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Recent advancements of antiangiogenic combination therapies in ovarian cancer

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Abstract

Ovarian cancer is a deadly malignancy with a growing therapeutic armamentarium, though achieving sustained benefit in the clinic remains largely elusive. Through biomarker and genetic analysis, several pathways of resistance and sensitivity to commonly used therapeutics have been identified, expanding the potential of identifying unique drug combinations and indicating new directions for improving clinical outcomes. Here, we review the mechanisms of angiogenic response and antiangiogenic therapy in ovarian cancer, as well as the interactions it exhibits with the immune and DNA damage response pathways. We discuss results from clinical trials examining the combinations of antiangiogenics, PARP inhibitors, and immune checkpoint inhibitors are also discussed, as well as several ongoing trials.

Keywords

Ovarian cancer; VEGF/VEGFR inhibitor; PARP inhibitor; immunotherapy; combination therapy

Introduction

Ovarian cancer is the most lethal gynecological malignancy [1], responsible for nearly 5% of all cancer deaths despite the fact that it only accounts for 2.5% of all malignancies in women [2]. The disease presents at late stages in most cases and ultimately proves fatal to over 75% of those diagnosed with advanced tumors [3], with 70–80% of patients developing a relapse

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Conflicts of Interest

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after upfront surgical debulking and chemotherapy [4]. The critical unmet need for more effective therapy has therefore spurred on the development of a more tailored and precision-based medicine.

Angiogenesis facilitates the growth and metastasis of ovarian cancer [5, 6] via several proangiogenic factors including the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), and angiopoeitin [6, 7]. Bevacizumab, a monoclonal antibody against VEGF-A, has been the primary antiangiogenic agent used in ovarian cancer [8, 9]. It was first approved, in combination with non-platinum-based chemotherapy, for the treatment of the platinum-resistant, recurrent ovarian cancers in 2014 [10], then, in combination with platinum-based chemotherapy, for the treatment of platinum-sensitive ovarian cancer [11, 12]. Adjuvant bevacizumab following initial surgical resection, followed by bevacizumab monotherapy maintenance, has also been approved for advanced ovarian cancers [13]. Most recently, a combination of bevacizumab and the PARP inhibitor (PARPi) olaparib was approved as a frontline maintenance therapy of BRCA mutant or homologous recombination (HR)-deficient (HRD) ovarian cancer [14].

Its utility, however, has been hindered by the development of resistance and limited efficacy in subsets of the patient population. As such, other agents that target pathways of angiogenesis have been investigated, such as imatinib, a PDGF receptor tyrosine kinase inhibitor (TKI), cediranib, a VEGF receptor (VEGFR) and PDGF TKI [7], and ramucirumab, an anti-VEGFR2 antibody [15]. Thus far, only limited clinical activity has been observed with these angiogenesis inhibitors, highlighting the need to develop alternative strategies including new combination therapies.

Among many, immune checkpoints and DNA damage repair (DDR) pathways are active therapeutic targets for combination therapy with angiogenesis blockades. Some promising clinical results have emerged from novel combinations integrating antiangiogenic agents with inhibitors of other pathways, primarily with PARPi, immune checkpoint blockades, or both [8]. The wide variability in responses to antiangiogenics has revealed a variety of resistance mechanisms and sensitivity factors that can be targeted with the appropriate combination therapies. Here, we review the VEGF/VEGFR pathway and its interactions with DDR pathways as well as its immunomodulatory effects, with a focus on the relevance to preclinical evidence and clinical development of dual (or triple) inhibition of these pathways. We use ovarian cancer as an example and refer to other gynecologic cancers, *i.e.,* endometrial cancer, where appropriate in this review.

Current paradigm of antiangiogenic use in the clinic

The addition of the anti-VEGF monoclonal antibody bevacizumab has become a widely accepted standard of clinical practice in ovarian cancer. For example, in the United States (US), bevacizumab in combination with chemotherapy was first approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of platinum-resistant recurrent ovarian cancer [8], as per the results of the AURELIA (NCT00976911) trial. In this trial, the addition of bevacizumab to chemotherapy extended median progression-free survival (PFS) from 3.4 months to 6.7 months (HR = 0.48, 95% CI 0.38–0.60, $p < 0.001$) in patients that had received ≤ 2 prior lines of therapy but demonstrated no benefit to overall survival (OS)

or quality of life [10]. No significant increases in toxicity or adverse events (AEs) were observed, save for a rise in grade ≥ 2 proteinuria (2% vs. 0%) and hypertension (7% vs. 1%).

Subsequently, in 2016, it was approved by the U.S. FDA, in combination with platinum-based chemotherapy, for platinum-sensitive recurrent ovarian cancer [16], based on the results of the GOG-0213 (NCT00565851) and OCEANS (NCT00434642) trials. The GOG-0213 trial reported some improvement of OS (42.2 vs. 37.3 months (mo), HR = 0.829, 95% CI 0.683–1.005, p = 0.056) with bevacizumab plus carboplatin and paclitaxel, followed by bevacizumab maintenance [11]. In the OCEANS trial, bevacizumab improved PFS (12.4 vs. 8.4 mo, HR = 0.484, 95% CI 0.388–0.605, p < 0.0001) and the objective response rate (ORR) (78.5% vs. 57.4%, p < 0.0001), but demonstrated no significant benefit to OS [12]. Like AURELIA, both trials reported grade ≥ 3 proteinuria (8% in GOG-0123, 8.5% in OCEANS) and hypertension (12% in GOG-0123, 17.4% in OCEANS) in the experimental group and no new safety concerns [11, 12].

In 2018, bevacizumab was also approved for adjuvant therapy, followed by bevacizumab maintenance, in advanced ovarian cancers [17], based on the results of the GOG-0218 (NCT00262847) trial, which demonstrated extended PFS (14.1 vs. 10.3 mo, HR = 0.717, 95% CI 0.625–0.824, p < 0.001) with treatment [13]. Most recently, a combination of bevacizumab and the PARPi olaparib was approved as a frontline maintenance therapy of BRCA mutant or HRD-positive ovarian cancer, following the results of the PAOLA-1 study [14]. Bevacizumab also has European Medicines Agency (EMA) approval in all of the above indications.

These data reinforce the question of when to use bevacizumab in the treatment lifetime of ovarian cancer as it is approved in various settings and whether bevacizumab could result in OS benefit. Regardless, current data suggest that the biology of angiogenesis in ovarian cancer remains an important target across time and various treatment methods.

There are other VEGF/VEGFR inhibitors actively being researched in epithelial ovarian cancer. Cediranib, a TKI against VEGFR1, 2, 3, PDGFR, and c-kit, has also demonstrated activity and tolerability [18]. Following the results of encouraging phase I trial, in which cediranib monotherapy showed antitumor activity and tolerable toxicity in solid tumors, including ovarian cancer [19], its use was further investigated in recurrent ovarian cancers in several phase II and III trials. In the phase III ICON6 (NCT00532194) trial, the combination of cediranib and standard platinum-based chemotherapy, followed by cediranib maintenance, extended PFS (11.0 vs. 8.7 mo, HR = 0.56, 95% CI 0.44–0.72, p < 0.0001) for platinum-sensitive recurrent ovarian cancer [20]. Two phase II trials of cediranib in recurrent ovarian cancer also demonstrated clinical activity, with median PFSs of 4.9 mo (NCT00278343) [21] and 5.2 mo (NCT01116648) [22]. Across all these trials, commonly observed serious AEs (grade 3 or 4) were class effects such as diarrhea and hypertension [20–22]. However, the underwhelming performance of cediranib against the competing bevacizumab and its lackluster activity in other tumor types hindered the momentum of development of this drug [18, 23]. Despite these setbacks, combinations such as cediranib with the PARPi olaparib has drawn continued interest in recurrent ovarian cancer.

Another multitarget TKI, sorafenib, has also been the subject of several clinical trials, but has demonstrated only modest benefit, in monotherapy or in combination with chemotherapy [25] or bevacizumab [26]. In a phase II trial involving 71 platinum-recurrent ovarian/primary peritoneal cancer patients, 14 (23.7%) of 59 patients had no disease progression at 6 months, with an average PFS = 2.1 months and average OS = 16.33 months [27]. Some encouraging results, however, have also been reported in the phase II TRIAS (NCT01047891) trial, in which sorafenib in combination with topotecan, followed by sorafenib maintenance in platinum-resistant ovarian cancer saw PFS (6.7 vs. 4.4 mo, HR = 0.60, 95% CI 0.43–0.83, p = 0.0018) and OS benefits (17.1 vs. 10.1 mo, HR = 0.65, 95% CI 0.45–0.93, p = 0.017). Overall, most toxicities of the sorafenib combinations were manageable with dose reductions, monitoring, and counseling, and did not seem to significantly impact the quality of life of patients [28].

A newer generation of antiangiogenic agents under investigation for the treatment of ovarian cancer includes nintedanib, pazopanib, and trebananib [8]. Nintedanib is a TKI of, among other targets, FGFR, PDGFR, and VEGFR [29]. The phase III AGO-OVAR12 (NCT01015118) of carboplatin and paclitaxel with or without nintedanib in the first-line setting for advanced ovarian cancer demonstrated a PFS benefit (17.2 vs. 16.6 mo, HR = 0.84, 95% CI 0.72–0.98, p = 0.024), with higher rates of hypertension (14%) and gastrointestinal AEs (diarrhea (77%), vomiting (45%), abdominal pain (46%), etc.) reported in the nintedanib group [30]. Pazopanib, a VEGFR, PDGFR, and c-kit TKi, as maintenance therapy in advanced ovarian cancer, extended PFS from 12.3 mo to 17.9 mo (HR = 0.77, 95% CI 0.64–0.91, p = 0.0021) in the phase III AGO-OVAR16 (NCT00866697) trial. Common AEs (≥5%) included hypertension, neutropenia, liver-related toxicities, and diarrhea [31]. Trebananib binds angiopoeitin-1 (Ang1) and angiopoietin-2 (Ang2) to prohibit their binding to the Tie2 receptor. Its clinical impact on recurrent ovarian cancer was studied in the phase III TRINOVA-1 (NCT01204749) trial, which showed a PFS benefit of 7.2 vs. 5.4 months (HR = 0.66, 95% CI 0.57–0.77, p <0.0001) for trebananib and paclitaxel. Of note, most of the class-effect AEs were not elevated in the trebananib group, although significantly greater rates (64% vs. 28%) of edema (localized, generalized, and lymphoedema) were observed [32]. The phase III TRINOVA-2 (NCT01281254), however, demonstrated no significant improvement in PFS for pegylated liposomal doxorubicin (PLD) with trebananib or placebo (7.6 vs. 7.2 mo, HR = 0.92, 95% CI 0.68–1.24, p = 0.57), though improvements in ORR (46% vs. 21%) and DOR (7.4 vs. 3.9 mo) were noted [33]. To date, none of the above antiangiogenic agents have gained approval in ovarian cancer.

A practical question in the clinic is whether we should re-challenge patients with bevacizumab or other angiogenesis inhibitors as part of a subsequent line of therapy. To date, several studies, although mostly retrospective, have suggested some benefit of re-exposure in the setting of bevacizumab with chemotherapy. MITO16B, a randomized phase III clinical trial prospectively assessed this question, demonstrating a PFS improvement upon re-exposure with bevacizumab (11.8 vs. 8.8 mo, HR = 0.51, 95% CI 0.41–0.64, p < 0.001) among patients with platinum-sensitive ovarian cancer [34]. The improvement was noted both in patients progressing during first-line bevacizumab maintenance and in those that developed disease recurrence after the end of first line maintenance treatment. However, oral VEGFR inhibitors, either alone or in combination with bevacizumab yielded minimal

activity in bevacizumab-exposed recurrent ovarian cancer patients [26, 35]. Further prospective studies are needed in the platinum-resistant settings as to whether re-exposure of bevacizumab would result in benefit after the use of bevacizumab plus chemotherapy combination.

To improve the limited activity in certain populations, a few clinical and molecular potential biomarkers of response to antiangiogenic therapy have been suggested, such as the presence of ascites [36] or increased IL6 levels in peripheral blood samples [37]. IL6 in particular is an effector of myriad pathways that influence metastasis, proliferation, angiogenesis, and invasion of ovarian cancer [38], and, by being a negative prognostic marker for disease progression, may predict greater benefit from antiangiogenic treatment. The presence of high VEGF in ascites has also been frequently associated with poorer prognoses and greater disease burden [36, 39, 40], though an association was only observed when assessed in tandem with $CD31^+$ microvessel density in the GOG-0218 bevacizumab trial [41]. Ascites production may itself be a consequence of increased VEGF levels, as high VEGF expression is associated with greater vascular permeability [42]. Other suggested predictive factors include increased mesothelin, Fms-related tyrosine kinase 4 (FLT4) (a VEGF-C and VEGF-D receptor), alpha-1-acid glycoprotein (AGP), or CA-125 [43], as well as secondary platinum resistance in the case of the AURELIA trial [44].

Finding biomarkers of response offers a means by which subsets of the patient population that can derive the greatest benefit from antiangiogenic treatment or maintenance can be identified. By sensitizing the tumor microenvironment and evading potential mechanisms of resistance, novel combinations with antiangiogenics can also offer a means by which the scope and power of antiangiogenic therapy can be expanded. This, in combination with precision-based and biomarker-driven medicine, offers new ways to bring more effective treatment options to patients, particularly to those who have already developed or may be predisposed to resistance to antiangiogenic therapy alone.

Mechanistic rationale for combining antiangiogenic and immune checkpoint blockade therapies

In addition to increasing the vasculature of the tumor microenvironment (TME), angiogenic factors like VEGF create an immunosuppressive environment by the release of inhibitory cytokines and the recruitment of immunosuppressive cell types. The combined targeting of angiogenesis and immune checkpoints can therefore ameliorate the impact of this relationship and facilitate a more robust immune response that potentiates the response of the TME to therapy.

Proangiogenic factors like VEGF, PDGF, FGF, and Ang1/2 promote vascularization by binding their respective receptors VEGFR, PDGFR, FGFR, and the angiopoeitin receptors Tie1 and Tie2. These receptors contain internal tyrosine kinase domains that activate signaling cascades associated with increased proliferation and migration of endothelial cells [45–49]. In tumors, however, these mechanisms generate aberrant vasculature that exhibits abnormal morphologies, permeability to large molecules, and inefficient oxygenation of the TME [48]. The permeable and tortuous structure of the vasculature within the tumor increases the interstitial pressure, which impairs sufficient drug delivery into the TME [50],

and presents a physical barrier to T cell infiltration [51]. The resultant hypoxia also subsequently triggers the release of cytokines like CXCL12, IL-6, IL-10, and CCL28 that induce both local and systemic immunosuppression by recruitment of immunosuppressive cells like regulatory T cells (T_{reg}), M2-type tumor associated macrophages (M2-TAMs), and myeloid-derived suppressive cells (MDSCs) [52, 53]. Increased VEGF levels found in tumors also inhibit the maturation of dendritic cells via the NFκB pathway; increase the expression of the immune checkpoint molecules PD-1, CTLA-4, and TIM-3 on T cells; and facilitate $CD8^+$ T cell exhaustion [53–55]. Other angiogenic factors can exert similar direct effects on immune cells. For instance, angiopoietin has been associated with the proliferation of T_{reg} cells via IL-10 signaling, and PDGF signaling is linked to the inhibition of the maturation and proliferation of dendritic and $CD4^+$ cells [56].

Together, these data suggest extensive crosstalk between angiogenic and immunogenic pathways and create a framework by which we can begin to understand how they influence one another in the clinical setting. For instance, it has been suggested that one of the primary driving factors of resistance to antiangiogenic therapy is due to the increased recruitment of immunosuppressive cell types, inhibited maturation of T cells and macrophages, and increased expression of PD-L1 and PD-1 [57–59]. In turn, angiogenic factors like VEGF and angiopoietin-2 (Ang2) can also drive immunotherapy resistance. The binding of VEGFR on the surface of dendritic cells, for instance, can negatively regulate their maturation and antigen-presenting activity, while Ang2 increases IL-10 secretion [60].

Antiangiogenic and immune checkpoint blockade therapy combinations

Immune checkpoint blockades (ICP) are one of the most commonly studied therapeutic approaches recently entering trials in the drug armamentarium for ovarian cancer. Comprehensive reviews have been published describing various immunotherapy approaches in ovarian cancer [61–64] and will therefore not be further discussed here. Furthermore, combinations with antiangiogenic agents have entered trials in recurrent and newly diagnosed ovarian cancer. Table 1 details the completed and ongoing clinical trials of antiangiogenic drugs and ICP.

Recently, primary results from the phase III IMagyn050/GOG3015/ENGOT-OV39 (NCT03038100) were reported. In this trial, 1301 patients with newly diagnosed, stage III/IV ovarian cancer who underwent either primary cytoreductive surgery with gross residual disease or neoadjuvant chemotherapy and interval surgery were randomized (1:1) to the placebo arm (platinum therapy plus placebo, followed by bevacizumab plus placebo maintenance) or the treatment arm (platinum therapy plus atezolizumab, followed by bevacizumab plus atezolizumab maintenance). Here, there was no statistically significant PFS improvement in either the intent-to-treat (ITT) population (HR 0.92 [95% CI 0.79–1.07]; median 18.4 mo with placebo vs 19.5 mo with atezolizumab) or the predefined PD-L1+ population (immune cells: IC <1% vs ≥1%) (HR 0.80 [0.65–0.99], median 18.5 vs 20.8 mo, respectively). Of interest, in exploratory PFS analyses, the PD-L1 IC ≥5% subgroup showed a trend towards improved PFS in the combination arm [65].

There are several other ongoing trials of dual inhibition of angiogenic and immune checkpoint pathways in recurrent ovarian cancer, with limited data thus far. In a single arm

phase II trial (NCT02873962) of the combination of bevacizumab and the anti-PD-1 antibody nivolumab, the ORR across all patients was 28.9% (11/38) and a lower clinical activity was seen in the platinum-resistant group (16.7% (3/18)). Approximately 90% of patients experienced AEs, with the most common being fatigue and myalgia. [66]. For platinum-sensitive recurrent disease, in the phase III ATALANTE (NCT02891824) trial, patients were assigned in a 1:2 ratio to a placebo arm (platinum-based chemotherapy, bevacizumab, plus placebo) or a treatment arm (platinum-based chemotherapy, bevacizumab, plus atezolizumab, a PD-L1 inhibitor). The phase II/III NRG-GY009 (NCT02839707) trial also explores the combination of bevacizumab and atezolizumab, this time in platinum-resistant tumors, by assigning 488 patients to one of three arms for treatment with PLD combined with bevacizumab and/or atezolizumab. Additionally, the randomized phase II EORTC-1508 trial (NCT02659384) assesses this combination, with the addition of acetylsalicylic acid, in platinum-resistant ovarian cancer.

Encouraging results have also emerged in other gynecologic cancers. The phase Ib/II KEYNOTE-146/Study 111 trial of the VEGFR1–3 TKI lenvatinib in combination with pembrolizumab demonstrated significant activity in advanced or recurrent endometrial carcinoma (n = 108), with an ORR = 38%, median duration of response (DOR) = 21.2 mo, median PFS = 7.4 mo, and median OS = 16.7 mo. This effect appeared independent of microsatellite-instability (MSI) status, but less than 10% of trial patients (4 of 53 patients) with known high MSI precluded any meaningful comparison based on MSI status [67, 68]. Subsequently, this combination was granted fast-tracked FDA approval for the treatment of pretreated endometrial carcinoma without high MSI or MMR deficiencies [69]. Preliminary results from the confirmatory randomized phase III trial KEYNOTE-775 (NCT03517449) presented at the SGO 2021 meeting reported improvements in PFS (7.2. vs. 3.8 mo, HR = 0.56), OS (18.3 vs. 11.4 mo, HR = 0.62), and ORR (31.9% vs. 14.7%) over physician's choice treatment for all patients, regardless of MMR status [70].

Overall, in light of the preclinical evidence that supports the combination of antiangiogenic and immune checkpoint inhibitor therapy, results of further clinical trials will hopefully establish its utility and efficacy in ovarian cancer and pave the way for the conception of new trials to come. Furthermore, translational research and biomarker development will be critical for the success of ICP combinations.

Mechanistic rationale for adding PARP inhibition to the combination of antiangiogenics and immunotherapy

PARP inhibition has become a significant mainstay in the treatment of ovarian cancer, with a series of FDA and EMA approvals in recent years cementing its position in the frontline treatment of advanced ovarian cancers. There are several comprehensive, published reviews and guidelines for the use of PARPi's in ovarian cancer [73–77], and they will thus not be discussed in further detail here.

Overlaps between the DDR pathways affected by PARP inhibition and angiogenesis lend great therapeutic potential to the combination of PARPi and antiangiogenic therapies. Mechanistically, the hypoxia induced by antiangiogenic treatment is known to repress HR by affecting key factors like BRCA1, BRCA2, and RAD51 [78, 79] resulting in a DDR

deficient state that generates sensitivity to PARP inhibition. The downregulation of HR can also be mediated independent of hypoxia, as in the case of cediranib, which inhibits PDGFR and suppresses the expression of HR repair genes [80]. Over time, however, hypoxia also results in an accumulation of HIF1 α, which allows the tumor to build resistance against antiangiogenic therapy and facilitate cancer metastasis by upregulating the expression of angiogenic and autocrine/paracrine growth factors [81]. PARP1 also plays a role in promoting HIF1 α stabilization and accumulation [82], and its inhibition can therefore ameliorate HIF1 α-mediated resistance to antiangiogenics [83].

As to its immunomodulatory effects, PARP inhibition also feeds into the immunogenic response of the TME by activation of the STING-cGAS pathway, which senses cytosolic DNA fragments generated by DNA damage and subsequently recruits $CD4^+$ and $CD8^+$ T cells and increases the secretion of IFNγ and TNFα [84, 85]. This effect is particularly pronounced in HRD-positive tumors or cells, which represents around 41–50% of ovarian cancer cases [86], as these cells are more likely to exhibit severe DNA damage that draws an immune response. Conversely, PD-1/PD-L1 expression is found elevated after PARP inhibition, which facilitates an immunosuppressive environment that allows tumor cells to escape cell death [87]. In either respect, however, the addition of a PD-1/PD-L1 blockade or other ICP inhibitors to PARP inhibition can confer greater benefit, either by potentiating the immune response elicited by PARPi-induced DNA damage or by allowing the bypass of a potential resistance mechanism to the prolonged efficacy of PARP inhibition. Therefore, in theory, the triple targeting of angiogenic, DNA damage response, and immune checkpoint pathways can enhance the antitumor effects of each mode of treatment and confer resistance escape mechanisms to one another

Antiangiogenic therapy and PARP inhibition combinations

Many reviews describing clinical trials examining the use of PARPi monotherapy or PARPi plus immunotherapy combinations in ovarian cancer have already been published [83, 88–90] and will not be discussed here. Our understanding of PARP inhibition and antiangiogenic combinations has also progressed significantly over the past few years, and key clinical trials are summarized in Table 2.

Briefly, two randomized phase III studies were launched in 2016 in platinum-sensitive (NRG-GY004) and platinum-resistant (NRG-GY005) diseases to test the olaparib and cediranib combination against standard-of-care (SOC) chemotherapy based on the promising results of this combination from the phase II trial of olaparib plus cediranaib vs. olaparib alone in platinum-sensitive recurrent ovarian cancer (NCT01116648) [91, 92]. Preliminary findings from a phase III NRG-GY004 trial (NCT02446600) reported that the combination of olaparib and cediranib failed to meet a primary endpoint of PFS in platinum-sensitive recurrent disease (10.4. [olaparib plus cediranib] vs 10.3 [SOC platinum-based chemotherapy] mo, HR = 0.856, 95% CI 0.66–1.11, p = 0.08), although the combination did have a superior PFS over the olaparib-only arm (8.2 mo). The phase II/III NRG-GY005 trial (NCT02502266) recently completed accrual and the results are awaited.

In addition, the single arm phase IIb CONCERTO (NCT02889900) trial studied this combination in more heavily pretreated (≥ 4 lines of chemotherapy), non-gBRCAm

recurrent platinum-resistant ovarian cancer, with 88.3% of patients already having been exposed to bevacizumab, representative of a difficult-to-treat population. Preliminary data presented at the 2020 ASCO Annual Meeting showed an ORR of 15.3%, including 1 CR and 8 PR, with a total of 4/9 responders having measurable response for more than 9 months, and no new concerning AEs were reported [93]. Biomarker studies were also included. Percent global loss of heterozygosity (gLOH), measured by Foundation Medicine, was available for 47 patients in the evaluable-for-response population. Of these, 15 had a tumor BRCAm and/or gLOH score ≥16% ($gLOH^{high}$), and 32 had a gLOH score <16% ($gLOH^{low}$). The ORR was 26.7% (4/15; 95% CI 7.8–55.1%) in the $gLOH^{high}$ group and 12.5% (4/32; 95% CI 3.5–29.0%) in the $gLOH^{low}$ group, requiring further investigation.

Another phase II trial (BAROCCO (NCT03314740)) compared weekly paclitaxel against continuous (cediranib dosed every day) and intermittent (cediranib dosed 5 days/week) regimens of olaparib plus cediranib in platinum-resistant ovarian cancer. While the median PFS for the continuous and intermittent arms were higher than that of the control arm (5.7, 3.8, and 3.1 mo, respectively), the comparisons were not statistically significant (HR = 0.76, 90% CI 0.49–1.17, $p = 0.28$ for continuous vs. control; HR = 1.08, 90% CI 0.71–0.64, $p = 0.76$ for intermittent vs. control). Subgroup analysis by BRCA status revealed a slightly more favorable comparison between the continuous and control arms among gBRCAwt patients (5.8 vs. 2.1 mo, HR = 0.63, 90% CI 0.36–1.10, $p = 0.10$), though still not significant [94].

The use of the olaparib and cediranib combination in the PARPi-resistant setting was also tested in the single arm multi-cohort phase II pilot EVOLVE (NCT02681237) trial. Three cohorts included platinum-resistant after progression on PARPi ($n = 10$), platinum-sensitive after progression on PARPi ($n = 11$), and progressive on a second line of standard chemotherapy following a prior PARPi progression ($n = 13$). The ORRs were 20%, 0%, and 8%, respectively, and the 1-year OS estimates were 82%, 69%, and 40%, respectively. When correlated with exome sequencing of archival and baseline samples from participants that focused on known pathways of PARPi resistance, data showed that patients with reversion mutations (n = 5) in HR genes (*e.g.,* BRCA1, BRCA2, or RAD51B) showed worse median PFS (1.8 mo (1.5 – n/a)) compared to those without reversion mutations (5.4 mo in HR mutated and 7.6 mo in HR WT), requiring further validation in a large cohort [95].

Other VEGF/VEGFR blockades and PARPis are actively studied in various settings. The NSGO-AVANOVA/ENGOT-ov24 (NCT02354131) phase II trial tested the combination of niraparib with bevacizumab in recurrent platinum-sensitive ovarian cancer and demonstrated improvement in PFS in the niraparib plus bevacizumab arm over the niraparib-only (control) arm (11.9 vs. 5.5 mo, HR = 0.35, 95% CI 0.21–0.57, $p < 0.0001$). Of note, post-hoc subgroup analysis showed greater benefit in patients with germline BRCA wild-type/unknown (gBRCAwt/u) status (11.3 vs. 4.2 mo, HR = 0.32, 95% CI 0.17–0.58). In addition, the gBRCAm group also showed some PFS improvement (14.4 vs. 9.0 mo, HR = 0.49, 95% CI 0.21–1.15). A different subset analysis based on HRD status, independent of BRCAm status, found that both HRD-positive and -negative groups had PFS improvements (11.9 vs. 6.1 mo in HRD-positive and 11.3 vs. 4.2 mo in HRD-negative) [96].

Moving to the maintenance setting, the phase III PAOLA-1 (NCT02477644) studied the combination of olaparib and bevacizumab following first-line platinum-based chemotherapy in newly diagnosed platinum-sensitive high-grade ovarian cancer. The olaparib plus bevacizumab arm showed significant PFS improvement over the bevacizumab plus placebo (control) arm (22.1 vs. 16.6 mo, HR = 0.59, 95% CI 0.49–0.72, $p < 0.001$). Subgroup analysis showed similar patterns in the BRCAm group (37.2 vs. 21.7 mo), HRD-positive group (37.2 vs. 17.7 mo), and the HRD-positive/BRCAwt group (28.1 vs. 16.6 mo). HRD-negative tumors, however, did not see significant PFS improvements (16.6 vs. 16.2 mo) [14]. The positive findings of this trial resulted an FDA approval in May 2020 for the use of olaparib and bevacizumab as maintenance therapy for advanced epithelial ovarian cancer with HRD-positive tumor. Additionally, the phase III ICON9 (NCT03278717) trial is examining the utility of olaparib and cediranib vs olaparib alone in the maintenance setting following a response to platinum-based chemotherapy for patients with recurrent platinum-sensitive ovarian cancer. Finally, the phase II OCTOVA (NCT03117933) trial compares the use of olaparib plus cediranib against olaparib alone or paclitaxel alone in platinum-resistant ovarian cancer.

Antiangiogenic therapy, PARP inhibition, and immunotherapy triplet combination trials

To date, only a few clinical trials contain arms with the triple targeting of angiogenesis, PARP, and immune checkpoints (Table 3). Preliminary results of the triplet combination arm of olaparib, durvalumab, a PD-L1 inhibitor, and bevacizumab within the MEDIOLA (NCT02734004) trial showed promising results in patients with germline BRCAwt, platinum-sensitive relapsed ovarian cancer: a disease control rate at 24 weeks of 77%, PFS 14.7 months, and response rate of 77% [97]. Furthermore, in a phase I study (NCT02484404) of olaparib, durvalumab, and cediranib in advanced gynecologic malignancies (n = 9, including 7 ovarian cancer participants), the triplet combination yielded an objective response rate of 44% (4/9, all partial responses) and a clinical benefit rate (CR + PR+ SC ≥ 6 mo) of 67% [98]. This combination continues to be investigated in phase II of the same study and will be further explored in the randomized trial setting for platinum-resistant recurrent ovarian cancer. The phase III DUO-O (NCT03737643) trial also contains a cohort utilizing the same triplet combination in the maintenance setting, following 6 cycles of platinum-based chemotherapy, bevacizumab, and durvalumab, for newly diagnosed advanced ovarian cancer patients without tumor BRCA mutations.

Another phase II (NCT02873962) trial contains an arm for the treatment of recurrent ovarian cancer with the combination of nivolumab, bevacizumab, and rucaparib. Finally, a phase I/II (NCT02484404) trial will assess the potential of olaparib, cediranib, and durvalumab among patients with pretreated recurrent ovarian cancer. PFS and ORR will be assessed across all these trials and, depending on their results, may warrant further expansion of this treatment modality via the generation of future clinical trials.

Conclusions

Antiangiogenic therapy has become a widely accepted component of the current paradigm for treating advanced ovarian cancer. To expand the breadth and efficacy of its usage,

however, the need for novel combinations has become more pressing, as new mechanisms of antiangiogenic resistance and restricted activity are being discovered outside the clinic. A wave of clinical trials in recent years addresses this need, bringing elements of antiangiogenic therapy together with well-established immune checkpoint or PARP inhibition. Despite the results of IMAGYN50 in newly diagnosed ovarian cancer, the therapeutic application of the dual inhibition of angiogenesis and immune checkpoints in ovarian cancer has yet to be amply characterized, as further clinical trials examining their use are still ongoing. The application of the combination of PARP inhibition and antiangiogenic agents, on the other hand, has progressed significantly over the past few years, with several critical phase III trials complete and an FDA approval in the recent months.

Genomic and tissue biomarker analyses can further augment our ability to identify subsets of the patient population that can benefit most from targeted combinations. Potential overlapping toxicities and adverse events must also be considered when assessing the suitability of combination treatments, particularly in the advanced cancer setting. Furthermore, there remains great opportunities to develop new, untried combinations that can yield greater responses and reduced toxicities. Ongoing and future trials will continue expanding the therapeutic possibilities of these combinations and define biomarkers of response that can help identify subsets of the ovarian cancer population that would attain the greatest benefit from these combinations.

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Highlights

- Antiangiogenic therapy has been a mainstay in the treatment of ovarian cancer
- Combinations with PARP inhibitors and immunotherapy can improve response to antiangiogenics
- New combination trials have shown preliminary activity and tolerability in ovarian cancers
- Further biomarker analysis is needed to identify populations most sensitive to these combinations

Table 1

Antiangiogenic therapy plus immune checkpoint blockade clinical trials.

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
Completed antiangiogenic therapy + ICB trials							
IMagyn050 NCT03038100 *Moore KN, et al.* Annals of Oncology (2020). Abstract.	Randomized, double-blind phase III	SOC plus bevacizumab (bev) plus atezolizumab (atezo)	Newly diagnosed, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (*n* = 1301)	Platinum-based chemotherapy (carboplatin plus paclitaxel) for 6 cycles plus bev 15 mg/kg IV for 2–6 cycles plus atezo 1200 mg IV q3w for 6 cycles or placebo Maintenance bev 15 mg/kg IV q3w plus atezo 1200 mg IV q3w for 16 cycles or placebo	Median PFS in intent-to-treat population: 18.4 mo placebo, vs. 19.5 mo atezo (HR = 0.92, 0.79–1.07) Median PFS in PD-L1$^{\pm}$ population: 18.5 mo placebo, vs. 20.8 mo atezo (HR = 0.80, 0.65–0.99)	ORR, duration of response, safety & tolerability	*No reported or published data; further analysis pending*
NCT02873962 *Liu JF, et al.* JAMA Oncol (2019).	Open-label, single arm phase II	Bevacizumab (bev) plus nivolumab (nivo)	Platinum-sensitive (*n* = 20) or platinum-resistant (*n* = 18) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (*n* = 38)	Bev 10 mg/kg IV q2w plus nivo 240 mg IV q2w	ORR: 28.9% (15.4–45.9)	ORR by platinum sensitivity: 40.0% (19.1–64.0) platinum-sensitive vs. 16.7% (3.6–41.4) platinum-resistant Median PFS: 9.4 mo (6.7-NA); 12.1 (8.4-NA) platinum-sensitive vs. 7.7 mo (4.7-NA) platinum-resistant	No grade 3/4 AEs ≥ 10% were observed Hypertension was observed in 26.3% of all patients (5.3% experienced grade 3/4)
Ongoing/incomplete antiangiogenic therapy + ICB trials							
ATALANTE NCT02891824 *Kurtz JE, et al.* Journal of Clinical Oncology (2018).	Randomized, double-blind, phase III	SOC plus bevacizumab (bev) plus atezolizumab (atezo)	Platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (*n* = 614)	Platinum-based chemotherapy (carboplatin plus gemcitabine/ paclitaxel/PLD) plus bev plus placebo (arm A) vs. atezo (arm B) for 6 cycles Maintenance with placebo (arm A) vs. atezo (arm B) until progression	PFS	TSST, OS, safety & tolerability	*No reported or published data*
EORTC-1508 NCT02659384	Randomized, triple-blind phase II	Bevacizumab (bev), atezolizumab (atezo), plus acetylsalicylic acid (ASA)	Platinum-resistant, recurrent epithelial ovarian, fallopian	Bev alone (arm 1) vs. bev plus atezo plus placebo (arm 2) vs. bev plus atezo plus ASA (arm 3)	PFS		*No reported or published data*

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
			tube, or primary peritoneal cancer				
NRG-GY009 NCT02839707	Randomized, open-label phase II/III	PLD plus bevacizumab (bev) plus atezolizumab (atezo)	Platinum-resistant recurrent high-grade ovarian, fallopian tube, or primary peritoneal cancer	PLD plus atezo (arm 1) vs. PLD + atezo + bev (arm 2) vs. PLD + bev (arm 3)	PFS (phases II & III) OS (phase UI)	ORR, PD-Ll expression, safety & tolerability	*No reported or published data*

*All reported ranges are 95% CI unless otherwise stated

Abbreviations:

AE: adverse event; *EORTC*: European Organization for Research and Treatment of Cancer; *HR*: hazards ratio; *ICB*: immune checkpoint blockade; *NA*: not applicable; *ORR*: objective response rate; *OS*: overall survival; *PFS2*: second progression-free survival; *PLD*: pegylated liposomal doxorubicin; *SOC*: standard of care; *TSST*: time to second subsequent therapy; *mo*: months; *q2w*: once every 2 weeks; *q3w*: once every 3 weeks

Table 2

Antiangiogenic therapy plus PARP inhibitor clinical trials.

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
Completed antiangiogenic therapy + PARPi trials							
PAOLA-I NCT02477644 *Ray-Coquard I, et al.* NEJM (2019). *Martin AG, et al.* Annals of Oncology (2020). Abstract.	Randomized, double-blind phase III	Bevacizumab plus olaparib	Newly diagnosed advanced/ high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, with complete or partial response to 1st line platinum-based chemotherapy (*n* = 806)	Bevacizumab 15 mg/kg IV q3w up to 15 mo plus olaparib 300 mg PO BID vs placebo up to 24 mo (*n* = 537 received o + b; *n* = 269p + b)	Median PFS for all: 22.1 mo o + b vs. 16.6 mo p + b (HR = 0.59, 0.49–0.72, *p* < 0.001) HRD including BRCAm: 37.2 mo o + b vs. 17.7 mo p + b (HR = 0.33, 0.49–0.72, *p* < 0.001) HRD without BRCAm 28.1 mo o + b vs. 16.6 mo p+ b (HR = 0.43, 0.28–0.66 *p* < 0.001)	Median PFS2 for all: o + b 36.5 mo vs. p + b 35.5 mo (HR = 0.78, 0.64–0.95, *p*= 0.0125) HRD including BRCAm: 50.3 mo o + b vs. 35.3 mo p + b HR = 0.56, 0.41–0.77, *p* < 0.001) HRD without BRCAm 50.3 mo o + b vs. 30.1 mo p + b (HR = 0.60, 0.38–0.96 *p* < 0.001)	Hypertension (19%), anemia (17%)
NSGO-AVANOVA/ ENGOT-ov24 *Mirza MR, et al.* Cancer Chemo & Pharmacology *(2019).* *Mirza MR, et al.* Lancet Oncology *(2019).*	Randomized, open-label phase I/II	Bevacizumab plus niraparib	Platinum-sensitive recurrent high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer (*n* = 12 (phase I), *n* = 97 (phase II))	Bevacizumab 15 mg/kg IV q3w plus niraparib 100–300 mg PO QD (n = 12) (phase I) Niraparib 300 mg PO QD with (n = 48) or without (n = 49) bevacizumab 15 mg/kg IV q3w (phase II)	RP2D (phase I): bevacizumab 15 mg/kg IV q3w plus niraparib 300 mg PO QD Median PFS (phase II): 11.9 mo n + b vs. 5.5 mo niraparib alone (HR = 0.35, 0.21–0.57, *p* < 0.0001)	Median PFS (phase I): 11.6 mo (8.4–20.1) Median OS (phase I): 25.3 mo (11.2-NA) ORR (phase I): 50% (21–79) ORR: 60% n + b vs. 27% niraparib alone (OR = 4.23, 1.79–9.97, p = 0.001) CBR (CR + PR + SD lasting ≥ 12 weeks): 79% n + b vs. 53% niraparib alone (OR = 3.36, 1.37–8.22, *p* = 0.008)	Hypertension (42%), anemia (25%), thrombocytopenia (16%) (phase I) Hypertension (21%), anemia (15%), thrombocytopenia (10%) (phase II)
NRG-GY004 NCT02446600 *Liu JF, et al.* Journal of Clinical Oncology (2020). Abstract.	Randomized, open-label phase III	Cediranib plus olaparib	Platinum-sensitive recurrent, high-grade ovarian, fallopian tube, or primary peritoneal cancer (n = 528)	Standard chemotherapy (paclitaxel/ gemcitabine/ doxorubicin plus carboplatin) (*n* = 166) vs. olaparib 300 mg PO BID (*n* = 183) vs. olaparib 200 mg PO BID plus cediranib	Median PFS: 8.2 mo o vs. 10.4c + o vs. 10.3 mo SOC (HR = 0.856, 0.66–1.11, *p* = 0.08 for c + o vs. SOC; HR = 1.20, 0.93–1.54 for o vs. SOC)	ORR: 52.4% o, 69.4% c + o, 71.3% SOC	Hypertension (31.4%), gastrointestinal events (30.1%), fatigue (17.5%) (in the c + o arm)

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
				30 mg PO QD (n = 179)			
NCT01116648 *Liu JF, et al.*Lancet Oncology *(2014).* *Liu JF, et al.* Annals of Oncology *(2019).*	Randomized, open-label phase II	Cediranib plus olaparib	Platinum-sensitive recurrent high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer (*n* = 90)	Olaparib 400 mg PO BID (*n* = 46) vs. olaparib 200 mg PO BID plus cediranib 30 mg PO QD (n = 44)	Median PFS: 16.5 mo c + o, 8.2 mo. o (HR = 0.50, 0.30–0.83, *p* = 0.006)	ORR: 79.6% c +o vs. 47.8% o (OR = 4.24, 1.53–12.22, *p* = 0.002) Median OS: 44.2 mo. c + o vs. 33.3 mo. o (HR = 0.64, 0.36–1.11, *p* = 0.11)	Hypertension (41%), fatigue (27%), diarrhea (23%)
EVOLVE NCT02681237 *Lheureux S, et al.* Clinical Cancer Research (2020).	Open-label, single-arm phase II	*Olaparib plus cediranib after prior PARPi progression*	Recurrent high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer (*n* = 34), divided into 3 cohorts: Platinum-sensitive after progression on PARPi (cohort 1) (*n* = 11) Platinum-resistant after progression on PARPi (cohort 2) (*n* = 10) Patients with progression on standard chemo after progression on PARPi (cohort 3) (*n* = 13)	Olaparib 300 mg PO BID plus cediranib 20 mg PO QD	ORR: 9% overall; 0% (cohort 1), 20% (cohort 2), 8% (cohort 3) Median 16-week PFS rate: 47% (33–67) overall; 55% (32–94) (cohort 1), 50% (27–93) (cohort 2), 39% (19–77) (cohort 3)	DCR (CR + PR + SD): 68% overall; 82% (cohort 1), 60% (cohort 2), 62% (cohort 3) CA-125 response rate: 15% overall; 18% (cohort 1), 10% (cohort 2), 15% (cohort 3) 1-year OS: 82% (62–100) (cohort 1), 69% (46–100) (cohort 2), 40% (18–92) (cohort 3)	Diarrhea (12%) Hypertension was observed in 24% of all patients (5.3% experienced grade 3/4)
CONCERTO NCT02889900 *Lee JM, et al.* Journal of Clinical Oncology (2020). Abstract.	Open-label, single-arm phase II	Cediranib plus olaparib	Platinum-resistant, high-grade gBRCAwt epithelial ovarian, fallopian tube, or primary peritoneal cancer, with ≥ 4 prior lines of therapy (*n* = 60)	Cediranib 30 mg PO QD plus olaparib 200 mg PO BID	ORR by independent central review: 15.3% (7.2–27.0)	Median duration of response: 8.3 mo (5.6–10.3) Median PFS: 5.1 mo (3.5–5.5) Median OS: 13.2 mo (9.4–16.4)	Hypertension (30%), fatigue (22%), diarrhea (13%)
BAROCCO NCT03314740 *Colombo N, et al.* Annals of Oncology (2019). Abstract.	Randomized, open-label phase II	Cediranib plus olaparib	Platinum-resistant recurrent high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (*n* = 123)	Paclitaxel 80 mg/m^2 IV qw (control) vs. cediranib 20 mg PO QD (continuous) plus olaparib 300 mg PO BID vs. cediranib 20 mg PO QD 5 days/week (intermittent)	PFS: 3.1 mo (control), 5.7 mo (continuous) (HR = 0.76, 90% CI 0.49–1.17, *p* = 0.28), 3.8 mo (intermittent) (HR = 1.08, 90% CI 0.36–1.10, *p* = 0.76)	ORR, PFS2, OS, quality of life, toxicity	*Farter details pending*

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
				plus olaparib 300 mg PO BID			
Ongoing/incomplete antiangiogenic therapy + PARPi trials							
ICON9 NCT03278717 *Elyashiv O, et al.* Int J Gynecol Cancer (2020).	Randomized, open-label phase III	Maintenance cediranib plus olaparib	Platinum-sensitive recurrent high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer (*n* = 618)	Olaparib 300 mg PO BID plus cediranib 20 mg PO QD vs. olaparib 300 mg PO BID alone	PFS OS	RR, PFS/OS from 2nd line chemotherapy, PFS per CA-125/GCIG criteria, TSST, quality of life (EORTC QLQ-c30 score)	*Accrual ongoing*
ETCTN9825 NCT02345265 *Liu JF, et al.* Journal of Clinical Oncology (2018). Abstract.	A phase II biomarker single-arm study	Cediranib plus olaparib	Platinum-sensitive or platinum-resistant/ refractory high-grade ovarian, fallopian tube, or primary peritoneal cancer (*n* = 70)	Cediranib 300 mg PO QD plus olaparib 200 mg PO BID	ORR: 77% (63–88) in platinum-sensitive cohort (*n* = 35), 20% (11–38) in platinum-resistant cohort (*n* = 35)	DCR (CR + PR + SD at 16 wks): 91% in platinum-sensitive cohort, 43% in platinum-resistant cohort	*Completed enrollment Further biomarker details pending*
OCTOVA NCT03117933	Randomized, open-label phase II	Cediranib plus olaparib	Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	Paclitaxel 80 mg/m^2 IV qw vs. olaparib 300 mg PO BID vs. olaparib PO BID plus cediranib 20 mg PO QD	PFS	OS, ORR, quality of life (EORTC QLQ-c30 score), safety & tolerability	*Completed enrollment*
NRG-GY005 NCT02502266	Randomized, open-label phase II/III	Cediranib plus olaparib	Platinum-resistant/ refractory ovarian, fallopian tube, or primary peritoneal cancer	Standard chemotherapy (paclitaxel, doxorubicin, topotecan) (arm 1) vs. cediranib PO QD plus olaparib PO BID (arm 2) vs. cediranib PO (arm 3)	ORR (phase II) PFS (phases II & III) OS (phase III co-primary)	ORR (phase III)	*Completed enrollment*

*All reported ranges are 95% CI unless otherwise stated

Abbreviations: *AE*: adverse event; *BID*: twice daily; *CBR*: clinical benefit rate; *CR*: complete response; *DCR*: disease control rate; *EORTC QLQ-c30*: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; *HR*: hazards ratio; *NA*: not applicable; *OR*: odds ratio; *ORR*: objective response rate; *OS*: overall survival; *PARP*: poly (ADP-ribose) polymerase; *PARPi*: poly (ADP-ribose) polymerase inhibitor; *PFS2*: second progression-free survival; *PFS*: progression-free survival; *PO*: by mouth; *PR*: partial response; Q*D*: once daily; *RP2D*: recommended phase 2 dose; *SD*: stable disease; *S*OC: standard of care; T*SS*T: time to second subsequent therapy; c + o: cediranib plus olaparib; mo: months; n + b: niraparib plus bevacizumab; o + b: olaparib plus bevacizumab; o: olaparib; p + b: placebo plus bevacizumab; q3w: once every 3 weeks; qw: once weekly; H*RD*: homologous recombination deficiency; *BR*CAm: *BR*CA mutation; g*BR*CAwt germline *BR*CA wild type

Table 3

PARP inhibitor plus immune checkpoint blockade clinical trials.

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
Completed PARPi plus ICB trials							
TOPACIO/ KEYNOTE-162 NCT02657889 *Konstantinopoulos PA, et al.* JAMA Oncology *(2019).*	Open-label, single-arm phase I/II	Niraparib plus pembrolizumab (pembro)	Advanced recurrent or metastatic TNBC (*n* = 5 (phase I)) or ovarian carcinoma (*n* = 9 (phase I), *n* = 53 (phase II))	Niraparib 200–300 mg (phase I) or 200 mg (phase II) PO QD plus pembro 200 mg IV q3w	RP2D (phase I): niraparib 200 mg PO QD plus pembro 200 mg IVq3w ORR (phase II): 18% (11–29) among ovarian carcinoma (*n* = 62) pts across phases I & II	DCR (CR + PR + SD): 65% (54–75) PFS: 3.4 mo (2.1–5.1)	Anemia (36%), thrombocytopenia (36%), neutropenia (14%) in phase I Anemia (21%) in phase II
Ongoing/incomplete PARPi plus ICB trials							
FIRST/ENGOT-ov44 NCT03602859 *Hardy-Bessard AC, et al.* Journal of Clinical Oncology (2019). Abstract.	Randomized, double-blind phase III	SOC plus dostarlimab first line treatment, then maintenance bevacizumab, niraparib, and dostarlimab	Advanced nonmucinous epithelial ovarian cancer	SOC (paclitaxel 175 mg/m^2, AUC 5–6 mg/mL/min q3w, bevacizumab 7.5–15 mg/kg q3w) for 1 cycle, then SOC plus dostarlimab (arm 3) vs. placebo (arms 1, 2) 1000 mg q6w for 5 cycles Maintenance with bevacizumab 7.5–16 mg/kg q3w plus niraparib (arms 2, 3)/ placebo (arm 1) 100 mg PO plus dostarlimab (arm 3) vs. placebo (arms 1, 2) 1000 mg q6w	PFS (all participants) PFS (PD-L1 positive tumors)	PFS (per BICR), OS, safety & tolerability, pharmacokinetics, quality of life (EORTC-QLQ), TFST, PFS2, ORR, duration of response, DCR	*No published data*
ATHENA NCT03522246	Randomized, double-blind phase III	Maintenance rucaparib plus nivolumab (nivo)	Newly diagnosed advanced epithelial ovarian, fallopian tube, or peritoneal cancer with investigator-assessed response to	Maintenance rucaparib PO plus nivo IV (arm A) vs. plus placebo IV (arm B) vs. maintenance placebo PO plus nivo IV (arm C) vs. plus placebo IV (arm D)	PFS	PFS (per BICR), OS, ORR, duration of response, safety & tolerability	*No published data*

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
			first-line platinum treatment				
JAVELIN OVARIAN PARP 100 NCT03642132 *Eskander RN, et al.* Journal of Clinical Oncology (2019). Abstract.	Randomized, open-label phase III	Platinum-based chemotherapy plus avelumab, then maintenance avelumab plus talazoparib	Treatment-naïve, advanced/ metastatic epithelial ovarian, fallopian tube, or primaty peritoneal cancer	Chemotherapy (paclitaxel 175 mg/m^2, carboplatin AUC 5–6 IV q3w) plus concurrent avelumab 800 mg IV q3w followed by avelumab plus talazoparib (arm A) vs. Chemotherapy followed by talazoparib maintenance 0.75 mg PO QD (arm B) vs. Chemotherapy pus concurrent bevacizumab followed by bevacizumab 15 mg/kg IV q3w maintenance (arm C)	PFS (per BICR)	OS, PFS2, quality of life (EQ-5D-5L)	*No published data*
ENGOT-ov43/ KEYLYNK-001 NCT03740165 *Vergote I, et al.* Journal of Clinical Oncology (2019). Abstract.	Randomized, double-blind phase III	Chemotherapy plus pembrolizumab (pembro), then maintenance olaparib	Advanced, non-BRCA mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer	Chemotherapy (carboplatin plus paclitaxel IV) for 5 cycles plus concurrent pembro followed by pembro plus olaparib maintenance (arm 1) for up to 35 cycles vs. Chemotherapy plus concurrent pembro followed by pembo plus placebo maintenance (arm 2) for up to 35 cycles Chemotherapy (arm 3)	PFS OS	PFS (per BICR), PFS2, safety & tolerability, quality of life (EORTC-QLQ-c30), TFST	*No published data*
NCT02571725 *Adams SF, et al.* Journal of Clinical Oncology (2017). Abstract.	Open-label phase I/II	Olaparib plus tremelimumab (treme)	Recurrent epithelial ovarian, fallopian tube, or primary periteonal carcinoma with gBRCA1/2m	Olaparib 300 mg PO BID plus treme 10 mg/kg (reduced to 3 mg/kg minimum if sufficient DLT) (phase I) or at RP2D	RP2D (phase I): olaparib 300 mg PO BID plus treme10 mg/kg IV q4w ORR (phase II)	PFS (phase II	*No published data*

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/ Schedule	Findings of Primary Endpoint(s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
			(*n* = 3 (phase I))	(phase II) IV q4w for first 6 interventions, then q12w			
NCT04034927	Randomized, open-label phase II	Olaparib plus tremelimumb (treme) vs. Olaparib alone	Platinum-sensitive, high-grade serious or endometrioid ovarian, fallopian tube, or primary peritoneal cancer	Olaparib plus treme q4w for first 4 interventions, then q12w vs. Olaparib	PFS Dose-limiting toxicities RECISTv1.1 response	ORR, OS, AE	*No published data*
MEDIOLA NCT02734004 *Drew Y, et al.* Annals of Oncology (2020). Abstract.	Open-label phase I/II	Olaparib plus durvalumab (durva)	Platinum-sensitive recurrent gBRCAm or non-gBRCAm ovarian cancer	Olaparib 300 mg PO BID plus durva 1.5 g IV q4w (phase II)	24-wk disease control rate: 28.1% (90% CI 15.5–43.9) Safety& tolerability	ORR: 31.3% (16.1–50.0) Median duration of response: 6.9 mo (IQR 5.7–11.1) Median PFS: 5.5 mo (3.6–7.5)	*No published data*
GUIDE2REPAIR NCT04169841 *Fumet JD, et al.* BMC Cancer (2020).	Open-label phase I/II	Olaparib plus durvalumab (durva) plus tremelimumab (treme)	Platinum-sensitive HRD + ovarian cancer	Olaparib 300 mg PO BID for 8 weeks, then olaparib 300 mg PO BID plus durva 1500 mg IV q4w plus treme 75 kg IV q4w for up to 4 doses, then durva 1.5 g IV q4w	12-week PFS from 1st dose of ICB	12-week DCR, OS, ORR, toxicity	*No published data*
NCT02953457	Open-label phase I/II	Olaparib plus durvalumab (durva) plus tremelimumab (treme)	Platinum-sensitive/ resistant/ refractory recurrent HRD + or somatic/ gBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancer	Olaparib PO BID up to 12 months plus durva IV q3w up to 13 courses plus treme IV q4w up to 4 courses	Dose-limiting toxicities (phase I) PFS (platinum-resistant group) PFS (platinum-sensitive group)	OS, biomarker analyses	*No published data*
NCT02484404	Open-label phase I/II	Olaparib plus durvalumab (durva)	Previously treated (≥2 lines) or platinum-resistant/ refractory recurrent ovarian, fallopian tube, or primary peritoneal cancer (phase II)	Olaparib 200–300 mg PO BID plus durva 3–10 mg/kg IV q2w OR 10 mg/kg IV q4w (phase I), RP2D olaparib plus durva (phase II)	RP2D (phase I) Safety and tolerability ORR	ORR, median duration of response, PK parameters (phase I) PFS, safety, biomarker analysis (phase II)	*No published data*

*All reported ranges are 95% CI unless otherwise stated

Abbreviations: *AE*: adverse event; *BICR*: blinded independent central review; *BID*: twice daily; *CR*: complete response; *DCR*: disease control rate; *DLT*: dose-limiting toxicity; *EORTC QLQ-c30*: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; *ICB*: immune checkpoint blockade; *IQR*: interquartile range; *ORR*: objective response rate; *OS*: overall survival; *PARPi*: poly (ADP-ribose) polymerase inhibitor; *PFS2*: second progression-free survival; *PFS*: progression-free survival; *PO*: by mouth; *PR*: partial response; *QD*: once daily; *RECIST*: response evaluation criteria in solid tumors; *RP2D*: recommended phase 2 dose; *SD*: stable disease; *SOC*: standard of care; TF*ST*: time to first subsequent therapy; mo: months; q2w: once every 2 weeks; q3w: once every 3 weeks; q4w: once every 4 weeks; HRD: homologous recombination deficiency; g*B*RCAm: germline *B*RCA mutated; g*B*RCA1/2m: germline *B*RCA1/2 mutated.

Table 4

Triplet combination (antiangiogenic therapy plus immune checkpoint blockade plus PARP inhibitor) clinical trials.

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/Schedule	Findings of Primary Endpoint (s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
Completed triplet combination trials							
NCT02484404 *Zimmer AS, et al.* J, Immunother. Cancer (2019).	Open-label, dose-escalation phase I	Olaparib plus durvalumab (durva) plus cediramb	Advanced breast or gynecologic malignancies (n = 9)	Olaparib 200–300 mg PO BID plus durva 1.5 g IV q4w plus cediranib 15–20 mg PO QD (5 days on/2 days off)	RP2D: olaparib 300 mg PO BID plus durva 1.5 mg IV q4w plus cediranib 20 mg PO QD (5 days on/2 days off)	ORR: 44% Median duration of response: 8.5 mo (7–26) CBR (CR + PR + SD ≥ 6 mo): 67%	Lymphopenia (33%), anemia (22%)
Ongoing/incomplete triplet combination trials							
AGO/DUO-O/ ENGOT-ov46 NCT03737643 *Harter P, et al.* Journal of Clinical Oncology (2019).	Randomized, double-blind phase III	Platinum-based chemotherapy plus durvalumab (durva) plus bevacizumab (bev), then maintenance bev (optional for tBRCAm cohort) plus durva plus olaparib	Newly diagnosed, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	Non-tBRCAm cohort: Platinum based chemotherapy and bev IV plus placebo (arm 1) OR plus durva (arms 2, 3) Maintenance bev with double placebo IV (arm 1) vs. durva plus placebo (arm 2) vs. durval plus olaparib (arm 3) tBRCAm cohort: Platinum-based chemotherapy plus durva IV for 6 cycles Maintenance durva IV plus olaparib PO BID, with bev IV optional	PFS	OS, ORR, duration of response	*No published data*
MEDIOLA NCT02734004 *Drew Y, et al.* Annals of Oncology (2020). Abstract.	Open-label phase I/II	Olaparib plus durvalumab (durva) plus bevacizumab (bev)	Platinum-sensitive recurrent ovarian cancer with no BRCAm (n = 31)	Olaparib 300 mg PO BID plus durva 1.5 g IV q4w plus bev 10 mg/kg q2w	24-week DCR: 77.4% (61.7–88.9)	ORR: 77.4% (58.9–90.4) Median duration of response: 11.1 mo(IQR 9.0–16.4) Median PFS: 14.7 mo (10.0–18.1)	*No published data*
NCT02873962	Open-label, single-arm phase II	Nivolumab (nivo) plus bevacizumab (bev) plus rucaparib	Platinum-sensitive or platinum-resistant recurrent epithelial ovarian, fallopian tube,	Nivo IV q2w plus bev IV q2s plus rucaparib PO QD	ORR	PFS, ORR, duration of response, biomarker analysis	*No published data*

Trial Name/NCT Number	Phase	Drugs	Eligible Patients	Dose/Schedule	Findings of Primary Endpoint (s)	Findings of Secondary Endpoint(s)	Notable common grade AEs (≥10%)
			or primary peritoneal cancer, with no germline or somatic deleterious BRCAm				

*All reported ranges are 95% CI unless otherwise stated

Abbreviations: *AE*: adverse event; *BID*: twice daily; *CBR*: clinical benefit rate; *CR*: complete response; *DCR*: disease control rate; *IQR*: interquartile range; *ORR*: objective response rate; *OS*: overall survival; *PFS*: progression-free survival; *PO*: by mouth; *PR*: partial response; *QD*: once daily; *RP2D*: recommended phase 2 dose; *SD*: stable disease; *mo*: months; *q2w*: once every 2 weeks; *q3w*: once every 3 weeks; *q4w*: once every 4 weeks; *tBRCAm*: tumor BRCA mutated; *BRCAm*: BRCA mutation