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Review Article

Rationale for combination PARP inhibitor and antiangiogenic treatment in advanced epithelial ovarian cancer: A review

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HIGHLIGHTS

- PARP inhibitors and antiangiogenic agents as monotherapy have changed the landscape of ovarian cancer treatment.
- Combination therapy with PARP inhibitors plus antiangiogenic agents is a novel treatment option in advanced ovarian cancer.
- PARP inhibitors combined with antiangiogenic agents demonstrated efficacy in the relapsed disease setting.
- Combination maintenance therapy offers a benefit over antiangiogenics alone in newly diagnosed HRD-positive ovarian cancer.
- It is important to further define which patients are candidates for monotherapy or combination therapy.

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ABSTRACT

Inhibitors of poly(ADP-ribose) polymerase (PARP) and angiogenesis have demonstrated single-agent activity in women with advanced ovarian cancer. Recent studies have aimed to establish whether combination therapy can augment the response seen with PARP inhibitors or antiangiogenic agents alone. This review provides an overview of PARP inhibitors and antiangiogenics as monotherapy in women with advanced ovarian cancer, explores potential mechanisms of action of PARP inhibitor and antiangiogenic combination treatments, reviews efficacy and safety data from trials evaluating this combination, and outlines ongoing and future trials evaluating this combination, discussing these in the context of the current and future treatment landscape for women with advanced ovarian cancer. Sentinel studies evaluating PARP inhibitor ($n = 8$), antiangiogenic ($n = 4$), and combination ($n = 7$) therapy were identified in women with newly diagnosed ($n = 7$) and recurrent ($n = 12$) ovarian cancer. PARP inhibitors included olaparib ($n = 9$), niraparib ($n = 4$), rucaparib ($n = 1$), and veliparib ($n = 1$). Antiangiogenic agents included bevacizumab ($n = 7$) and cediranib ($n = 4$). PARP inhibitors combined with antiangiogenics demonstrated efficacy based on objective response rates and progression-free survival (PFS) in the relapsed disease setting. Maintenance therapy with the PARP inhibitor, olaparib, plus antiangiogenic therapy offered a significant PFS benefit versus the antiangiogenic alone in women with newly diagnosed advanced ovarian cancer who tested positive for homologous recombination deficiency. Combination therapy was tolerated, with no new safety signals reported compared with monotherapy trials. PARP inhibitors and antiangiogenics have changed the landscape of ovarian cancer treatment. The PARP inhibitor plus antiangiogenic combination is a novel treatment option that appears promising in the first-line advanced and recurrent ovarian cancer settings, although the role of this combination in recurrent disease requires further elucidation. Defining which patients are candidates for monotherapy or combination therapy is critical, taking into consideration safety profiles of therapies alone or in combination, and how these treatments should be sequenced in clinical practice.

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Contents

1. Introduction

In patients with advanced and recurrent epithelial ovarian, tubal and peritoneal cancers (collectively referred to as ovarian cancer), targeted therapies including inhibitors of poly(ADP-ribose) polymerase (PARP) and angiogenesis have been investigated with the aim to prolong progression-free survival (PFS) and overall survival (OS) [1]. Most clinical studies in ovarian cancer to date have focused on PARP inhibitors or the antiangiogenic drug bevacizumab as monotherapy and/or maintenance treatment, with both PARP inhibitors and bevacizumab demonstrating efficacy in first-line and recurrent advanced ovarian cancer settings [2–11]. Clinical trials have aimed to establish whether combination therapy can augment the response seen with PARP inhibitors or antiangiogenic drugs alone. This review primarily focuses on PARP inhibitor and antiangiogenic agents used in combination. It describes the role of PARP inhibitors and antiangiogenic agents in patients with ovarian cancer and explores potential mechanisms of action of the combination. We also review efficacy and safety data; outline ongoing and future trials evaluating the combination in treatment and maintenance settings; and, lastly, discuss treatment options in the context of the current and future treatment landscape for women with newly diagnosed advanced or recurrent ovarian cancer.

2. PARP inhibitor and antiangiogenic treatment mechanisms and current indications for patients with ovarian cancer

Angiogenesis, the process of new blood vessel formation, plays a pivotal role in normal ovarian physiology, as well as ovarian cancer progression [12]. Among the many factors regulating angiogenesis are vascular endothelial growth factors (VEGFs A–D) and their receptors (VEGFRs 1–3), which are expressed at varying levels on epithelial ovarian cancer cells; additionally, increased VEGF signaling has been associated with development of malignant ascites and tumor progression [12,13]. Two angiogenesis inhibitors, bevacizumab and cediranib, with distinct mechanisms of action [14], have demonstrated antitumor activity in patients with ovarian cancer [7,8,15,16]; the monoclonal antibody bevacizumab targets VEGF-A and the small-molecule inhibitor cediranib targets multiple factors, including VEGFRs 1–3 and c-Kit [17].

Bevacizumab in combination with platinum-based chemotherapy, followed by bevacizumab alone as maintenance was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of patients with FIGO (International Federation of Gynecology and Obstetrics) stage III or IV epithelial ovarian cancer after initial surgical resection following results of the GOG-0218 [8] and ICON7 [7] studies (Table 1). Bevacizumab is also approved in combination with, and as maintenance following, platinum-based chemotherapy for patients with platinum-sensitive recurrent/relapsed (PSR) ovarian cancer. For patients with platinum-resistant recurrent ovarian cancer who have received ≤2 prior chemotherapy regimens, bevacizumab is approved by the FDA and EMA in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan [18,19]. For both relapsed disease indications, the EMA specifies that patients must not have received prior bevacizumab or other antiangiogenic treatment [18].

PARP inhibitors, in addition to inhibiting PARP catalytic activity, trap PARP on DNA at single-strand breaks, preventing their repair, resulting in double-strand breaks that cannot be accurately repaired in tumors with defects in homologous recombination repair (HRR), such as BRCA mutations (BRCAm) [20]. Dependency on secondary, lower-fidelity repair mechanisms (e.g. nonhomologous end-joining) makes HRR-deficient (HRD) cells sensitive to PARP inhibition via multiple mechanisms, including synthetic lethality (DNA damage accumulation within the tumor cell and ultimately cell death) and replication arrest resulting from physical obstruction of replication forks by PARP trapping [21,22].

The PARP inhibitor olaparib was approved for first-line maintenance treatment of BRCAm FIGO stage III or IV epithelial ovarian cancer in the US, EU, Japan and other countries [23,24] following the SOLO1 study results [5]. Niraparib was approved in the first-line maintenance setting in the intention-to-treat (ITT) population (patients with newly diagnosed FIGO stage III or IV ovarian cancer; all comers) [25,26] following the PRIMA study results [3] (Table 1). More recently, the FDA and EMA approved olaparib in combination with bevacizumab as maintenance therapy in patients with newly diagnosed stage III or IV ovarian cancer who have HRD-positive tumors with a deleterious or suspected deleterious BRCAm and/or genomic instability, and have a complete or partial response to first-line platinum-based therapy [23,24], based on the results of the PAOLA-1 study [11]. In the relapsed disease setting, three PARP inhibitors, olaparib, niraparib and rucaparib, are FDA and EMA approved as maintenance therapies for women with recurrent epithelial ovarian cancer who had a complete or partial response to second-line or greater platinum-based chemotherapy, regardless of *BRCA1* or *BRCA2* mutation status (Table 1) [23–28].

3. Rationale for PARP inhibitor and antiangiogenic combination treatments for ovarian cancer

Where both antiangiogenic agents and PARP inhibitors have demonstrated activity as monotherapies in relapsed ovarian cancer [2–8,29,30], combining these agents has been of interest, especially as they have mostly limited overlapping toxicities. Mechanistically, combining antiangiogenic therapy with PARP inhibition could hypothetically result in increased antitumor activity [31,32].

Although further research is required for validation, preclinical studies suggest antiangiogenic agents affect HRR through various mechanisms [32,33]. By inhibiting angiogenesis, antiangiogenic agents induce hypoxia in the tumor microenvironment, downregulating *BRCA1/2* and *RAD51*, key factors involved in HRR [32–34]. Bevacizumab

Table 1
Efficacy results from key PARP inhibitor and antiangiogenic maintenance monotherapy trials in ovarian cancer.

Study and phase	Patient population	No. of patients	Interventions	Median PFS (months)	Median OS (months)	Quality of evidence[a]
Bevacizumab in combination with first-line platinum-based chemotherapy followed by maintenance bevacizumab						
GOG-0218 [8,63] NCT00262847 Phase III	Stage III–IV	1873 (1:1:1)	Arm 1: 6 cycles of carboplatin + paclitaxel + placebo for cycles 2–22 Arm 2: 6 cycles of carboplatin + paclitaxel + bevacizumab (15 mg/kg) on day 1 of cycles 2–6 and + placebo for cycles 7–22 Arm 3: 6 cycles of carboplatin + paclitaxel + bevacizumab (15 mg/kg) on day 1 of cycles 2–22	Arm 1: 10.3 Arm 2: 11.2 Arm 3: 14.1 (Arm 2 vs Arm 1 HR, 0.908; 95% CI 0.795–1.040; $p = 0.16$) (Arm 3 vs Arm 1 HR, 0.717; 95% CI 0.625–0.824; $p < 0.001$)	Arm 1: 41.1 Arm 2: 40.8 Arm 3: 43.4 (Arm 2 vs Arm 1 HR, 1.06; 95% CI 0.94–1.20; $p = 0.34$) (Arm 3 vs Arm 1 HR, 0.96; 95% CI 0.85–1.09; $p = 0.53$)	1
ICON7 [7,72] NCT00483782 Phase III	High-risk early stage (Stage I–IIA) and Stage IIB–IV	1528 (1:1)	Carboplatin + paclitaxel + bevacizumab (7.5 mg/kg) given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 cycles or until disease progression vs carboplatin + paclitaxel + placebo	19.0 vs 17.3 (HR, 0.81; 95% CI 0.70–0.94; $p = 0.004$)	45.5 vs 44.6 (restricted mean)	1
Bevacizumab in combination with platinum-based chemotherapy followed by maintenance bevacizumab in patients with platinum-sensitive relapsed ovarian cancer						
OCEANS [29,64] NCT00434642 Phase III	Platinum-sensitive recurrent	484 (1:1)	Gemcitabine + carboplatin and bevacizumab (15 mg/kg) given concurrently every 3 weeks for 6–10 cycles and continued until disease progression or unacceptable toxicity vs gemcitabine + carboplatin + placebo	12.4 vs 8.4 (HR, 0.484; 95% CI 0.39–0.61; $p < 0.0001$) [64]	33.6 vs 32.9 (HR, 0.95; 95% CI 0.77–1.18; $p = 0.65$) [29]	1
GOG-0213 [30] NCT00565851 Phase III	Platinum-sensitive recurrent	674 (1:1)	Carboplatin + paclitaxel + bevacizumab (15 mg/kg) given concurrently every 3 weeks for 6 cycles and continued until disease progression or unacceptable toxicity vs carboplatin + paclitaxel + placebo	13.8 vs 10.4 (HR, 0.628; 95% CI 0.53–0.74; $p < 0.0001$)	42.2 vs 37.3 (HR, 0.829; 95% CI 0.68–1.01; $p = 0.056$)[b]	1
PARP inhibitors as first-line maintenance treatment						
SOLO1 [5,65] NCT01844986 Phase III	Stage III–IV, BRCAm, complete or partial response after platinum-based chemotherapy	391 (2:1)	Maintenance olaparib tablets (300 mg bid) vs maintenance placebo (treatment until investigator-assessed objective disease progression or up to 2 years: patients with an ongoing partial response at 2 years could continue receiving the intervention)	Primary analysis: Not reached vs 13.8[c] (HR, 0.30; 95% CI 0.23–0.41; $p < 0.001$) 5-year follow-up: 56.0 vs 13.8[c] (HR, 0.33; 95% CI 0.33–0.43)	Data not yet mature (HR, 0.95; 95% CI 0.60–1.53)	1
PRIMA [3] NCT02655016 Phase III	Stage III–IV, and a complete or partial response after platinum-based chemotherapy	733 (2:1)	Maintenance niraparib tablets (200 or 300 mg od individualized or fixed starting dose) vs maintenance placebo (until investigator-assessed objective disease progression or up to 3 years)	Overall population: 13.8 vs 8.2[d] (HR, 0.62; 95% CI 0.50–0.76; $p < 0.001$) HRD-positive population: 21.9 vs 10.4[d] (HR, 0.43; 95% CI 0.31–0.59; $p < 0.001$) HRD-positive, BRCAm population: 22.1 vs 10.9[d] (HR, 0.40; 95% CI 0.27–0.62) HRD-positive, non-BRCAm population: 19.6 vs 8.2[d] (HR, 0.50; 95% CI 0.31–0.83) HRD-negative population: 8.1 vs 5.4[d] (HR, 0.68; 95% CI 0.49–0.94) HRD-unknown population: median not reported[d,e] (HR, 0.85; 95% CI 0.51–1.43)	Data not yet mature (HR, 0.70; 95% CI 0.44–1.11)	1
PARP inhibitors as first-line maintenance treatment (following combination with chemotherapy)						
VELIA [9]	Stage III–IV	1140	Arm 1: 6 cycles of carboplatin + paclitaxel and placebo for cycles	Overall population (Arm 1 vs Arm 3):	Data not yet mature	1

NCT02470585 Phase III		(1:1:1)	0–36 Arm 2: 6 cycles of carboplatin + paclitaxel + veliparib (150 mg bid), then placebo maintenance for cycles 7–36 Arm 3: 6 cycles of carboplatin + paclitaxel + veliparib (150 mg bid), then veliparib maintenance 300 mg bid for 2 weeks, then 400 mg bid to cycle 36	17.3 vs 23.5[c] (HR, 0.68; 95% CI 0.56–0.83; $p < 0.001$) BRCAm population (Arm 1 vs Arm 3): 22.0 vs 34.7[c] (HR, 0.44; 95% CI 0.28–0.68; $p < 0.001$) HRD-positive population: 20.5 vs 31.9[c] (HR, 0.57; 95% CI 0.43–0.76; $p < 0.001$)		
PARP inhibitors as maintenance treatment for platinum-sensitive recurrent disease						
Study 19 [54,66,67] NCT00753545 Phase II	Platinum-sensitive relapsed	265 (1:1)	Maintenance olaparib capsule (400 mg bid) vs maintenance placebo	Overall population: 8.4 vs 4.8[c] (HR, 0.35; 95% CI 0.25–0.49; $p < 0.001$) [54] BRCAm population: 11.2 vs 4.3[c] (HR, 0.18; 95% CI 0.10–0.31; $p < 0.0001$) [67] BRCAwt population: 7.4 vs 5.5[c] (HR, 0.54; 95% CI 0.34–0.85; $p = 0.0075$) [67]	Overall population: 29.8 vs 27.8 (HR, 0.73; 95% CI 0.55–0.95; nominal $p = 0.021$[f]) [66] *BRCA*m population: 34.9 vs 31.9 (HR, 0.73; 95% CI 0.45–1.17; $p = 0.19$) [67] *BRCA*wt population: 24.5 vs 26.2 (HR, 0.99; 95% CI 0.63–1.55; $p = 0.96$) [67]	1
SOLO2 [6,68] NCT01874353 Phase III	Platinum-sensitive relapsed, BRCAm	295 (2:1)	Maintenance olaparib tablets (300 mg bid) vs maintenance placebo	19.1 vs 5.5[c] (HR, 0.30; 95% CI 0.22–0.41; $p < 0.0001$)	51.7 vs 38.8 (HR 0.74; 95% CI 0.54–1.00; $p = 0.0537$)	1
OPINION [69] NCT03402841 Phase III	Platinum-sensitive relapsed, non-gBRCAm	279	Maintenance olaparib tablets (300 mg bid)	Overall population: 9.2 (95% CI 7.6–10.9) HRD-positive (excluding sBRCAm): 9.7 (95% CI 8.1–11.1) HRD-negative patients: 7.3 (95% CI 5.5–9.1) sBRCAm: 14.5[g] (95% CI 9.2 to NE)	Data not yet mature	2
NOVA [4,73] NCT01847274 Phase III	Platinum-sensitive recurrent	553 (2:1)	Maintenance niraparib tablets (300 mg od) vs maintenance placebo	gBRCAm population: 21.0 vs 5.5[d] (HR, 0.27; 95% CI 0.17–0.41; $p < 0.001$) gBRCAwt population: 9.3 vs 3.9[d] (HR, 0.45; 95% CI 0.34–0.61; $p < 0.001$) Non-gBRCAm HRD-positive population: 12.9 vs 3.8[d] (HR, 0.38; 95% CI 0.24–0.59; $p < 0.001$) BRCAwt HRD-positive population: 9.3 vs 3.7 (HR, 0.38; 95% CI 0.23–0.63; $p < 0.001$)	gBRCAm population: 45.9 vs 43.2 (restricted mean) Non-gBRCAm population: 38.5 vs 39.1 (restricted mean)	1
ARIEL3 [2] NCT01968213 Phase III	Platinum-sensitive recurrent	564 (2:1)	Maintenance rucaparib tablets (600 mg bid) vs maintenance placebo	Overall population: 10.8 vs 5.4[c] (HR, 0.37; 95% CI 0.30–0.45; $p < 0.0001$) BRCAm population:	Data not yet mature	1

(continued on next page)

Table 1 (*continued*)

Study and phase	Patient population	No. of patients	Interventions	Median PFS (months)	Median OS (months)	Quality of evidence[a]
				16.6 vs 5.4[c] (HR, 0.23; 95% CI 0.16–0.34; $p < 0.0001$) HRD-positive population: 13.6 vs 5.4[c] (HR, 0.32; 95% CI 0.24–0.42; $p < 0.0001$) BRCAwt high-LOH: 9.7 vs 5.4[c] (HR, 0.44; 95% CI 0.29–0.66; $p < 0.0001$) BRCAwt low-LOH; 6.7 vs 5.4[c] (HR, 0.58; 95% CI 0.40–0.85; $p = 0.0049$)	

bid, twice daily; BRCAm, *BRCA1* or *BRCA2* mutation; BRCAwt, *BRCA1* or *BRCA2* wild-type; CI, confidence interval; gBRCAm, germline *BRCA1* or *BRCA2* mutation; gBRCAwt, germline BRCA wild-type; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; NE, not evaluable; non-BRCAm, not BRCAm; od, once daily; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; sBRCAm, somatic BRCA mutation.

[a] Quality of evidence was rated as follows: 1. Properly powered and conducted randomized clinical trial; 2. Well-designed controlled trial without randomization; prospective comparative cohort trial; 3. Case-control studies; retrospective cohort study; 4. Case series with or without intervention; cross-sectional study; 5. Opinion of respected authorities; case reports.

[b] Post hoc analysis demonstrated an adjusted HR of 0.823 (95% CI 0.680–0.996); $p = 0.045$.

[c] Investigator-assessed.

[d] Assessed by blinded independent central review.

[e] Adjusted for baseline prognostic factors.

[f] The predefined threshold for statistical significance was $p < 0.0095$.

[g] Median unstable because of a lack of events – less than 50% maturity.

treatment has been associated with increased hypoxia-induced HRR deficiencies in tumor cells [35]. Additionally, VEGFR3 inhibition may downregulate *BRCA1/2* in ovarian cancer cells, potentially leading to tumor cell growth arrest. This hypothesis is based on VEGFR3 inhibition-mediated BRCA downregulation reversing chemotherapy resistance and restoring chemosensitivity in cells in which a *BRCA2*m had reverted to wild-type [32]. Where cells with increased HRD may be more vulnerable to PARP inhibition, antiangiogenics could combine with PARP inhibitors to produce synergistic antitumor effects [31].

PARP1 may also play a role in angiogenesis [36,37]. *PARP1* knockout mice exhibit decreased angiogenesis despite presence of growth factors, suggesting potential antiangiogenic effects of PARP inhibitors [36]. *PARP1* overexpression in human epithelial ovarian cancer tissues has been associated with factors such as higher pathology grade and lymph node metastasis, suggesting PARP1 may be involved in ovarian cancer progression [37]. PARP1 may also enhance angiogenesis in epithelial ovarian cancer cells through VEGF-A upregulation [37]. However, further confirmatory studies are required. PARP inhibitors may also exert anti-inflammatory effects by attenuating the PARP-1-mediated upregulation of pro-inflammatory cytokines [38].

Preclinical studies suggest mechanisms through which PARP inhibitor and antiangiogenic combination treatment may provide enhanced benefit in ovarian cancer [32,39]. Potential mechanisms, outlined in Fig. 1 and Table 2, provide a rationale for combining PARP inhibitors and antiangiogenic agents through both direct and indirect (through tumor microenvironment modification) changes in tumor cell genomic makeup to augment therapeutic gain [39]. However, the underlying mechanism(s) of these combinations are still not fully understood, may vary by antiangiogenic agent and have not been proven in clinical trials to date. Further research is required to elucidate the exact mechanisms through which this combination exerts its anticancer effects.

4. Clinical experience combining PARP inhibitor and antiangiogenic agents for relapsed ovarian cancer

Phase I clinical trials established the activity, safety and tolerability of PARP inhibitors (olaparib [40,41], niraparib [42], veliparib [43]) administered in combination with antiangiogenic agents (cediranib [40], bevacizumab [41–43]). Rucaparib is being investigated in combination with lucitanib in the ongoing phase I/II SEASTAR study in patients with advanced solid tumors (NCT03992131).

Following evidence of efficacy and tolerability of combination treatment, phase II studies were performed. Cediranib plus olaparib capsules in PSR ovarian, fallopian tube or primary peritoneal cancers improved median PFS by 8.3 months compared with olaparib capsules alone (Table 3) [44]. Post hoc exploratory analyses suggested greater activity of cediranib plus olaparib in the BRCA wild-type/unknown population, with a median 18-month PFS improvement versus olaparib monotherapy (Table 3) [44]. However, although the recent GY004 phase III study demonstrated cediranib plus olaparib had similar activity to standard-of-care treatment in PSR ovarian cancer, the study did not meet the primary endpoint of improved PFS [45]. While the BAROCCO study of heavily pretreated patients with platinum-resistant recurrent ovarian cancer demonstrated antitumor activity with combination cediranib and olaparib, there was no significant improvement in PFS with either the continuous or intermittent cediranib plus olaparib compared with weekly paclitaxel in the ITT population (primary analysis); a similar result was observed in the BRCA wild-type population (Table 3) [46]. Cediranib plus olaparib clinical activity was also reported in a biomarkers of response study in patients with platinum-sensitive or -resistant ovarian cancer, where germline BRCAm (gBRCAm) presence appeared to confer increased likelihood of response; however, responses were also confirmed in BRCA wild-type patients [47]. More recently, the EVOLVE study demonstrated clinical activity of cediranib plus olaparib following progression while on a PARP inhibitor in platinum-sensitive and -resistant

ovarian cancer (Table 3) [48]. Most importantly, this study identified possible mechanisms of PARP inhibitor resistance, including mutation reversion in BRCA and other homologous repair genes, upregulation of *BRCA1/2*, *CCNE1* amplification and retinoic acid-inducible gene I (RIG-I)-like receptor downregulation. However, EVOLVE was a small study ($n = 34$) and confirmation is needed.

AVANOVA-2 evaluated niraparib plus bevacizumab treatment versus niraparib alone in PSR ovarian cancer, with the combination significantly improving the confirmed objective response rate (60% vs 27%) and median PFS by 6.4 months compared with niraparib alone (Table 3) [10]. Preplanned exploratory subgroup analyses indicated that the PFS benefit observed with the combination occurred regardless of HRD status or duration of chemotherapy-free interval [10].

PARP inhibitors combined with antiangiogenic agents demonstrated efficacy based on objective response rates and PFS [10,44–48]; however, combination therapy has not been shown to be superior to standard-of-care chemotherapy options [45,46].

Table 2
Potential mechanisms of PARP inhibitor plus antiangiogenic combination treatment.

	Potential mechanism of combined treatment
1	Antiangiogenic agents induce hypoxia in the tumor microenvironment by downregulating key factors involved in HRR [32–34]
2	Inhibition of VEGFR3 is thought to downregulate BRCA expression, induce cell cycle arrest, and induce chemosensitization; therefore, VEGFR3 inhibition could allow BRCA wild-type patients (or patients whose BRCAm has reverted to wild-type) to benefit from PARP inhibitors [32]
3	VEGFR2-mediated inhibition of angiogenesis decreases perfusion and increases hypoxia. HRR gene downregulation, e.g. *BRCA1* or *BRCA2* and *RAD51*, occurs with hypoxia, thus reducing protein production and DNA repair potential. Therefore, enhanced PARP inhibitor sensitivity could be observed in the hypoxic setting [33,70]
4	Preclinical synergy between PARP inhibition and antiangiogenics may result in inhibition of ovarian cancer cell invasion and microvascular endothelial cell tube formation [59]

BRCAm, *BRCA1* or *BRCA2* mutation; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase; VEGFR, vascular endothelial growth factor receptor.

5. Clinical experience with first-line treatment of advanced ovarian cancer with combined PARP inhibitor and antiangiogenic agents

The phase III PAOLA-1 study evaluated first-line PARP inhibitor and antiangiogenic combination treatment [11]. Patients with advanced ovarian cancer, with or without BRCAm, received olaparib plus bevacizumab or placebo plus bevacizumab as first-line maintenance. Patients had no evidence of disease, or complete or partial response following platinum-based chemotherapy and bevacizumab. The primary endpoint was met, with a statistically significant improvement in median PFS for olaparib plus bevacizumab versus bevacizumab alone (22.1 vs 16.6 months; HR, 0.59; 95% CI 0.49–0.72; $p < 0.001$; Table 3) in the ITT population (all comers) [11]. Substantial PFS benefit was observed with combination treatment versus bevacizumab alone in predefined patient subgroups with HRD-positive tumors (including BRCAm; 37.2 vs 17.7 months; HR, 0.33; 95% CI 0.25–0.45) and HRD-positive tumors without BRCAm (28.1 vs 16.6 months; HR, 0.43; 95% CI 0.28–0.66), leading to FDA and EMA approval of the combination as maintenance in HRD-positive newly diagnosed patients. However, no significant benefit was observed for those with HRD-negative tumors (Table 3). Consistent with the PFS analysis in the ITT population, combination treatment delayed time to first subsequent treatment (TFST) compared with bevacizumab alone (median TFST 24.8 vs 18.5 months, respectively) [11]. One limitation is the lack of a maintenance olaparib-only arm and the resultant inability to determine whether

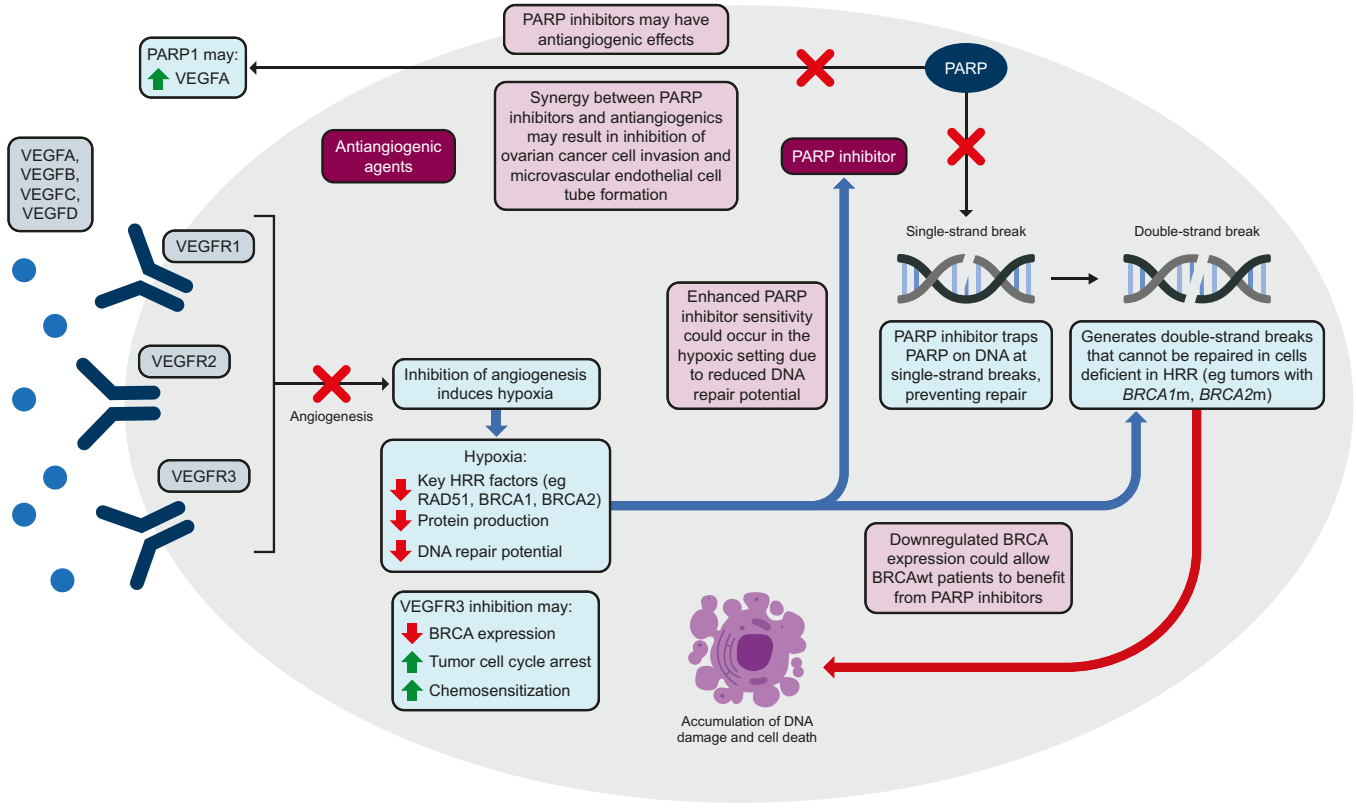

Fig. 1. Potential mechanisms of PARP inhibitor plus antiangiogenic combination treatment [31–34,36,37,59,70].
*BRCA1*m, *BRCA1* mutation; *BRCA2*m, *BRCA2* mutation; BRCAwt, BRCA wild-type; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Table 3
Efficacy results from key PARP inhibitor and antiangiogenic combination trials in ovarian cancer.

Study and phase	Patient population	No. of patients	Interventions	Median PFS (months)	Median OS (months)	Quality of evidence[a]
Bevacizumab in combination with first-line platinum-based chemotherapy followed by maintenance bevacizumab and olaparib						
PAOLA-1 [11,71] NCT02477644 Phase III	Newly diagnosed Stage III–IV, NED, complete or partial response after platinum-based chemotherapy + bevacizumab	806 (2:1)	Maintenance bevacizumab + olaparib vs maintenance bevacizumab + placebo	Overall population: 22.1 vs 16.6 (HR, 0.59; 95% CI 0.49–0.72; $p < 0.001$) HRD (including BRCAm) population: 37.2 vs 17.7 (HR, 0.33; 95% CI 0.25–0.45) HRD, non-BRCAm population: 28.1 vs 16.6 (HR, 0.43; 95% CI 0.28–0.66) HRD-negative population: 16.6 vs 16.2 (HR, 1.00; 95% CI 0.75–1.35) HRD-negative or unknown population [71]:[b] 16.9 vs 16.0 (HR, 0.92; 95% CI 0.72–1.17)	Data not yet mature	1
Bevacizumab in combination with first-line platinum-based chemotherapy followed by maintenance bevacizumab and niraparib						
OVARIO [49] NCT03326193 Phase II	Newly diagnosed Stage IIIB–IV, complete or partial response after platinum-based chemotherapy + bevacizumab	105	Maintenance niraparib + bevacizumab	Median not reached; PFS rate at 6 months: 89.5%	Data not yet mature	2
Cediranib and olaparib in patients with platinum-sensitive relapsed ovarian cancer						
GY004 [45] NCT02446600 Phase III	Platinum-sensitive recurrent	565 (1:1:1)	Arm 1: platinum-based chemotherapy vs Arm 2: olaparib vs Arm 3: olaparib + cediranib	Overall population (Arm 1 vs Arm 2 vs Arm 3): 10.3 vs 8.2 vs 10.4 (HR, 0.856; 95% CI 0.66–1.11; $p = 0.08$ for olaparib + cediranib vs chemotherapy; HR, 1.20; 95% CI 0.93–1.54 between olaparib and chemotherapy) gBRCA population: HR for PFS was 0.55 (95% CI 0.73–1.30) for cediranib +olaparib vs chemotherapy and 0.63 (95% CI 0.37–1.07) for olaparib vs SOC Non-gBRCA population: HR for PFS was 0.97 (95% CI 0.73–1.30) for cediranib + olaparib vs chemotherapy and 1.41 (95% CI 1.07–1.86) for olaparib vs SOC	No between-group differences at 44% events	1
Liu et al [44] NCT0111648 Phase II	Platinum-sensitive recurrent	90 (1:1)	Cediranib + olaparib vs olaparib	Overall population: 16.5 vs 8.2 (HR, 0.50; 95% CI 0.30–0.83; $p = 0.006$) gBRCAm population:[b] 16.4 vs 16.5 (HR, 0.76; 95% CI 0.38–1.49; $p = 0.42$) BRCAwt/unknown population:[b] 23.7 vs 5.7 (HR, 0.31; 95% CI 0.15–0.66; $p = 0.0013$)	Overall population: 44.2 vs 33.3 (HR, 0.64; 95% CI 0.36–1.11; $p = 0.11$) gBRCAm population:[b] 44.2 vs 40.1 (HR, 0.86; 95% CI 0.41–1.82; $p = 0.70$) BRCAwt/unknown population:[b] 37.8 vs 23.0 (HR, 0.44; 95% CI 0.19–1.01; $p = 0.047$)	**1**
Bevacizumab and niraparib in patients with platinum-sensitive relapsed ovarian cancer						
AVANOVA-2	Platinum-sensitive recurrent	97	Bevacizumab + niraparib	Overall population:	Overall population: HR, 0.77; 95% CI 0.42–1.41	1

[10,74] NCT02354131 Phase II			vs niraparib	11.9 vs 5.5 (HR, 0.35; 95% CI 0.21–0.57; $p < 0.0001$) BRCAm population: 14.4 vs 9.0 (HR, 0.49; 95% CI 0.21–1.15) Non-BRCAm population: 11.3 vs 4.2 (HR, 0.32; 95% CI 0.17–0.58) HRD, non-BRCAm population:[b] 11.9 vs 4.1 (HR, 0.19; 95% CI 0.06–0.59)		
Cediranib and olaparib in patients with platinum-resistant relapsed ovarian cancer						
BAROCCO [46] NCT03314740 Phase II	Platinum-resistant recurrent	123	Arm 1: olaparib + continuous cediranib vs Arm 2: olaparib + intermittent cediranib (5 days/week) vs Arm 3: weekly paclitaxel	Overall population (Arm 1 vs Arm 2 vs Arm 3): 5.7 vs 3.8 vs 3.1 Arm 1 vs Arm 3: HR, 0.76; 90% CI 0.49–1.17; $p = 0.28$ Arm 2 vs Arm 3: HR, 1.08; 90% CI 0.71–1.64; $p = 0.76$ BRCAwt population (Arm 1 vs Arm 2 vs Arm 3): 5.8 vs 3.8 vs 2.1 Arm 1 vs Arm 3: HR, 0.63; 95% CI 0.36–1.10; $p = 0.10$	Data not yet mature	1
Cediranib and olaparib following progression while on a PARP inhibitor in patients with ovarian cancer						
EVOLVE [48] NCT02681237 Phase II	Cohort 1: Platinum-sensitive Cohort 2: Platinum-resistant Cohort 3: Further progression after chemotherapy	34	Olaparib + cediranib	16-week PFS Cohort 1: 54.5%; 95% CI 31.8–93.6 Cohort 2: 50.0%; 95% CI 26.9–92.9 Cohort 3: 38.5%; 95% CI 19.3–76.5)	1-year OS Cohort 1: 81.8%; 95% CI 61.9–100 Cohort 2: 68.6%; 95% CI 44.5–100 Cohort 3: 40.4% 95% CI 17.8–91.5	2

BRCAm, *BRCA1* or *BRCA2* mutation; CI, confidence interval; gBRCA, germline BRCA; gBRCAm, germline *BRCA1* or *BRCA2* mutation; BRCAwt, *BRCA1* or *BRCA2* wild-type; HR, hazard ratio; HRD, homologous recombination repair deficiency; NED, no evidence of disease; non-BRCAm, not BRCAm; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; SOC, standard of care.

[a] Quality of evidence was rated as follows: 1. Properly powered and conducted randomized clinical trial; 2. Well-designed controlled trial without randomization; prospective comparative cohort trial; 3. Case-control studies; retrospective cohort study; 4. Case series with or without intervention; cross-sectional study; 5. Opinion of respected authorities; case reports.

[b] Post hoc exploratory analysis.

olaparib alone is driving improved efficacy or whether the combination has synergistic effects.

OVARIO was a single-arm study of niraparib plus bevacizumab maintenance therapy in patients ($N = 105$) with newly diagnosed advanced ovarian cancer who had a complete or partial response following platinum-based chemotherapy and bevacizumab. Preliminary data from OVARIO show that the 6-month PFS rate was 89.5% but median PFS had not been reached (median follow-up not reported) (Table 3) [49].

Published phase III studies of first-line advanced ovarian cancer maintenance therapy with PARP inhibitor monotherapy or in combination with an antiangiogenic agent report positive results (SOLO-1, PRIMA, PAOLA-1 and VELIA) [3,5,9,11]. Based on the collective results from PAOLA-1, SOLO-1 and PRIMA, PARP inhibitor maintenance therapy is a treatment option for patients with newly diagnosed advanced disease. The use of PARP inhibitor maintenance therapy with or without bevacizumab will be dependent upon regulatory agencies (currently, olaparib is approved for use in combination with bevacizumab), patient and tumor characteristics, financial considerations and patient preferences.

The benefit of adding a PARP inhibitor to maintenance bevacizumab, continuing maintenance bevacizumab alone, or switching to a PARP inhibitor alone for women who have received initial therapy with combined chemotherapy is an important, and controversial, clinical question. This question is probably most relevant to women with tumor *BRCA1* or *BRCA2* mutation (tBRCAm) cancers, given the significant PFS improvement with olaparib maintenance in SOLO-1, in which only BRCAm patients were enrolled [5]. The PFS improvement between olaparib plus bevacizumab and placebo plus bevacizumab in the tBRCAm subgroup (HR, 0.31; 95% CI 0.20–0.47) [11] in PAOLA-1 was consistent with that reported for olaparib versus placebo in SOLO1 (HR, 0.30; 95% CI 0.23–0.41) [5]. The relative PFS improvement of adding olaparib to maintenance bevacizumab compared with olaparib alone in women with newly diagnosed tBRCAm ovarian cancer cannot confidently be determined from current data.

Without randomized comparison, and to account for different trial populations, e.g. patients in PAOLA-1 had more advanced disease than those in SOLO1 [5,11], a population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1 studies attempted to evaluate the efficacy of olaparib with bevacizumab versus without bevacizumab, olaparib versus bevacizumab, and bevacizumab versus placebo [50]. Data from patients with BRCAm cancers with complete baseline data in PAOLA-1 were matched (variables adjusted for were tumor location, ECOG [Eastern Cooperative Oncology Group] status, histologic type, FIGO stage, type of surgery, residual disease, response to first-line treatment and age) and pooled with patients with complete baseline data from SOLO1. After adjustment of the PAOLA-1 population, weighted Cox regression and Kaplan-Meier analyses were performed to estimate the comparative efficacy of different maintenance treatments on investigator-assessed PFS, albeit with the limitation that it is a nonrandomized comparison. This analysis demonstrated numerically higher PFS with the olaparib plus bevacizumab combination versus olaparib alone in women with BRCAm newly diagnosed advanced ovarian cancer, although statistical significance was not shown (Kaplan-Meier estimate of PFS at 24 months: 82% vs 73%, respectively; HR, 0.71; 95% CI 0.45–1.09) [50]. While these results are of interest, they should be interpreted with caution, and direct cross-trial comparisons should generally be avoided.

In consideration of whether combined bevacizumab and PARP inhibitor maintenance therapy in first-line ovarian cancer has added benefit compared with PARP inhibitor maintenance monotherapy, the PRIMA study can also provide insight, while recognizing that cross-trial comparisons in this setting are exploratory, given study design and population differences. This study of niraparib maintenance demonstrated PFS benefit across prespecified exploratory biomarker subgroups. The primary PFS analyses in PRIMA and PAOLA-1 were in all comers, with both studies demonstrating significant PFS improvement with PARP inhibitor maintenance treatment (as monotherapy vs placebo in PRIMA and in combination with bevacizumab in PAOLA-1 vs placebo plus bevacizumab), with similar hazard ratios (PRIMA HR, 0.62; 95% CI 0.50–0.76; PAOLA-1 HR, 0.59; 95% CI 0.49–0.72), although the relative benefit in HRD-specific subgroups differed (see Tables 1 and 2). Point estimates for median PFS differed between these trials, but this may reflect patient population and study design differences as opposed to study regimen efficacy. A population-adjusted indirect comparison using individual patient data from PAOLA-1 matched with the PRIMA population baseline characteristics found that adding olaparib to bevacizumab significantly improved PFS versus niraparib alone in biomarker-unselected patients (HR, 0.57; 95% CI 0.47–0.69) and in HRD-positive patients (HR, 0.57; 95% CI 0.41–0.80) or versus bevacizumab alone in biomarker-unselected patients (HR, 0.60; 95% CI 0.49–0.75) and in HRD-positive patients (HR, 0.40; 95% CI 0.28–0.57) [51]. Despite matching, this analysis has the limitation that it is a nonrandomized comparison, especially as patient-level data from PRIMA were not used. Overall, current data do not answer whether combined PARP inhibitor and bevacizumab maintenance might be superior to PARP inhibitor maintenance alone.

6. Safety and tolerability profiles of PARP inhibitors and antiangiogenic agents as monotherapies and in combination

The most frequent nonhematological adverse events (AEs) associated with PARP inhibitor treatment include fatigue/asthenia, nausea, vomiting and headache, with hematological AEs (anemia, thrombocytopenia and neutropenia) also reported [2–6,52–56]. Most AEs occurring during treatment are managed effectively with dose reductions or interruptions, with few AEs requiring treatment discontinuation [2–6,52–56]. All PARP inhibitors have overlapping AEs of special interest, including myelodysplastic syndromes/acute myeloid leukemia (reported in <1–2% of ovarian cancer patients across clinical trials) [2–6,57]. Pneumonitis is noted for olaparib (occurring in <1% of patients) [23,24]. Hypertension, including hypertensive crisis, is noted for niraparib (with regular blood pressure monitoring recommended during the first year of treatment) [25,26], and patients with a low baseline body weight (<77 kg) or platelet counts <150,000/μL may benefit from a 200 mg/day starting dose to reduce risk of grade ≥3 thrombocytopenia [58].

Cediranib and bevacizumab have different safety profiles because of their different mechanisms of action. The most frequently occurring AEs with maintenance cediranib in ovarian cancer are fatigue, diarrhea, nausea/vomiting and hypertension [16]. The most common all-grade, nonhematological AE associated with bevacizumab maintenance is hypertension [7,8]; other AEs of special interest occurring with bevacizumab treatment include gastrointestinal events, surgery and wound healing complications, thromboembolic events, hemorrhage and proteinuria [18,19]. Regimens to manage hypertension, such as antihypertensive therapy, are often needed for patients receiving either cediranib or bevacizumab, and blood pressure should be monitored closely [18,19,39].

Safety profiles of PARP inhibitor and antiangiogenic combinations are generally consistent with each monotherapy, with fatigue, diarrhea, hypertension and nausea being the most frequently reported all-grade AEs [10,11,39,40,42,49,59]. AEs were generally manageable through supportive treatment and dose adjustments without needing to discontinue treatment [5,6,11]. The higher rate of discontinuation in PAOLA-1 may partly be explained by the different reporting of discontinuation due to treatment-emergent AEs (TEAEs) in PAOLA-1 (occurring in 20% of patients in the olaparib plus bevacizumab group) compared with studies evaluating maintenance with PARP inhibitor monotherapy (SOLO1, SOLO2 and PRIMA) [3,5,6,11]. The overall discontinuation rates due to TEAEs, patient decision and reasons other than disease progression or completion of protocol-defined therapy at 2 years were

Table 4
Ongoing trials that evaluate PARP inhibitors in combination with antiangiogenic treatments.

Study	Study design	Interventions	Patient population (n)	Treatment setting	Key inclusion criteria	Study endpoints	Current status; anticipated primary completion date
Phase III studies							
ICON9 NCT03278717	Randomized, open-label	Maintenance olaparib + cediranib vs maintenance olaparib	Platinum-sensitive recurrent (target $n = 618$)	3L+	• 4–6 cycles of 2L platinum-based chemotherapy • CR or PR or NED following prior platinum-based chemotherapy • Known BRCAm status	**Primary:** • PFS • OS **Secondary:** • Toxicity • TSST • QoL • ORR	Recruiting; December 2023
Phase II/III studies							
GY005 NCT02502266	Randomized, open-label	Physician's choice of chemotherapy vs olaparib + cediranib vs cediranib vs olaparib[a]	Platinum-resistant/refractory recurrent (target $n = 680$)	≤4L	• High-grade serous or endometrioid OR clear cell, mixed epithelial, undifferentiated carcinoma, OR transitional cell carcinoma with a gBRCAm	**Primary:** • PFS • OS **Secondary:** • ORR • Toxicity	Recruiting; June 2023
Phase II studies							
NCI9825 NCT02345265	Single-arm, open-label	Olaparib + cediranib	Platinum-sensitive or platinum-resistant/refractory ($n = 72$)	2L+ for platinum-sensitive cohort 2L only in the platinum-resistant/recurrent setting	• High-grade serous or endometrioid OR other high-grade histologies with a BRCAm	Primary: • PFS • ORR • Biomarker analyses Secondary: • OS • Genetic alterations • Circulating endothelial cells	Completed; May 2020
CONCERTO NCT02889900	Single-arm, open-label	Olaparib + cediranib	Platinum-resistant recurrent ($n = 62$)	4L+	• High-grade serous or endometrioid or clear cell • Non-BRCAm	Primary: • ORR Secondary: • DoR • PFS • DCR • OS • TDT • QoL	Completed; August 2019
OCTOVA NCT03117933	Randomized, open-label	Paclitaxel vs olaparib vs olaparib + cediranib	Platinum-resistant recurrent ($n = 139$)	NS	• Epithelial ovarian, primary peritoneal or fallopian tube • No prior single-agent paclitaxel for relapsed disease	Primary: • PFS Secondary: • OS • ORR • QoL • Toxicity	Recruitment complete; March 2021
Phase I/II studies							
MITO25 NCT03462212	Randomized, open-label	Platinum-based chemotherapy + concurrent and maintenance bevacizumab vs platinum-based chemotherapy + concurrent and maintenance bevacizumab + maintenance rucaparib vs platinum-based chemotherapy + maintenance rucaparib	Newly diagnosed Stage IIIB–IV advanced ovarian cancer ($n = 290$)	1L	• High-grade or predominantly high-grade (>50%) serous or endometrioid OR other histotype with a BRCAm • One attempt at optimal debulking surgery for Stage III disease or biopsy and/or upfront surgery for Stage IV disease	Primary: • PFS Secondary: • ORR • PFS2 • OS • TFST • TSST • QoL Toxicity	Recruitment complete; May 2019

(continued on next page)

Table 4 (*continued*)

Study	Study design	Interventions	Patient population (*n*)	Treatment setting	Key inclusion criteria	Study endpoints	Current status; anticipated primary completion date
Phase I studies							
NCT02121990	Single-arm, open-label	Cisplatin (IP) + paclitaxel (IP/IV) + bevacizumab + olaparib	Newly diagnosed Stage ≤IB (*n* = 17)	1L	• One of the following histological types: – High-grade serous – Endometrioid – Undifferentiated – Clear cell – Mixed epithelial – Nonspecified adenocarcinoma – Carcinosarcoma • Received appropriate surgery with available tissue • Agree to BRCA testing	Primary: • MTD Secondary: • Toxicity	Completed; August 2020
MOLTO NCT02855697	Single-arm, open-label	Two maintenance olaparib courses ± cediranib (with the second maintenance course)	Platinum-sensitive recurrent (*n* = 28)	2L+	• High-grade serous or endometrioid • gBRCAm	Primary: • Feasibility of a second course of olaparib (i.e. proportion remaining on olaparib for >6 months in the second course of maintenance olaparib Secondary: • TFST • TSST • PFS	Recruitment complete; September 2021

1L, first-line; 2L, second-line; 2L+, second-line or greater; 3L+, third-line or greater; 4L, fourth-line; 4L+, fourth-line or greater; BRCAm, *BRCA1* or *BRCA2* mutation; CR, complete response; DCR, disease control rate; DoR, duration of response; gBRCAm, germline *BRCA1* or *BRCA2* mutation; IP, intraperitoneal; IV, intravenous; MTD, maximum tolerated dose; NED, no evidence of disease; non-BRCAm, not BRCAm; NS, not stated; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PR, partial response; QoL, quality of life; TDT, time to discontinuation of treatment; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment.

similar in the PAOLA-1 (25% of patients in the olaparib plus bevacizumab group) and SOLO1 (28% of patients in the olaparib group) clinical trials [5,11]. The AVANOVA and OVARIO trials, which both evaluated niraparib plus bevacizumab, reported similar all-cause grade ≥3 AEs, including thrombocytopenia, anemia and hypertension [10,49]. Of interest, in PAOLA-1 overall and grade ≥3 hypertension were reduced when olaparib was combined with bevacizumab compared with bevacizumab monotherapy [11]. The mechanism (s) resulting in this observation are unknown, although different hypotheses exist.

7. Ongoing studies of PARP inhibitors in combination with antiangiogenics and other agents

Several ongoing studies are evaluating PARP inhibitor and antiangiogenic combinations in various ovarian cancer settings (Table 4), which may provide additional information to address unanswered questions, including the most appropriate combination to use for efficacy, safety and quality of life; which patients benefit most from this combination (i.e. all patients or biomarker-selected patients); and in what clinical setting these therapies will confer the most benefit.

Additional studies in patients with ovarian cancer are also investigating combinations of PARP inhibitors, antiangiogenic treatment and other therapeutic agents, including immunotherapies (Supplementary Table S1), and PARP inhibitors in combination with other targeted agents such as WEE-1 inhibitors (NCT03579316), ATR inhibitors (NCT03462342), MEK inhibitors (NCT03162627), AKT inhibitors (NCT02208375; NCT02338622) and mTORC1/2 inhibitors (NCT02208375), to determine whether including additional targets will further increase efficacy.

8. Current treatment landscape and future directions for patients with advanced ovarian cancer

For over two decades, platinum-based doublet chemotherapy has been the standard-of-care treatment for patients with newly diagnosed advanced ovarian cancer [60]. However, the treatment landscape in first-line disease has rapidly evolved. Bevacizumab, in combination with standard carboplatin plus paclitaxel and then as maintenance therapy, was the first targeted treatment option for newly diagnosed advanced epithelial ovarian cancer [18,19]. Results from the phase III SOLO1 study, which demonstrated substantial efficacy of olaparib maintenance therapy following first-line platinum-based chemotherapy in women with a BRCAm [5], led to FDA and EMA approval of olaparib in this setting [23,24]. Following the publication of the PRIMA study [3], niraparib received FDA and EMA approval for first-line maintenance treatment for advanced ovarian cancer patients in the ITT population (all comers) [25,26].

PARP inhibitor and antiangiogenic combinations have demonstrated clinical activity and may potentially increase PFS compared with either treatment alone in various settings. Accordingly, and following the PAOLA-1 study results, the FDA and EMA recently approved use of olaparib in combination with bevacizumab as maintenance therapy in patients with HRD-positive tumors, who have a deleterious or suspected deleterious BRCAm and/or genomic instability, and have a complete or partial response to first-line platinum-based therapy [23,24]. Combination treatment is well tolerated in patients with

newly diagnosed advanced ovarian cancer and provides an additional treatment option for these patients, but several questions remain unanswered, particularly since direct head-to-head comparisons remain limited. It is not apparent if the different mechanisms of action of the VEGFR tyrosine kinase inhibitor cediranib and the anti-VEGF antibody bevacizumab make one agent more effective or tolerable when combined with a PARP inhibitor; further data are required to explore patient quality of life and patient-centered survival outcomes (i.e. quality-adjusted PFS [QA-PFS] and quality-adjusted time without symptoms and toxicity [Q-TWiST]). As PARP inhibitors have moved into the first-line maintenance setting, the best approach to sequence treatments must also be considered; should we give patients all available drugs upfront when they are more likely to tolerate such combinations, or will this limit treatment options in later lines? Should patients who have received bevacizumab in combination with platinum-based chemotherapy continue bevacizumab maintenance alone, in combination with a PARP inhibitor, or switch to PARP inhibitor maintenance treatment? Should patients with HRD-negative tumors receive bevacizumab maintenance alone given the absence of a significant benefit with a PARP inhibitor plus bevacizumab versus bevacizumab? In terms of sequencing, an ongoing study (NCT03106987) is assessing re-treatment with maintenance olaparib in patients with relapsed ovarian cancer who have had disease progression following maintenance therapy with a PARP inhibitor. Data are needed concerning re-treatment with PARP inhibitors following maintenance therapy with a PARP inhibitor in the first-line setting.

Finally, the mechanisms of inherent and adaptive resistance to antiangiogenic treatments and PARP inhibitors should also be considered [61,62], as should potential new patient profiles that may emerge following relapse after first-line PARP inhibitor treatment. As PARP inhibitors and antiangiogenics move into earlier lines of therapy, it remains unknown whether combined antiangiogenic and PARP inhibitor therapy will remain active in patients who have demonstrated resistance to or have previously received one or the other agent. Findings from ongoing trials of PARP inhibitors with antiangiogenics as well as combinations with other therapies will be important in shaping our understanding of how best to utilize these agents moving forward (Table 4 and Supplementary Table S1).

9. Conclusions

Until recently, treatment options for patients with advanced ovarian cancer were limited. As we enter an era with more treatment options becoming available, so come new challenges for clinical practice. The PARP inhibitor plus antiangiogenic combination is a novel treatment option that appears to offer significant PFS benefit as maintenance therapy in the first-line setting to women with advanced ovarian cancer who are HRD positive compared with antiangiogenic drugs alone. It is now important to define which patient groups are candidates for monotherapy or combination treatment, taking into consideration safety profiles of therapies alone or in combination, tumor biomarkers, financial toxicity, patient preferences and how these treatments should be sequenced in clinical practice.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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