Update on anti-angiogenic agents and PARP inhibitors: is the combination a potential or a reality?

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Abstract
Epithelial ovarian cancer (OC) is one of the most common and lethal cancers in women in the developed world. Despite progress in the treatment of OC, most patients experience recurrence within 18 months and long-term survival is low. The development of molecular targeted therapies to complement chemotherapy and surgery has largely focused on inhibition of angiogenesis and interruption of the DNA repair process. Inhibition of angiogenesis is a valuable therapeutic strategy at different points in the treatment pathway, with blockade of the vascular endothelial growth factor VEGF pathway a key target for inhibiting angiogenesis. Targeting the DNA repair processes with inhibitors of poly-ADP ribose polymerase (PARP), particularly in BReast CAncer susceptibility gene (BRCA) mutated tumours, has also shown promising anticancer activity. Prevention of DNA repair and targeting of angiogenesis through PARP inhibition has been extensively explored in OC and significant activity and clinical benefit has been shown with molecularly targeted therapy. Combining anti-angiogenic therapy and PARP inhibitors may offer new therapeutic opportunities in OC, and a number of clinical studies have been exploring the combination of these two molecularly targeted therapies. The identification of reliable predictive markers of response and translational research to establish factors predictive of response to combinations of anti-angiogenic and PARP inhibitor drugs will be required before these therapies can be fully implemented into clinical practice. However, combining anti-angiogenic agents with PARP inhibitors provides new opportunities to improve the treatment options for women with OC.

Key words: angiogenesis, anti-angiogenic agents, DNA repair, epithelial ovarian cancer, PARP inhibitors, targeted cancer therapies

Introduction

In the developed world epithelial ovarian cancer (OC) is the fifth most common cancer and the fourth cause of cancer death in women. Every year 220,000 women develop epithelial OC worldwide [1]. Debulking surgery followed by platinum-taxane chemotherapy is the current standard of care. Although significant progress has been made in the treatment of OC, most patients develop a recurrence within 18 months and the reported 5-year survival rate is still low [2, 3]. During the last decade the focus of clinical research has shifted towards developing molecular targeted therapy to complement chemotherapy and surgery. Developments in treatment have occurred in two main areas. Firstly, inhibition of angiogenesis [4] has been shown to be a valuable therapeutic strategy at different points in the treatment pathway. The key target for inhibiting angiogenesis is blockade of vascular endothelial growth factor VEGF pathway, blocking its ligand or receptor, or targeting the angiopoietin pathway [5]. The second area is targeting DNA repair processes, particularly in BReast CAncer susceptibility gene (BRCA) mutated tumours [6]. These tumours have a deficiency in homologous recombination (HRD) repair of DNA damage and depend on single-strand repair pathways initiated by activation of poly-ADP ribose polymerase (PARP). Inhibition of PARP in cells with HRD leads to genomic instability and cell death due to a process called 'synthetic lethality' [7]. BRCA mutations in OC occur more commonly than previously thought, particularly in high-grade tumours. It is estimated that at least 15% of high-grade serous OCs (HGSOC) have a germline BRCA1 or BRCA2 mutation, and in approximately another 35% there is acquired HRD due to somatic BRCA mutations, silencing by methylation, mutation in other repair genes, and inactivation of other pathway proteins [8, 9]. Targeting of angiogenesis and prevention of DNA repair through

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PARP inhibitors has been extensively explored in OC and new opportunities for treatment have emerged. In addition, preclinical data suggests that inhibition of angiogenesis increases the degree of HRD [10-12], and this has led to clinical studies exploring the combination of these two molecularly targeted therapies. Here we review the current data from clinical trials with anti-angiogenic therapy and PARP inhibitors in OC, and the emerging data and studies on the combination of these two therapies.

Anti-angiogenic targeted therapy

Pharmacodynamic properties

Angiogenesis plays an important role in carcinogenesis through the promotion of tumour growth and dissemination [13, 14].

Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor that induces proliferation, migration and survival of vascular endothelial cells. The two most important strategies to block angiogenesis are inhibition of binding between VEGF and its receptor, and the direct inhibition of receptors. The greatest experience has been with bevacizumab, a recombinant humanized monoclonal antibody that prevents the ligand from binding the vascular endothelial growth factor A (VEGF-A). Bevacizumab has multiple effects on the cell *in vitro*. Firstly, it inhibits VEGF blocking signal transduction through VEGFR1 and VEGFR2 receptors. It induces increased cell permeability, nitric oxide, and migration and tissue factor production in vascular endothelial cells and monocytes [15]. In patients with previously untreated advanced breast cancer, bevacizumab decreases phosphorylation of VEGFR2 and increases tumour cell apoptosis by changing permeability parameters [16]. Additionally, it inhibits metalloproteinase (MMP)-9 expression, which is thought to contribute to tumour progression [17]. As a single agent, it has been shown to have anti-tumour activity in OC [18]. While bevacizumab is the most studied anti-angiogenic agent in OC, there are other strategies to effectively block the VEGF including receptor tyrosine-kinase inhibitors (TKIs) that often have a broad spectrum of activity, inhibiting other surface receptor tyrosine kinases. The key drugs that have been tested are pazopanib, nintedanib and cediranib (Table 1). Pazopanib is an oral TKI that inhibits several kinase receptors, including those for VEGFR-1,-2, and -3, platelet-derived growth factor (-α and -β), and fibroblast growth factor. It also targets stem cell-factor receptor (c-kit), interleukin 2-inducible T-cell kinase, lymphocyte-specific protein tyrosine kinase, and colony-stimulating factor 1 receptor [19, 20]. Nintedanib (BIBF 1120) is an orally administered potent blocker of the receptors of vascular endothelial growth factor (VEGFR-1–3), platelet-derived growth factor (PDGFR-α/β) and fibroblast growth factor (FGFR-1–3) [21].

Cediranib is an oral tyrosine kinase inhibitor that blocks all three VEGFRs (VEGFR-1, -2, and -3) [22].

Preclinical investigations have shown broad-spectrum anti-tumour activity with a pharmacokinetic profile that supports once-daily oral administration [23].

Inhibition of the angiopoietin axis is another strategy that has been explored in OC. The lead compound, AMG-386 (trebananib), is a recombinant peptide-Fc fusion protein (peptibody) that binds to and inhibits angiopoeitin-1 and -2, preventing activation through the Tie-2 receptor [24]. Trials have been performed in both first-line and recurrent OC. Whilst this compound is active [25], it is unclear whether it is a clinically useful addition to the group of anti-angiogenic therapies for OC.

Bevacizumab in first-line and recurrent disease

Bevacizumab has proven to be highly active in the treatment of first-line OC with significant prolongation in progression-free survival (PFS) in patients with advanced disease (hazard ratio [HR]: 0.72, 95% confidence interval [CI] 0.63–0.82; p<0.001 and HR 0.81, 95% CI 0.70–0.94; p=0.004, in GOG218 and ICON7, respectively) [26, 27]. Similarly, a benefit in PFS has been seen in two randomised trials in which bevacizumab was combined with chemotherapy and then given as maintenance treatment until progression in patients with a first 'platinum-sensitive' recurrence of OC (HR 0.484; 95% CI 0.388–0.605; p<0.0001 and HR 0.61; p<0.0001 in OCEANS and GOG 213 trials, respectively) [28, 29]. Bevacizumab in combination with chemotherapy has also been given to a third group of patients with 'platinum-resistant' recurrence and this led to a significant improvement in the tumour response rate, PFS and improvement in patient-reported outcome [30, 31]. The European Medicines Agency (EMA) has approved bevacizumab, at a dose of 15mg/kg for OC in first-line therapy with platinum and paclitaxel, and as maintenance for up to 15 months [32]. In some countries an alternative dose and treatment duration of bevacizumab is used based on the results seen in the ICON7 trial [27]. In ICON7 bevacizumab was given at 7.5 mg/kg for up to 12 months. Furthermore, a preplanned subgroup analysis demonstrated that the PFS benefit was confined to patients at high risk of recurrence (>1 cm residual disease and/or Stage IV) (HR 0.81, 95% CI 0.70–0.94; p=0.004). The clinical characteristics of this subgroup were similar to those enrolled in GOG 218, and the magnitude of benefit in PFS was comparable. The updated analysis showed that it was only the high risk group in ICON7 who derived an

improvement in overall survival (OS) from bevacizumab (HR 0.78 (95% CI; 0.63–0.97), translating into a mean difference in survival of 4.8 months [33]. The EMA has also approved second-line use of bevacizumab in combination with carboplatin and gemcitabine followed by maintenance therapy. Neither first nor second-line use are approved in the USA. However, both the EMA and the Federal Drug Administration (FDA) have approved the use of bevacizumab in combination with weekly paclitaxel, liposomal doxorubicin and topotecan in patients with 'platinum-resistant' disease [30]. In spite of these trials many questions remain about the best use of bevacizumab in OC. Firstly, there are questions about the optimum dose, with no apparent detriment using half the dose recommended in the pivotal trial submitted for licensing. In the two first-line trials bevacizumab was given for different durations. From both studies it appears that maximum differences in PFS occurs around the time the treatment stops. This has led to the BOOST trial (NCT 01462890) in which 15 months treatment with bevacizumab is being compared to 30 months treatment. Secondly, the absence of any survival benefit seen in patients treated on the OCEANS trial, or supporting data of patient benefit such as quality of life leads to concerns about the value of this regimen in this setting. However, the recently reported GOG 213 trial of bevacizumab in combination with carboplatin and paclitaxel and then as maintenance demonstrated an improvement in PFS and no detriment in quality of life [29]. Currently, bevacizumab is considered an option for first 'platinum-sensitive' recurrence in patients who have not received bevacizumab in the first-line setting. However, the situation is made more complex by the results of the AURELIA trial, in which significant benefit was seen in patients with 'platinum-resistant' disease [30]. Currently, there are no validated predictive markers for response to bevacizumab so that selection of patients for therapy is based on clinical criteria. This has led some physicians to reserve the use of bevacizumab for patients with 'platinum-resistant' relapse, where the effect of chemotherapy alone is generally poor and short-lived. Resistance to bevacizumab occurs in nearly all patients at some point, and the mechanisms underlying resistance are unclear. It is unclear whether patients will respond again on retreatment, and this is being tested in a clinical trial where patients who have received first-line bevacizumab are re-treated with the drug on progression (MITO16/MANGO-2b, NCT01706120). In summary, bevacizumab has clearly been shown to be active in different phases of the treatment pathway. The results of ongoing 'second generation' studies will help to define the position of the drug in the treatment of advanced OC.

Tyrosine kinase inhibitors

Several TKIs have now been evaluated in phase I/II studies and in randomised phase III clinical trials and most of the trials have demonstrated a significant benefit in PFS in either the first-line or recurrent disease setting

As first line maintenance treatment, pazopanib improved the PFS by 5.6 months compared with placebo after first-line treatment for stages II–IV [34]. However, toxicity was significant with 58% patients requiring a dose reduction and 33% discontinued therapy due to adverse events. Furthermore, there was a decrement in the quality of life (QOL) in AGO-OVAR-16 for patients randomised to pazopanib [35].

The first-line trial with nintedanib (BIBF 1120), given with chemotherapy and then as maintenance had less reported toxicity than pazopanib and showed a significant benefit in terms of PFS but the incremental improvement was small and of questionable clinical value (median PFS: 17.3 *versus* 16.6 months) [36].

Thus far, there has only been one randomised trial (ICON6) of a TKI in first 'platinum-sensitive' recurrent OC. In ICON6, cediranib with chemotherapy followed by maintenance therapy was compared to platinum-based chemotherapy alone led to a 2.7 month improvement in median PFS which was significant (from 17.6 to 20.3 months; HR 0.70, p=0.042) [37]. A third arm with cediranib given only during chemotherapy showed an intermediate effect, suggesting that cediranib added to the action of chemotherapy as well as being beneficial as maintenance therapy beyond chemotherapy. Non-randomised trials with TKIs in patients with multiply pretreated OC, both in the 'platinum-sensitive' and '-resistant' settings show some degree of activity; tumour response occurred in some patients but a greater proportion of patients had stable disease as their recorded outcome. However, in MITO-11, a randomised trial in patients with 'platinum-resistant' and 'platinum-refractory' disease, pazopanib added to weekly paclitaxel led to a significant improvement in PFS. In fact, patients were randomly assigned to receive paclitaxel and pazopanib or paclitaxel only. PFS was significantly longer in the pazopanib plus paclitaxel group than with paclitaxel alone (median 6.35 months [95% CI 5.36–11.02] vs 3.49 months [CI 2.01–5.66]; HR 0.42 [95% CI 0.25–0.69]; p=0.0002, respectively). Adverse events were more common in the pazopanib arm. The most common grade 3-4 adverse events were neutropenia, fatigue, leucopenia, hypertension [38].

Although TKIs have the advantage of being an oral medication, the rate of discontinuation of therapy is higher than comparable studies with bevacizumab (33.3% *vs* 17%, respectively) [26, 34]. Fatigue, hypertension and

diarrhoea are the main side effects leading to dose reduction or discontinuation. The much greater experience of these agents in renal cell cancer has led to the development of management guidelines that might in future make it easier to use TKIs in the treatment of OC [39]. However, gastrointestinal perforation, a specific concern with bevacizumab, appears to be less common with TKIs. In the first-line pazopanib trial this occurred in 1% of patients compared to 2.8% in those receiving bevacizumab. The manufacturer of pazopanib does not currently plan to take forward the further development of pazopanib in OC, although the provocative results of MITO-11 are worthy of further exploration of the drug in this setting. At the moment, cediranib is the only TKI that is being taken forward for licensing, and the results of ICON6 have been submitted to the EMA. The future of TKIs in OC may lie in combination with other targeted therapies, as we will discuss below.

PARP inhibitors

Pharmacodynamic properties

Many of the current anticancer therapies act through damaging DNA. Cancer cells are more susceptible to DNA damage than normal cells, because of multiple mutations, some of which may affect the DNA repair pathways. For cells to survive, damage to DNA, which occurs spontaneously in all cells, needs to be repaired. There are many processes by which this takes place and one of these involves PARP, an important enzyme that is involved in the repair of single-strand DNA breaks. The PARP proteins are a family of 17 enzymes involved in a large range of cellular processes including DNA transcription, DNA damage response, genomic stability maintenance, cell cycle regulation, and cell death [40].

PARP1 is the best characterized member of the PARP family and is involved in base excision repair (BER) in response to single-stranded DNA breaks (SSBs). It is a component of the BER complex, which consists of DNA ligase III, DNA polymerase beta, and the XRCC1 protein [41]. PARP1 also has a role in nucleotide excision repair (NER). Both BER and NER are key pathways that enable repair of DNA damage that can be caused by certain alkylating and chemotherapeutic agents [42, 43]. Inhibitors of PARP lead to an accumulation of double-strand DNA breaks. PARP emerged as an important therapeutic target following the observation that inhibitors of PARP led to deficient repair of double-stranded DNA breaks in cells with homozygous deficiency of BRCA1 or BRCA2 and a 1000-fold increase in cytotoxicity due to lethal genomic instability [6, 44]. Trials in patients began shortly afterwards.

PARP inhibitors: updating trials

The first clinical demonstration of the anti-tumour activity and potential clinical value of PARP inhibitors was demonstrated in a phase I trial using olaparib (AZD2281) in BRCA mutated cancers [45]. In this study 60 patients were enrolled and 22 had a BRCA mutated cancer or a strong family history of BRCA-associated cancers. A clinical benefit rate (CBR), defined as a radiological response, tumour marker response or stabilisation for more than 4 months was seen in 12 out of 19 (63%) patients with a confirmed BRCA mutation. The cohort of patients was expanded with BRCA1/2 mutation–associated gynaecologic malignancies (ovarian, primary peritoneal, and fallopian tube cancers) where a CBR of 46% was observed. A RECIST (Response Evaluation Criteria in Solid Tumours) radiological response or CA125 response was observed in 40% of patients. There was a correlation of response with 'platinum-sensitivity'; the CBR was 69% in patients with 'platinum-sensitive' tumours and 45% and 23% in patients with 'platinum-resistant' and 'refractory' disease, respectively [46].

In addition to patients with a germ line BRCA mutation there is evidence that HRD occurs in a much larger group of patients, perhaps as many as 50% of patients with HGSOC [8], potentially widening the use of PARP inhibitors in OC. This feature of wider HRD deficiency, sometimes called 'BRCAness' [47] was demonstrated clinically in a phase II study of olaparib 400 mg twice daily monotherapy in patients with high-grade serous OC without a BRCA mutation, where a response was seen in 11 out of 46 patients (24%) [48].

These emerging data coupled with interest in exploring whether olaparib maintenance might lead to useful prolongation of disease control led to the design of a randomised phase II trial in which patients with high grade serous cancer which had responded to platinum-based chemotherapy were randomised to olaparib maintenance therapy or placebo. In this study maintenance olaparib significantly improved PFS compared to placebo (from 4.8 months in the placebo group to 8.4 months in the experimental group after the completion of chemotherapy), representing a 65% reduction in risk of progression in patients with platinum-sensitive HGSOC following a response to two or more lines of platinum-based therapy (HR 0.35; 95% CI 0.25–0.49; $p<0.0001$) [49].

A subgroup of analysis in patients with a germline or somatic BRCA mutation (51%) showed that this population had the greatest benefit from maintenance with olaparib, reducing the risk of progression by 82% and with a median PFS of 11.2 *versus* 4.3 months for placebo arm (HR 0.18; 95% CI 0.10–0.31; $p<0.0001$) [50]. The combination of

therapeutic efficacy with minimal toxicity has ultimately led to the approval of olaparib maintenance therapy by the EMA for the treatment of recurrent platinum-sensitive HGSOC and a BRCA mutation.

The activity of olaparib has also been directly compared to pegylated liposomal doxorubicin (PLD) in patients with BRCA mutated OC. A phase II study compared two doses of olaparib, 200 or 400 mg with PLD 50 mg/m^2. No statistically significant differences were reported for the objective response rate, duration of response, changes in tumour size, or OS. The tumour response rates were 25% and 31% with 200 mg and 400 mg olaparib, respectively, and 18% with PLD. PFS was 6.5 months (95% CI 5.5–10.1), 8.8 months (95% CI 5.4–9.2), and 7.1 months (95% CI 3.7–10.7) for the three arms, respectively [51].

The activity of PLD was higher than previously observed in a phase III randomised study [52], suggesting that this drug may have greater activity in patients carrying a BRCA mutation. A recent retrospective comparison supports this hypothesis; PLD was more active in women with a BRCA mutated OC and this difference seemed independent of platinum sensitivity [53]. Notwithstanding these results, the FDA has accepted the use of olaparib as a single agent for treatment of patients with OC and a BRCA mutation who have had 3 or more previous lines of treatment. This is based mainly on data from a single arm phase II trial that included patients with OC as well as other tumour types [54] and additional data accumulated from other trials in this setting [55].

Extensive preclinical studies have shown that PARP inhibitors increase the cytotoxic effects of chemotherapy [56, 57]. A phase I study of olaparib with carboplatin (AUC4/5) showed clinical benefit in 85% of 27 women with BRCA1/2 mutation-associated recurrent breast and OCs [58]. However, in the 'platinum-sensitive' setting the addition of olaparib to chemotherapy does not appear to confer additional benefit. In the randomised, phase II study reported by Oza et al [59] the rate of progression during chemotherapy was similar for the arms with and without olaparib; the benefit in PFS was seen during the maintenance phase of olaparib. In this study, 38 patients were known to have a BRCA mutation, and the benefit in PFS in this group was similar that reported in the Study 19 trial [50].

These are at least five PARP inhibitor agents: olaparib, rucaparib, niraparib, BMN-673 and ABT-888 (veliparib). The most important are reported in Table 2.

Two agents are currently undergoing clinical trials as maintenance therapy after platinum-based chemotherapy. The NOVA trial (NCT01847274) uses niraparib (MK-4827), a drug that has been shown to have activity as a single agent in patients with BRCA mutated OC [60]. The second, rucaparib, shown to be active in patients with BRCA mutated OC [61], is being evaluated in a similar setting in the ARIEL3 trial (NCT01968213). Both these trials are enrolling patients with BRCA mutation or BRCA wild type with built-in translational research to develop a companion diagnostic to identify tumours with HRD. Olaparib has now been reformulated as a tablet and it is being evaluated in ongoing maintenance trials in the first-line setting (SOLO1; ClinicalTrials.gov: NCT01874353) and after platinum-based therapy in patients with relapsed high-grade tumours (SOLO2; ClinicalTrials.gov: NCT01874353). Veliparib has activity as a single agent with 20% and 35% of patients with platinum-resistant or -sensitive ovarian responding, respectively [29]. In patients who have received several lines of therapy, a randomised phase II trial reported that it does not appear to add to the activity of cyclophosphamide in either wild type or BRCA mutated tumours [62]. However, the drug is now in a first-line phase III trial (NCT00989651) in unselected patients with ovarian, tubal or peritoneal cancer, or carcinsarcoma, following a phase I trial with different schedules of platinum, paclitaxel and bevacizumab [63]. Telazoparib (BMN-673) is a highly potent PARP inhibitor with activity in breast and OC [64]. At the moment there is no clear development strategy for this drug in OC.

Inhibitors of PARP and anti-angiogenic agents: an effect combination therapy?

Preclinical data suggests that inhibition of angiogenesis induces hypoxia and this increases DNA damage when a second DNA hit was included in a mouse model [65].

It has been shown in a mouse model that PARP inhibition, or deletion of the PARP1 gene reduces angiogenesis [11]. Similarly, downregulation of homologous repair genes, eg BRCA and Rad51 occurs in the presence of hypoxia, or VEGFR3 inhibition [10, 66]. In a phase I study of olaparib and cediranib in recurrent OC or triple negative breast cancer there was an objective response rate (ORR) of 44%. Responses were not limited to the BRCA mutation carriers. Grade 3 or 4 toxicities were observed in 75% of patients, the most common being hypertension (25%), fatigue (18%), and neutropenia (11%) [67]. Following these observations Liu and colleagues performed a randomised phase II trial in platinum-sensitive OC comparing this combination to single agent olaparib (NCT01116648). Patients were randomly assigned to receive olaparib, 400 mg twice daily (n=46), or to receive a combination of olaparib, 200 mg twice daily and cediranib, 30 mg daily (n=44). There was an ORR of 79.6% with the cediranib and olaparib compared to 47.8% with

olaparib alone. The PFS of 17.7 months with the combination compared to 9.0 months (HR 0.42; 95% CI 0.23–0.76; p=0.005) [68]. As in the phase I trial, toxicity was problematic with a dose reduction being required in 77% of patients in the combination arm compared to 24% in the olaparib-alone arm. A subgroup analysis showed there was a greater difference in PFS with the combination in patients without a BRCA mutation. The interesting results seen in this trial has led to the design of further studies combining a PARP inhibitor with an anti-angiogenic drug. An example is a randomised phase III in which olaparib maintenance is added to bevacizumab in patients who have not progressed on first-line chemotherapy and bevacizumab (PAOLA1 trial). In recurrent OC, trials are being developed comparing cediranib/olaparib with chemotherapy (NCI-CTEP) or adding olaparib to cediranib maintenance after chemotherapy and cediranib (ICON 9). A similar approach is being developed with niraparib and bevacizumab in platinum-sensitive relapsed OC (Avanova; NCT02354131).

Table 1. Receptor tyrosine-kinase inhibitors in ovarian cancer (Phase II-III randomised studies)

TKI	Trial		PFS	HR	CI	p value
Pazopanib	AGO-OVAR16	Du Bois et al. 2014 [34]	17.9	0.77	0.64–0.91	0.0021
Nintedanib	AGO-OVAR12	Du Bois et al. 2013 [36]	17.3	0.84	0.72–0.98	0.0239
Cediranib	ICON6	Ledermann et al. 2013 [37]	20.3	0.70	0.45–0.74	0.042
Sorafenib	Phase II trial	Herzog et al. 2013 [69]	15.7	1.09	0.72–1.63	0.655

CI: confidence interval; HR: hazard ratio; PFS: progression free survival; TKI: tyrosine-kinase inhibitor.

Table 2. Key studies reported with PARP inhibitors to show activity in ovarian cancer

Phase		Setting	Schedule	Overall response rate
I	Fong et al. 2010 [46]	Recurrent OC/BRCA1/2 mutations	Olaparib 40–600 mg bid (dose escalation) and 200 mg bid (dose expansion)	CBR 69% in platinum-sensitive (13 pts) CBR 45% in platinum-resistant (24 pts) CBR 23% in platinum-refractory (13 pts)
I	Sandhu et al. 2013 [60]	Recurrent solid tumors (29/100 pts BRCA1/2 mutation-positive)	Niraparib 30–400 mg qd (dose escalation)	40% in BRCA mutation-positive OC (8/20 pts) 50% in BRCA mutation-positive Breast Cancer (2/4 pts) 43% in CRPC (9/21 pts)
I	Kristeleit et al. 2013 [70]	Recurrent solid tumors (11/29 pts BRCA1/2 mutation-positive)	Rucaparib 40–500 mg qd (dose escalation)	2 PR (2 pts with BRCA mutations) 10 SD (9/10 pts with BRCA mutations)
I	De Bono et al. 2013 [71]	Advanced solid tumors (39 pts; 25/39 pts BRCA1/2 mutation-positive)	BMN673 25–1100 µg qd (dose escalation)	RECIST and/or CA-125 responses in 11/17 pts with BRCA1/2 mutation-positive OC ORR: 2/6 pts with BRCA1/2 mutation-positive Breast Cancer
I	Campone et al. 2012 [72]	Advanced solid tumors (27 pts)	CEP-9722 150–1000 mg qd (dose escalation)	Only safety data reported
II	Audeh et al. 2010 [73]	Recurrent OC/BRCA1/2 mutations (57 pts)	Olaparib 400 mg bid (33 pts) *vs* 100 mg bid (24 pts)	33% *vs* 13%
II	Tutt et al. 2010 [74]	Advanced Breast Cancer/ BRCA1/2 mutations (54 pts)	Olaparib 400 mg bid (27 pts) *vs* 100 mg bid (27 pts)	41% *vs* 22%
II	Gelmon et al. 2011 [48]	OC (63 pts; 17/63 BRCA1/2 mutation-positive)	Olaparib 400 mg bid	41% BRCA mutation-positive 24% BRCA mutation-negative
II	Ledermann et al. 2012 [49]	Platinum-sensitive-relapsed (265 pts)	Olaparib 400 mg bid *vs* placebo	12% *vs* 4%
II	Kaye et al. 2012 [51]	Recurrent OC/BRCA1/2 mutations (97 pts)	Olaparib 200 mg bid *vs* 400 mg bid *vs* PLD 50 mg/m^2	25% *vs* 31% *vs* 18%

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>>> **Table 2.** Key studies reported with PARP inhibitors to show activity in ovarian cancer

Phase	Setting	Schedule	Overall response rate
II Coleman et al. 2015 [75]	Recurrent OC/BRCA1/2 mutations (51 pts)	Veliparib 400 mg bid	20%
II Ramanathan et al. 2013 [76]	OC and Breast Cancer with BRCA1/2 mutations (46 pts)	Talazoparib (BMN 673) od	CBR Breast 78% CBR Ovarian 82%
II Kaufman et al. 2015 [54]	Recurrent OC Breast Cancer BRCA1/2 mutation-positive and solid tumours (298 pts)	Olaparib 400 mg bid	OC 31.1% Breast Cancer 26.9% Pancreatic Cancer 12.9% Prostate Cancer 21.7%
II Oza et al. 2015 [59]	Platinum-sensitive recurrent OC (162 pts)	Olaparib (200 mg bid days 1–10) plus chemotherapy + Olaparib in maintenance *vs* Carboplatin and Paclitaxel without maintenance	PFS 12.2 months *vs* 9.6 months
II Shapira-Frommer et al. 2015 [61]	OC recurrence BRCA1/2 mutation-positive	Rucaparib	74%

CBR: clinical benefit rate; CRPC: castrate-resistant prostate cancer; OC: ovarian cancer; ORR: overall response rate; PFS: progression free survival; PLD: pegylated liposomal doxorubicin; PR: partial response; pts: patients; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Conclusions

Whilst chemotherapy remains an important therapeutic modality, molecularly targeted therapy clearly has significant activity and clinical benefit. Inhibitors of angiogenesis are active in all phases of the disease, and bevacizumab is accepted as a useful additional component to therapy, although doubt remains about where in the treatment pathway it should best be used. Thus far, the oral drugs have not received market authorisation in OC but they are clearly active and have a different toxicity profile to intravenous bevacizumab. The greatest disadvantage of all these agents is the absence of well-defined predictive markers of response. For costly drugs such as these the lack of selectivity represents a challenge to healthcare funders. PARP inhibitors, however, are the first drugs that selectively target BRCA mutated tumours, and the HRD hallmark represents the first molecularly defined predictive marker for response in OC. Expansion of the use of PARP inhibitors beyond tumours with germ-line or somatic BRCA mutations will occur as tests for HRD are better defined and validated. This will offer new targeted therapies for a greater proportion of patients with OC. Combining anti-angiogenic agents with PARP inhibitors provides a new opportunity to improve further the treatment options for women with OC. Questions relating to the group most likely to benefit and the optimum combination of drugs are now being addressed in clinical trials. For recurrent disease it will be important to establish whether these drugs might in some situations replace standard cytotoxic chemotherapy. In parallel with the ongoing trials, it is vital that translational research is undertaken to establish the factors that predict the response to combinations of anti-angiogenic and PARP inhibitor drugs. The implementation of future therapies into clinical practice will depend on having active drugs with a high probability of benefit in a selected group of patients.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol 2014;6:229-39.
3. Oberaigner W, Minicozzi P, Bielska-Lasota M et al. Survival for ovarian cancer in Europe: the across-country variation did not shrink in the past decade. Acta Oncol 2012;51:441-53.
4. Spannuth WA, Sood AK, Coleman RL. Angiogenesis as a strategic target for ovarian cancer therapy. Nat Clin Pract Oncol 2008;5:194-204.
5. Yap TA, Carden CP, Kaye SB. Beyond chemotherapy: targeted therapies in ovarian cancer. Nat Rev Cancer 2009;9:167-81.
6. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.
7. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol 2011;5:387-93.
8. Cancer Genome Atlas Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.

9. Press JZ, De Luca A, Boyd N et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
10. Bindra RS, Gibson SL, Meng A et al. Hypoxia-induced down-regulation of BRCA1 expression by E2Fs. Cancer Res 2005;65:11597-604.
11. Tentori L, Lacal PM, Muzi A et al. Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis. Eur J Cancer 2007;43:2124-33.
12. Bindra RS, Schaffer PJ, Meng A et al. Down-regulation of Rad51 and decreased homologous recombination in hypoxic cancer cells. Mol Cell Biol 2004;24:8504-18.
13. Brown MR, Blanchette JO, Kohn EC. Angiogenesis in ovarian cancer. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:901-18.
14. Burger RA. Overview of anti-angiogenic agents in development for ovarian cancer. Gynecol Oncol 2011;121:230-8.
15. Wang Y, Fei D, Vanderlaan M et al. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. Angiogenesis 2004;7:335-45.
16. Wedam SB, Low JA, Yang SX et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol 2006;24:769-77.
17. Belotti D, Calcagno C, Garofalo A et al. Vascular endothelial growth factor stimulates organ-specific host matrix metalloproteinase-9 expression and ovarian cancer invasion. Mol Cancer Res 2008;6:525-34.
18. Burger RA, Sill MW, Monk BJ et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:5165-71.
19. Harris PA, Boloor A, Cheung M et al. Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-b enzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. J Med Chem 2008;51:4632-40.
20. Burris HA, 3rd, Dowlati A, Moss RA et al. Phase I study of pazopanib in combination with paclitaxel and carboplatin given every 21 days in patients with advanced solid tumors. Mol Cancer Ther 2012;11:1820-8.
21. Hilberg F, Roth GJ, Krssak M et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774-82.
22. Wedge SR, Kendrew J, Hennequin LF et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res 2005;65:4389-400.
23. Drevs J, Siegert P, Medinger M et al. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007;25:3045-54.
24. Gerald D, Chintharlapalli S, Augustin HG et al. Angiopoietin-2: an attractive target for improved antiangiogenic tumor therapy. Cancer Res 2013;73:1649-57.
25. Monk BJ, Poveda A, Vergote I et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:799-808.
26. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83.
27. Perren TJ, Swart AM, Pfisterer J et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.
28. Aghajanian C, Blank SV, Goff BA et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45.
29. Coleman RL, Brady RF, Herzog TJ et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer [Abstract LBA3]. Presented at: Society of Gynecologic Oncology's Annual Meeting on Women's Cancer 2015; March 28-31 2015; Chicago, IL, USA.
30. Pujade-Lauraine E, Hilpert F, Weber B et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302-8.
31. Stockler MR, Hilpert F, Friedlander M et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol 2014;32:1309-16.
32. European Medicines Agency (EMA) 2013. Avastin (bevacizumab): Summary of product characteristics. Available from: http://www.ema.europa.eu/ Accessed February 2013.
33. Oza AM, Cook AD, Pfisterer J et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16:928-36.
34. Du Bois A, Floquet A, Kim JW et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol 2014;32:3374-82.
35. Friedlander MK, Meier W, Lesoin A et al. Quality of life in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC) receiving either pazopanib monotherapy or placebo after first-line chemotherapy: AGO-OVAR16 results [Poster]. Presented at: European Society for Medical Oncology Cancer Congress; September 27 - October 1 2013; Amsterdam, The Netherlands.
36. Du Bois A, Kristensen G, Ray-Coquard I et al. AGO-OVAR 12: a randomized placebo-controlled GCIG/ENGOT-intergroup phase III trial of standard frontline chemotherapy ± nintedanib for advanced ovarian cancer [Abstract]. Int J Gynecol Cancer 2013;23:7-8.
37. Ledermann JA, Perren TJ, Raja FA et al. Randomized double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial [Abstract]. Eur J Cancer 2013;49:Abs 10.
38. Pignata S, Lorusso D, Scambia G et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian

cancer (MITO 11): a randomised, open-label, phase 2 trial. Lancet Oncol 2015;16:561-8.
39. Schmidinger M. Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. EJC Suppl 2013;11:172-91.
40. D'Amours D, Desnoyers S, D'Silva I et al. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J 1999;342 (Pt 2):249-68.
41. Caldecott KW, Aoufouchi S, Johnson P et al. XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular 'nick-sensor' in vitro. Nucleic Acids Res 1996;24:4387-94.
42. Flohr C, Burkle A, Radicella JP et al. Poly(ADP-ribosyl)ation accelerates DNA repair in a pathway dependent on Cockayne syndrome B protein. Nucleic Acids Res 2003;31:5332-7.
43. Helleday T, Petermann E, Lundin C et al. DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 2008;8:193-204.
44. Bryant HE, Schultz N, Thomas HD et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913-7.
45. Fong PC, Boss DS, Yap TA et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-34.
46. Fong PC, Yap TA, Boss DS et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512-9.
47. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004;4:814-9.
48. Gelmon KA, Tischkowitz M, Mackay H et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852-61.
49. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382-92.
50. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15:852-61.
51. Kaye SB, Lubinski J, Matulonis U et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 2012;30:372-9.
52. Gordon AN, Fleagle JT, Guthrie D et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312-22.
53. Safra T, Borgato L, Nicoletto MO et al. BRCA mutation status and determinant of outcome in women with recurrent epithelial ovarian cancer treated with pegylated liposomal doxorubicin. Mol Cancer Ther 2011;10:2000-7.
54. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33:244-50.
55. Kim G, Ison G, McKee AE et al. FDA Approval Summary: Olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. Clin Cancer Res 2015;21:4257-61.
56. Calabrese CR, Almassy R, Barton S et al. Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. J Natl Cancer Inst 2004;96:56-67.
57. Curtin NJ, Szabo C. Therapeutic applications of PARP inhibitors: anticancer therapy and beyond. Mol Aspects Med 2013;34:1217-56.
58. Lee JM, Annunziata CM, Minasian L et al. Phase I study of the PARP inhibitor olaparib (O) in combination with carboplatin (C) in BRCA1/2 mutation carriers with breast (Br) or ovarian (Ov) cancer (Ca) [Abstract]. J Clin Oncol 2011;29:Abstr 2520.
59. Oza AM, Cibula D, Benzaquen AO et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015;16:87-97.
60. Sandhu SK, Schelman WR, Wilding G et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013;14:882-92.
61. Shapira-Frommer R, Oza AM, Domchek SM et al. A phase II open-label, multicenter study of single-agent rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious BRCA mutation [Abstract]. J Clin Oncol 2015;33:Abstr 5513.
62. Kummar S, Oza AM, Fleming GF et al. Randomized trial of oral cyclophosphamide and veliparib in high-grade serous ovarian, primary peritoneal, or fallopian tube cancers, or BRCA-mutant ovarian cancer. Clin Cancer Res 2015;21:1574-82.
63. Bell-McGuinn K, Brady W, Schilder R et al. A phase I study of continuous veliparib in combination with IV carboplatin/paclitaxel or IV/IP paclitaxel/cisplatin and bevacizumab in newly diagnosed patients with previously untreated epithelial ovarian, fallopian tube, or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study [Abstract]. J Clin Oncol 2015;33:Abstr 5507.
64. Shen Y, Rehman FL, Feng Y et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. Clin Cancer Res 2013;19:5003-15.
65. Economopoulou M, Langer HF, Celeste A et al. Histone H2AX is integral to hypoxia-driven neovascularization. Nat Med 2009;15:553-8.
66. Lim JJ, Yang K, Taylor-Harding B et al. VEGFR3 inhibition chemosensitizes ovarian cancer stemlike cells through down-regulation of BRCA1 and BRCA2. Neoplasia 2014;16:343-53 e1-2.
67. Liu JF, Tolaney SM, Birrer M et al. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cedi-

ranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer 2013;49:2972-8.
68. Liu JF, Barry WT, Birrer M et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207-14.
69. Herzog TJ, Scambia G, Kim BG et al. A randomized phase II trial of maintenance therapy with Sorafenib in front-line ovarian carcinoma. Gynecol Oncol 2013;130:25-30.
70. Kristeleit R, Shapiro G, Lorusso D et al. A phase I dose-escalation and PK study of continuous oral rucaparib in patients with advanced solid tumors [Abstract]. J Clin Oncol 2013;31:Abstr 2585.
71. De Bono JS, Mina LA, Gonzalez M et al. First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors [Abstract]. J Clin Oncol 2013;31:Abstr 2580.
72. Campone M, Plummer R, Stephens P et al. Phase I dose-escalation study to evaluate the safety, pharmacokinetics, and pharmacodynamics of CEP-9722 (a PARP1-2 inhibitor) as single-agent and in combination with temozolomide in patients with advanced solid tumors (NCT00920595) [Abstract]. J Clin Oncol 2012;31:Abstr 3052.
73. Audeh MW, Carmichael J, Penson RT et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376:245-51.
74. Tutt A, Robson M, Garber JE et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235-44.
75. Coleman RL, Sill MW, Bell-McGuinn K et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol 2015;137:386-91.
76. Ramanathan R, Wainberg Z, Mina L et al. PARP inhibition with BMN 673 in ovarian and breast cancer patients with deleterious mutations of BRCA1 and BRCA2 [Abstract 29LBA]. Presented at: 17th European Cancer Congress (ECCO); September 27 - October 1; Amsterdam, The Netherlands.