	pembrolizumab	Recurrent ovarian cancer (cohort A: progression-free interval 3–12 months; cohort B: progression-free interval ≥3 months)	376 (285 cohort A; 91 cohort B)	Not reported	Cohort A: 8.1% cohort B: 9.9%	Cohort A: 2.1 months cohort B: 2.1 months	Cohort A: 18.7 cohort B: 17.6
KEYNOTE-158 (Marabelle et al. 2020)[29]	II	pembrolizumab	Advanced microsatellite instability-high/ mismatch repair-deficient ovarian cancer	15	13.4	33.3%	2.3	Not reached
UMIN000005714 (Hamanishi et al. 2015)[30]	II	Nivolumab	Platinum-resistant recurrent ovarian cancer	20	11.0	15%	3.5	20.0
NINJA (Omatsu et al. 2020)[31]	III	Nivolumab vs gemcitabine/pegylated liposomal doxorubicin	Platinum-resistant recurrent ovarian cancer	316	Not reported	8% vs 13%	2.0 vs 3.8	10.1 vs 12.1
Infante et al. 2016 [32]	Ia	Atezolizumab	Recurrent ovarian cancer	9	Not reported	22%	2.9	11.3 (immune cell score 2)/17.4 (immune cell score 3)
JAVELIN (Disis et al. 2019)[33]	Ib	Avelumab	Platinum-resistant recurrent ovarian cancer	125	26.6	9.6%	2.6	11.2
JAVELIN 200 (Pujade-Lauraine et al. 2021)[34]	III	Avelumab vs avelumab+pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin	Platinum-resistant recurrent ovarian cancer	566	not reported	3.7% vs 13.3% vs 4.2%	Avelumab vs pegylated liposomal doxorubicin: 1.9 vs 3.5 months; HR 1.68; p>0.999	Avelumab vs pegylated liposomal doxorubicin: 11.8 vs 13.1 months; HR 1.14; p=0.8253
NCT01611558[35]	II	Ipilimumab	Platinum-sensitive recurrent ovarian cancer	40	not reported	10.3%	–	–
Zamarin et al. 2020 [37]	II	Nivolumab vs nivolumab+ipilimumab	Recurrent ovarian cancer	100	not reported	12.2% vs 31.4%	2 vs 3.9 months (HR 0.53)	21.8 vs 28.1 months (HR 0.79)
Johnson et al. 2019 [36]	I	PF-06801591	Advanced ovarian cancer	15	Not reported	20%	5.3	Not reached

HR, hazard ratio; PD-L1, programmed death ligand 1.

a median overall survival of 11.2 months (95% CI 8.7 to 15.4) among 124 patients with refractory or recurrent ovarian cancer progressing after a median of three prior lines of therapy.[33] Responses were observed regardless of PD-L1 expression. More recently, the phase III JAVELIN 200 trial randomized 566 patients with recurrent platinum-resistant ovarian cancer to pegylated liposomal doxorubicin, avelumab, or the combination of both.[34] The study failed to show an advantage over chemotherapy either in terms of progression-free survival (median 3.5 vs 1.9 months, HR 1.68; p>0.999) or overall survival (median 13.1 vs 11.8 months, HR 1.14; p=0.8253). The objective response rate was 3.7% and 4.2%, respectively. However, the population enrolled had poor prognosis, with almost one quarter of patients refractory and around 50% primarily resistant to platinum.

Anti-CTLA-4 antibodies were also investigated in recurrent ovarian cancer. In a phase II study assessing the activity and safety of ipilimumab in patients with platinum-sensitive tumors, the objective response rate was 10.3%, and 50% of patients reported grade 3 adverse events.[35] This high rate of toxicity, potentially related to the high dose of ipilimumab administered, discouraged pursuing anti-CTLA-4 in recurrent ovarian cancer, with most trials focusing on anti-PD-(L)1 s.

The anti-PD-1 antibody PF-06801591 was evaluated in a phase I dose-escalation study including 15 patients with advanced ovarian

cancer and achieved an objective response rate of 20% and a median progression-free survival of 5.3 months, with the median overall survival still not reached.[36]

Dual checkpoint inhibition was also explored in the recurrent setting of ovarian cancer. In the randomized phase II NRG-GY003 trial, 100, mostly (62%) platinum-resistant, patients with a platinum-free interval less than 12 months received either nivolumab or nivolumab and ipilimumab.[37] The combination demonstrated increased objective response rate (12.2% vs 31.4%, OR 3.28, 85% CI 1.54 to infinity; p=0.034) and progression-free survival (median 3.9 vs 2 months, HR 0.528, 95% CI 0.339 to 0.821; p=0.004) compared with nivolumab alone. The median overall survival was numerically but not statistically higher with the combination (28.1 vs 21.8 months, HR 0.789, 95% CI 0.439 to 1.418; two-sided p=0.43). Toxicity was higher in the combination arm, with 49% versus 33% grade 3 treatment-related adverse events. PD-L1 expression was not significantly associated with response in either treatment groups.

Despite lower than expected objective response rates (between 3.6% and 22%) in these studies, the high number of patients with poor prognosis (either due to the high number of previous lines of therapy or to being platinum resistant/refractory) included should be considered. In addition, for patients who respond to immunotherapy, the duration of response seems to be longer compared with chemotherapy.

The selection of patients for each treatment and identification of biomarkers of response are still unmet needs in recurrent ovarian cancer. There is an overall discrepancy between PD-L1 expression and response rates, suggesting that PD-L1 is not an adequate biomarker of response to immunotherapy in this disease. Microsatellite instability may be a possible predictive marker of response to immunotherapy in many cancer types, and eventually helpful in selecting patients for this approach.[38 39] The frequency of the microsatellite instability-high phenotype in ovarian cancer is around 12%, with an overrepresentation of non-serous histology.[40] The results of a subgroup analysis of 15 patients with ovarian cancer enrolled in the phase II KEYNOTE-158 study showed an objective response rate of 33.3%, suggesting that immunotherapy should be further explored in microsatellite instability-high/mismatch repair-deficient disease.[29]

The phase II DART study of dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) blockade in rare tumors, including clear-cell carcinomas, is currently ongoing and recruiting patients (NCT02834013).

In a platinum-resistance setting, although the objective response rates achieved with immunotherapy seem promising, the superiority of immunotherapy over chemotherapy has not been demonstrated.

Overall, immunotherapy in monotherapy has offered limited therapeutic benefits in ovarian cancer. Therefore, the research focus is now in assessing combinations of checkpoint inhibitors with drugs with different mechanisms of action (anti-vascular endothelial growth factors (VEGFs), PARP inhibitors, multi-kinase inhibitors, vaccines), trying to improve the clinical benefit of immunotherapy.

DUAL COMBINATION THERAPY

The potential synergy between PARP inhibitors and other cell signaling pathways has prompt the investigation of various combination strategies with these agents in recurrent ovarian cancer.

PARP inhibitors with anti-angiogenic agents

Several randomized trials have evaluated the potentially synergistic effect of VEGFR inhibitor and PARP inhibitor combinations, suggesting their superiority over PARP inhibitors alone (Table 4).

Preclinical evidence showed a synergy between olaparib and cediranib in the inhibition of cell invasion and microvascular endothelial cell tube formation in ovarian cancer (unpublished data) and a phase I dose-finding study indicated promising preliminary activity of the combination against recurrent ovarian cancer, with an objective response rate of 44%.[41] This fueled the investigation of these agents in a randomized phase II trial.[42] Ninety women with platinum-sensitive, relapsed, high-grade serous, or endometrioid ovarian cancer stratified by BRCA mutation status were allocated to olaparib 400 mg twice daily (n=46) or olaparib 200 mg twice daily plus cediranib (n=44). The primary endpoint was met, with significantly longer median progression-free survival with the combination versus single agent (17.7 vs 9.0 months, HR 0.42; p=0.005), but no significant overall survival difference (44.2 vs 33.3 months, HR 0.64; p=0.11). In subgroup analyses, statistically significant improvements were found in median progression-free survival (23.7 vs 5.7 months; p=0.002) and overall survival (37.8 vs 23.0 months; p=0.047) in germline BRCA-wild type/unknown patients.

The combination of cediranib plus olaparib and olaparib as single agent were also assessed in the randomized, phase III GY004 trial, which compared these regimens with standard-of-care (SOC) platinum-based therapy in recurrent platinum-sensitive high-grade ovarian cancer.[43] A total of 528 patients (23.7% with germline BRCA mutations) received the platinum-based doublet (n=166), olaparib (300 mg twice daily; n=183), or cediranib plus olaparib (30 mg daily and 200 mg twice daily, respectively; n=179). The median progression-free survival was comparable between regimens, with 10.3, 8.2, and 10.4 months for chemotherapy, monotherapy, and combination therapy, and response rates were 71.3%, 52.4%, and 69.4%, respectively. In patients with germline BRCA mutations, the HR for improvement in median progression-free survival versus chemotherapy was 0.55 for cediranib plus olaparib and 0.63 for olaparib alone. No overall survival differences were observed between treatments. Patients receiving cediranib plus olaparib more frequently reported grade 3 or higher adverse events compared with chemotherapy. Overall, although the combination displayed similar activity to the platinum-based SOC, it did not meet the primary endpoint of superior progression-free survival.

The phase II AVANOVA2 trial investigated niraparib plus bevacizumab versus niraparib alone in platinum-sensitive recurrent ovarian cancer.[44] The trial enrolled 97 patients who received either niraparib plus bevacizumab or niraparib alone. The combination significantly improved the progression-free survival, which reached a median of 11.9 months with the duplet versus only 5.5 months with the single agent (HR 0.35, 95% CI 0.21 to 0.57; p<0.0001). The progression-free survival benefit was seen regardless of homologous recombination deficiency/BRCA status or chemotherapy-free interval. Among 91 patients evaluated for response, objective

Table 4 Combinations of PARP inhibitors with anti-angiogenic agents for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Follow-up (median months)	Objective response rate (%)	Progression-free survival (median months)	Overall survival (median months)
Liu et al. 2014[42]	II	Olaparib+ cediranib vs olaparib	High-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer	90	16.6	79.6% vs 47.8% (p=0.002)	17.7 vs 9.0 (p=0.005)	Immature
Liu et al. 2019 (update)[60]	II	Olaparib+ cediranib vs olaparib	High-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer	90	46	Not reported	16.5 vs 8.2 months (p=0.007).	44.2 vs 33.3 (p=0.11)
GY004 (Liu et al. 2019)[43]	III	Olaparib+ cediranib vs. olaparib vs standard of care	High-grade serous or endometrioid or BRCA-related platinum-sensitive recurrent ovarian cancer	528	29.1	69.4% vs 52.4% vs 71.3%	10.4 vs 8.2 vs 10.3	No significant difference/ no significant difference
AVANOVA 2[44]	II	Niraparib+ bevacizumab vs niraparib	High-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer	97	16.9	62% vs 30% (p=0.003)	11.9 vs 5.5 (p<0.0001)	Immature
CONCERTO[45]	IIb	Olaparib+ cediranib	BRCA wild-type recurrent platinum-resistant ovarian cancer	60	not reported	15.3	5.1	13.2
BAROCCO (Colombo et al. 2019)[46]	II	Olaparib+ cediranib continuous/ intermittent schedule vs weekly paclitaxel	Platinum-resistant recurrent ovarian cancer	123	Not reported	Not reported	5.7/3.8 vs 3.1	Not reported
OCTOVA (Nicum et al. 2021)[47]	II	Olaparib vs olaparib+ cediranib	High grade platinum-resistant ovarian cancer	139	Not reported	Not reported	Not reported	Not reported

BRCA, BReast CAncer gene; PARP, poly-ADP ribose polymerase.

response rate was 62% with the combination and 30% with monotherapy (OR 3.84, 95% CI 1.60 to 9.21; p=0.003). Overall survival data were still immature. Grade 3 or higher adverse events occurred in 65% versus 45% of patients, respectively.

In platinum-resistant disease, three phase II/IIb trials have been recently completed. The phase IIb, single-arm CONCERTO trial investigated cediranib plus olaparib in 60 BRCA-wild type patients with at least three prior lines of chemotherapy.[45] The primary endpoint of objective response rate was 15.3% (95% CI 7.2% to 27.0%), with a median progression-free survival of 5.1 months (95% CI 3.5 to 5.5), median duration of response of 8.3 months (95% CI 5.6 to 10.3), and median overall survival of 13.2 months (95% CI 9.4 to 16.4). The combination of cediranib and olaparib given in a continuous or intermittent schedule was compared with weekly paclitaxel in patients with platinum-resistant recurrent ovarian cancer in the phase II BAROCCO study.[46] Among 123 patients with a median platinum-free interval of 1.8 months, 59% of whom with more than three previous lines of chemotherapy, the median progression-free survival was 5.7, 3.8, and 3.1 months in the overall study cohort and 5.8, 3.8, and 2.1 months in the germline BRCA-wild type cohort (n=109), respectively. Treatment discontinuations due to adverse events occurred in 18%, 7%, and 11% of patients in each arm. Recently, the phase II OCTOVA trial reported greater efficacy for olaparib plus cediranib compared with olaparib alone in a cohort of 139 patients with platinum-resistant ovarian cancer and a median of two prior lines of chemotherapy, 29% of whom had germline BRCA1/2 mutations.[47] The progression-free survival was increased with the duplet compared with olaparib alone (HR 0.70, 60% CI 0.57 to 0.86; p=0.08).

Ongoing studies include the phase II ANNIE trial, currently recruiting patients with platinum-resistant recurrent ovarian cancer for treatment with niraparib plus anlotinib; the phase II multicohort OPAL study, exploring novel combinations of niraparib with agents with scientific rationale for synergistic activity with the PARP inhibitor; the phase II AVANIRA3 study, investigating niraparib plus bevacizumab in the treatment of FIGO III/IV platinum refractory/ resistant ovarian cancer; and the phase II/III NRG-GY005/COCOS study, comparing single-agents olaparib or cediranib, the combination of both, or standard chemotherapy in patients with recurrent, platinum-resistant/refractory ovarian cancer.

PARP inhibitors with immunotherapy

Despite evidence of immune cell infiltration and high PD-L1 expression in ovarian cancer,[48] the efficacy of checkpoint inhibitors as single agents proved disappointing. Modest activity was observed, with only 8–15% of responses that were seldom durable.[27 33] New strategies were hence required to improve the efficacy of immune checkpoint blockade, and a strong rationale supported its combination with PARP inhibitors, prompting clinical trials exploring the combination of PARP inhibitors with checkpoint inhibitors (Table 5).

Table 5 Combinations of PARP inhibitors with immunotherapy agents for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Follow-up (median months)	Objective response rate (%)	Progression -free survival (median months)	Overall survival (median months)
MEDIOLA (Drew et al. 2018)[49]	I/II	Olaparib+ durvalumab	Recurrent platinum-sensitive ovarian cancer	32	Not reported	72%	11.1	Not reported
MEDIOLA (Drew et al. 2020)[61]	II	Olaparib+ durvalumab olaparib+ durvalumab+ bevacizumab	Recurrent platinum-sensitive non-germline BRCA-mutated ovarian cancer	32 31	Not reported Not reported	31.3% 77.4%	5.5 14.7	Not reported Not reported
TOPACIO (Konstantinopoulos et al. 2019)[50]	I/II	Niraparib+ pembrolizumab	Platinum-resistant recurrent epithelial ovarian cancer	60	12.4	18%	3.4	Not reported
Lampert et al. 2020 [51]	II	Olaparib+ durvalumab	Platinum-resistant recurrent ovarian cancer	35	Not reported	14%	3.9	Not reported
Gaillard et al. 2020 [52]	I/II	Tremelimumab vs tremelimumab +olaparib	Platinum-resistant recurrent ovarian cancer	24	Not reported	1 partial response and 3 disease stabilizations with tremelimumab +olaparib; 6 disease stabilizations with tremelimumab	2 >6 month progression-free survival with tremelimumab +olaparib	Not reported

BRCA, BReast CAncer gene; PARP, poly-ADP ribose polymerase.

MEDIOLA was a phase II trial of olaparib plus the anti-PD-L1 durvalumab in patients with relapsed, platinum-sensitive, germline BRCA-mutated and non-mutated epithelial ovarian cancer.[49] Thirty-two patients were eligible and treated with the combination, achieving a 28 week disease control rate of 65.6% (95% CI 49.6% to 79.4%) and an impressive objective response rate of 71.9% (95% CI 53.2%5 to 86.25%), with seven complete responses. The median progression-free survival was 11.1 months (95% CI 8.2 to 15.9), and the median overall survival was not reached, with 87.0% of patients alive at 24 months. In the safety analysis, anemia, elevated lipase, neutropenia, and lymphopenia were the most common grade 3 or higher adverse events, with five patients discontinuing olaparib and three durvalumab due to toxicity.

TOPACIO was a phase I/II study exploring the combination of niraparib and pembrolizumab in patients with recurrent, platinum-resistant ovarian cancer irrespective of BRCA status.[50] The ovarian cancer cohort included 62 patients with platinum-resistant disease or ineligible for platinum-based chemotherapy and was clinically diverse, with most patients with BRCA-wild type tumors, platinum-resistant or refractory disease, and prior bevacizumab exposure. The combination of niraparib and pembrolizumab achieved a promising objective response rate of 18% (90% CI 11% to 29%) and disease control rate of 65% (90% CI 54% to 75%), including three (5%) with confirmed complete response, eight (13%) with partial response, and 28 (47%) with stable disease. Of note, five of eight patients with response lasting more than 6 months had platinum-resistant or platinum-refractory BRCA-wild type disease. Also nine patients with stable disease received treatment for more than 6 months, two of whom had treatment for over 1 year. After a median follow-up of 12.4 months, the median duration of response was not reached (range 4.2 to ≥14.5 months). At data cut-off, three patients were still receiving treatment, with a median progression-free survival of 3.4 months (95% CI 2.2 to 5.1). Toxicity was as expected. The incidence of immune-related adverse events of grade 3 or higher was 8%, comparable to that observed in other trials of pembrolizumab monotherapy. Exploratory analyses showed the same benefit regardless of BRCA or homologous recombination deficiency status, PD-L1 expression, platinum sensitivity or resistance, and prior bevacizumab use. Although this evidence requires testing in future trials, the combination seems promising in this population with limited treatment options, including in the subgroup with platinum-resistant disease, no BRCA mutations, or homologous recombination deficiency, in whom responses were higher than expected with chemotherapy or either agent as monotherapy.

A small proof-of-concept phase II study with 35 patients with ovarian cancer who were heavily pre-treated (86% with platinum-resistant and 77% with BRCA-wild type disease) with olaparib and durvalumab achieved an objective response rate of 14% (95% CI 4.8% to 30.3%).[51] Although not meeting the primary endpoint of over 17.1% objective response rate, the study achieved an interesting disease control rate of 71% (95% CI 53.7% to 85.4%, including partial response and stable disease) and a median progression-free survival of 3.9 months, with one third of this mostly platinum-resistant, heavily pre-treated population experiencing clinical benefit lasting longer than 6 months. Interestingly, translational research in this study revealed that treatment-enhanced interferon γ production was associated with improved progression-free survival (HR 0.37, 95% CI 0.16 to 0.87), while elevated VEGFR3 levels were associated with worse progression-free survival (HR 3.22, 95% CI 1.23 to 8.40).[51] These results suggest that olaparib plus durvalumab induces immunomodulatory effects, and that VEGF/VEGFR pathway blockade might be necessary to improve efficacy of the combination.[51]

Finally, in a phase I/II dose escalation study of the anti-CTLA-4 tremelimumab alone or in combination with olaparib in 24 patients with advanced ovarian cancer, two patients achieved more than 6 month progression-free survival with the duplet, one achieved partial response also with the duplet, and nine achieved stable

Table 6 Combinations of immunotherapy with anti-angiogenic agents for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Follow-up (median months)	Objective response rate (%)	Progression-free survival (median months)	Overall survival (median months)
Lee et al. 2017[54]	I	Durvalumab+ cediranib	Recurrent platinum-sensitive/resistant ovarian cancer	26	Not reported	50%	Not reported	Not reported
Liu et al. 2019[55]	II	Nivolumab+ bevacizumab	Relapsed platinum-sensitive/resistant ovarian cancer	38	Not reported	28.9%	8.1	Not reported
LEAP 005 (González-Martín et al. 2020)[56]	II	Lenvatinib+ pembrolizumab	Previously treated ovarian cancer	31	7.8	32%	4.4	Not reported
EORTC-1508 (Banerjee et al. 2021)[57]	II	Atezolizumab+ bevacizumab (±acetylsalicylic acid) vs bevacizumab vs atezolizumab vs atezolizumab+ acetylsalicylic acid	Recurrent platinum-resistant ovarian cancer	122	Not reported	15.2% atezolizumab+ bevacizumab + acetylsalicylic acid 19.4% atezolizumab+ bevacizumab 9.7% bevacizumab	4.0 atezolizumab+ bevacizumab + acetylsalicylic acid 4.1 atezolizumab+ bevacizumab 2.3 bevacizumab 2.1 atezolizumab 2.2 atezolizumab+ acetylsalicylic acid	11.6 atezolizumab+ bevacizumab + acetylsalicylic acid 12.1 atezolizumab+ bevacizumab 10.4 bevacizumab

disease (six with single-agent tremelimumab and three with the duplet), showing the modest clinical benefit of the combination in this setting.[52]

The combination of niraparib plus dostarlimab versus chemotherapy of physician's choice is currently being investigated in patients who are not candidates for platinum re-treatment in the randomized phase III NItCHE-MITO33 trial.[53] The niraparib and dostarlimab combination is also being explored in patients with BRCA-mutated ovarian cancer in a phase I study.

Anti-angiogenic agents with immunotherapy

Dual inhibition of angiogenic and immune checkpoint pathways has been tested in recurrent ovarian cancer in few studies to date (Table 6).

The safety and clinical activity of durvalumab in combination with cediranib was initially investigated in a dose-escalation phase I study in female cancer, including recurrent platinum-sensitive and platinum-resistant ovarian cancer.[54] A 50% response rate was observed in the 12 evaluable patients who received the combination, as well as a 75% disease control rate. Grade 3 and 4 adverse events reported with the duplet included hypertension (one of six) and fatigue (one of six).

A single-arm phase II trial assessed the activity of combined nivolumab and bevacizumab in women with platinum-resistant (n=18) and platinum-sensitive (n=20) relapsed ovarian cancer.[55] The objective response rate across all patients was 28.9%, with lower clinical activity in the platinum-resistant (16.7%, 95% CI 3.6% to 41.4) compared with the platinum-sensitive (40.0%, 95% CI 19.1% to 64.0%) setting. Approximately 90% of patients experienced at least one treatment-related adverse event, most commonly fatigue and myalgia.

The combination of lenvatinib plus pembrolizumab in patients with previously treated ovarian cancer was investigated in the multi-cohort, phase II LEAP-005 study.[56] Efficacy endpoints were favorable among 31 patients enrolled, with an objective response rate of 32% (95% CI 17% to 51%), disease control rate of 74% (95% CI 55% to 88%), a median progression-free survival of 4.4 months (95% CI 4.0 to 8.5), and a median duration of response not reached (range 1.5+ to 7.9+).

The randomized phase II EORTC-1508 trial explored the combination of bevacizumab and atezolizumab, with the addition of acetylsalicylic acid, in platinum-resistant ovarian cancer.[57] A total of 122 patients were randomly assigned to receive different combinations of the study treatments. While tumor response did not differ, the median time to first subsequent therapy was significantly longer in patients receiving bevacizumab plus atezolizumab with or without acetylsalicylic acid (5.8 months, 95% CI 4.2 to 8.7; and 5.3 months, 95% CI 4.0 to 7.5) compared with bevacizumab alone (3.0 months, 95% CI 2.3 to 4.4; p=0.033), suggesting that the chemotherapy-free combination could delay the time to the next cancer treatment. In addition, a numerical increase in median progression-free survival was also observed with the combination (4.0 months, 95% CI 2.3 to 5.7, and 4.1 months, 95% CI 2.2 to 5.4 vs 2.3 months, 95% CI 2.0 to 4.1 with bevacizumab alone). The addition of acetylsalicylic acid did not appear to improve treatment efficacy.

TRIPLE COMBINATION THERAPY

Beyond doublet regimens, chemotherapy-sparing triple combinations of PARP inhibitors with checkpoint inhibitors and VEGFR inhibitors are also being investigated in recurrent platinum-sensitive or platinum-resistant disease (Table 7).

The previously mentioned MEDIOLA phase II trial added new cohorts to explore the safety and efficacy of olaparib, durvalumab, and bevacizumab in women with recurrent, platinum-sensitive, non-germline BRCA-mutated ovarian cancer.[58] Very favorable response rates and disease control rates were achieved with the triplet, with a confirmed objective response rate of 77.4% (95% CI 58.9% to 90.4%) and a 24 week disease control rate of 77.4% (90% CI 61.7% to 88.9%). Responses were durable, with a median duration of response of 11.1 months and a median progression-free survival of 14.7 months (95% CI 10.0 to 18.1). The efficacy of the triplet was shown regardless of genomic instability status and

Table 7 Triple combinations for the treatment of recurrent ovarian cancer

Trial name/ identification	Phase	Treatment(s)	Disease setting	Sample size	Follow-up (median months)	Objective response rate (%)	Progression-free survival (median months)	Overall survival (median months)
MEDIOLA (Drew et al. 2020)[58]	II	Olaparib+ durvalumab + bevacizumab	Recurrent platinum-sensitive non-germline BRCA-mutated ovarian cancer	32	Not reported	77.4%	14.7	Not reported
OPAL (Liu et al. 2021)[13]	II	Dostarlimab+ niraparib + bevacizumab	Recurrent, platinum-resistant ovarian cancer	41	Not reported	17.9	7.6	Not reported
GINECO BOLD (Freyer et al. 2021)[47]	II	Durvalumab+ bevacizumab +olaparib	Recurrent platinum-sensitive/resistant advanced high-grade ovarian cancer	74	15.5	Not reported	4.1 months in platinum-resistant disease; 4.9 months in platinum-sensitive disease	18.8 months in platinum-resistant disease; 18.5 months in platinum-sensitive disease

BRCA, BReast CAncer gene.

was well tolerated, with a safety profile in line with the previously reported for the respective single agents.

Anti-tumor activity and tolerability were also observed in patients with platinum-resistant ovarian cancer receiving the triple combination of niraparib, dostarlimab, and bevacizumab in the phase II OPAL trial.[13] A total of 9.8% of patients had BRCA-mutated and 82.9% had BRCA-wild type tumors, with 7.3% with unknown BRCA status. The objective response rate was 17.9% (90% CI 8.7% to 31.1%), the median progression-free survival was 7.6 months (95% CI 4.2 to 10.6), and the disease control rate was 76.9% (90% CI 63.2% to 87.4%). The safety profile of the triplet was consistent with that of individual agents, with 22.0% of patients reporting grade 3 hypertension and thrombocytopenia each.

Results of the GINECO BOLD study were recently presented.[47] This phase II trial explored the activity of bevacizumab, olaparib, and durvalumab in 74 patients with platinum-resistant (n=41) and platinum-sensitive (n=33) recurrent high-grade advanced ovarian cancer, regardless of prior lines of therapy. With a median follow-up of 15.5 month, the study reported safety and efficacy of the chemotherapy-sparing combination, with a 3 month and 6 month disease control rate of 70% and 30% in the platinum-resistant cohort (where 17% of patients are still under treatment) and a 6 month disease control rate of 44% in the platinum-sensitive cohort. The median progression-free survival was 4.1 and 4.9 months and the median overall survival was 18.8 and 18.5 months in platinum-resistant and platinum-sensitive patients, respectively. Safety data were not reported.

Other chemotherapy-sparing triple combinations including PARP inhibitors, anti-PD-L1, and VEGFR inhibitors are being investigated, including dostarlimab, niraparib, and bevacizumab in the randomized phase III NSGO/AVANOVA trial; durvalumab, olaparib, and cediranib in a phase II study (NCT02484404) after preliminary phase I activity shown in a small number of patients (n=7)[13] ; and nivolumab, rucaparib, and bevacizumab in another phase II study (NCT02873962). Also the mitogen-activated protein kinase kinase inhibitor cobimetinib in combination with niraparib, with or without atezolizumab, is being explored in a phase Ib study in patients with platinum-sensitive advanced ovarian cancer (NCT03695380).

CONCLUSION

Although chemotherapy remains the cornerstone of recurrent advanced ovarian cancer treatment, new and exciting data are emerging in favor of chemotherapy-free alternatives. This approach has been gaining momentum due to its efficacy, manageable toxicity profile, and ease of administration, representing a more patient-friendly option and potentially associated with improved quality of life. The data presented, together with ongoing trials including larger patient numbers, will predictably confirm this change in the treatment paradigm of advanced ovarian cancer, away from cytotoxic chemotherapy.

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