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Current and Future Developments of PARP Inhibitors in the Treatment of Breast and Ovarian Cancer

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Abstract

The use of Poly ADP-ribose polymerase (PARP) inhibitors has recently been expanded. PARP inhibitors were initially only registered for patients with BRCA mutated high-grade serous epithelial ovarian, including primary peritoneal and fallopian tube cancer (EOC). Currently, PARP inhibitors are also registered for patients with recurrent EOC who are in a complete or partial response to platinum-based chemotherapy, irrespective of their BRCA status. Current findings indicate that patients with BRCA mutations and/or a BRCA like tumour defined by a BRCAness profile, benefit the most. Combination therapies of PARP inhibitors with immunotherapy and/or angiogenesis inhibitors are fast evolving and studied from first line therapy to recurrent disease. This review summarizes the current findings, obstacles and future developments of PARP inhibitor with a focus on female cancer.

Keywords: Breast cancer; Ovarian cancer; BRCA1; BRCA2; PARP inhibitors; Homology-directed repair deficiency

Introduction

Loss of function germline mutations in **BRCA1** and **BRCA2** increase the risk of breast and ovarian cancers and have been associated with increased risks of several additional types of cancer. The cumulative breast cancer risk till 80 years is 72% for BRCA1 and 69% for BRCA2 carriers [1]. The cumulative ovarian cancer risk, including primary peritoneal and fallopian tube cancer (EOC) till 80 years is 44% for BRCA1 and 17% for BRCA2 carriers [1].

In 2005, the first two publications demonstrating the substantial sensitivity of BRCA deficient cell lines to inhibition of PARP, have led to an unprecedented and swift implementation of PARP inhibitors in clinical practice [2,3]. Several PARP inhibitors such as olaparib, niraparib, veliparib, rucaparib, and talazoparib are being tested in clinical trials and olaparib, niraparib and rucaparib have been registered for use in a clinical setting.

Current challenges include the selection of patients who benefit most from PARP inhibition, selecting optimal use of PARP inhibitors as monotherapy, maintenance or combination therapy and the occurrence of drug resistance. This review summarizes the proceedings and discusses the future developments of PARP inhibitors with focus on its use in patients with breast and ovarian cancer.

Literature Review

DNA damage response

DNA breaks can be roughly divided in two groups: single strand breaks (SSBs) and double-strand breaks (DSBs). SSBs can be accurately repaired using the other strand as a template, a process in which the enzyme Poly (ADP-ribose) polymerases (PARP) is involved. DSBs can be induced by radiation or X-rays, free radicals, chemicals and during replication of SSBs [4]. DSBs are mainly repaired through two pathways: the homology-directed repair (HDR) pathway and the non-homologous end joining (NHEJ) pathway, although other mechanisms also exist [4,5]. The HDR pathway has very few errors and duplicates the DNA using the homologous sequence of the sister chromatid as a template to repair the DSB. HDR takes place during S and G2 cell cycle phase. The NHEJ pathway is more error prone, which may lead to alterations in DNA sequence and loss of genetic information [4,6].

BRCA1 and BRCA2 are involved in the DNA damage response, the network of interacting pathways that are essential for the response upon DNA damage. Both proteins are involved in the error-free repair of DSBs by HDR [4]. BRCA1 signals DNA damage and ensures cell cycle regulation [6], while BRCA2 interacts and facilitates the loading and formation of RAD51 filaments on the damaged DNA strand [7]. In the presence of loss of function mutations in either of these genes (e.g. in BRCA1 or BRCA2 mutated tumours), HDR is deficient, DSBs will be repaired via error prone repair pathways leading to the accumulation of mutations, eventually resulting in cell death [8]. This may ultimately lead to enhanced risk for breast and ovarian cancer.

PARP inhibitors: Mechanism of action and synthetic lethality

Poly (ADP-ribose) polymerases (PARPs) regulate a number of biological processes [9]. PARP-1 is part of the PARP protein family and is involved in base excision repair (BER). DNA modifications, either induced endogenously or exogenously, can be repaired by BER. After excision of the damaged base, an SSB is produced [9]. Normally, PARP-1 binds to the SSB and attracts other proteins to initiate SSB repair [10]. Initially, it was proposed that inhibition of PARP-1 would lead to stalling of the replication fork at the SSB [11], leading to accumulation of double strand breaks (DSBs) in replicating cells. However, recent data suggest that some PARP inhibitors might also 'trap' PARP1 on the DNA and thereby interfere with the catalytic cycle of PARP [12] (Figure 1). The ability of PARP inhibitors to trap PARP1 on DNA has been shown to add to the observed cytotoxicity [13]. More recent data suggest that PARP also has a function in the repair of DSBs [5].

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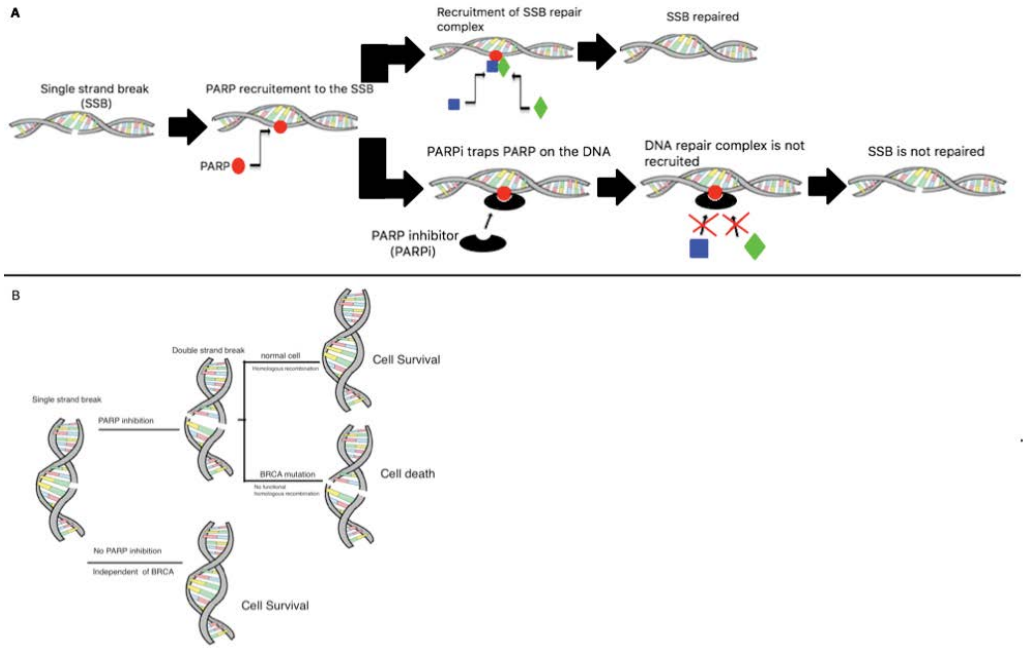

Figure 1: Mechanism of PARP inhibition based on synthetic lethality **(A):** When an SSB is present in the DNA, PARP will be recruited to the SSB site. PARP recruits a complex to perform SSB repair. In the presence of PARP inhibitors parylation is inhibited and PARP1 is trapped on the DNA and the SSB will not be repaired. (adapted from Livraghi and Garber [14]) **(B):** In the presence of PARP, SSBs will be repaired. However, in the presence of PARP inhibitors, SSBs will not be repaired what will result replication fork stalling, which eventually may collapse and result in DSBs. DSBs can be repaired through HDR which will result in cell survival. However, in HDR deficient tumours (e.g. in BRCA1 or BRCA2 mutated tumours), the error free repair of DSBs fails, which will ultimately lead to tumour cell death.

The effectiveness of PARP inhibitors in tumours related to BRCA1 and BRCA2 is based on the concept of synthetic lethality, whereby a deficiency in either one of two genes has no effect on the viability of the cell but the combination of defects in both genes will result in cell death (described in detail in several reviews [12,14]).

Thus, especially in BRCA deficient and HDR deficient cells, inhibition of PARP enzyme will lead to cell death (Figure 1). Normal cells have a sufficient HDR function and will therefore survive PARP inhibitor therapy. This leads to in a more precise and less toxic therapy compered to chemotherapy [14]. Therefore, PARP inhibitors are potent drugs, particularly in BRCA mutated types of cancer and other HDR deficient malignancies [15].

Clinical Development of PARP Inhibitors

Currently many PARP inhibitors are in clinical trials as monotherapy and/or as combination therapy. First, the European Medical Association (EMA) and the Food and Drug Administration (FDA) registered olaparib as maintenance therapy of platinum-sensitive relapsed germline BRCA mutated (gBRCAm) high-grade serous EOC that responded to platinum-based chemotherapy [16,17]. Recently, olaparib tablets were registered recently by the EMA irrespective of BRCA status [16]. The FDA also registered olaparib as monotherapy for treating patients with gBRCAm recurrent EOC after receiving three or more prior lines of chemotherapy [17]. Moreover, the FDA also registered olaparib for the treatment of patients with gBRCAm, HER2-negative metastatic breast cancer who have previously been treated with chemotherapy [16]. Rucaparib was registered by the FDA in 2016 as monotherapy for the treatment of patients with BRCA mutated recurrent EOC who have received two or more chemotherapies [18] and in 2018 rucaparib was registered as maintenance treatment for patients with recurrent EOC who are in complete or partial response to platinum-based chemotherapy [19]. Niraparib, was registered in 2017 as maintenance treatment for adult patients with recurrent platinum-sensitive EOC who are in a complete or partial response to platinum-based chemotherapy irrespective of BRCA status of the tumor [20]. Recently, the EMA also granted registration of niraparib for the same indication [21].

Olaparib (AstraZeneca)

One of the most investigated PARP inhibitors is olaparib. [22] was the first to investigate pharmacokinetics and pharmacodynamics in patients with, among others, breast and ovarian cancer. Of the 60 patients enrolled, 22 had a BRCA1 or BRCA2 germline mutation. Results revealed a maximum tolerated dose (MTD) of 400 mg BID olaparib capsules. Adverse events were mainly grade 1-2 and included vomiting, taste alteration, nausea, fatigue and anorexia. Subsequent phase II trials in patients with a gBRCAm, revealed an overall response rate (ORR) of 41% in patients with advanced breast cancer [23] and of 33% in recurrent EOC [24,25] showed a tumour response rate in metastatic breast cancer patients with ≥ 3 chemotherapy regimens of 12.9% (95% CI, 5.7 to 23.9). For platinum resistant relapsed EOC, the ORR was 31.1% (95% CI, 24.6 to 38.1). Based on these promising results, a subsequent trial (study 19) was initiated by Ledermann et al. [26]. This phase II trial compared the efficacy of olaparib to placebo as maintenance therapy after response to platinum-based chemotherapy in 265 patients with platinum-sensitive recurrent serous EOC. Overall results showed that olaparib increased median progression free survival (PFS) when compared to placebo (8.4 months vs 4.8 months respectively; HR 0.35; p<000.1) [26]. The subgroup analysis by overall BRCA mutation (BRCAm) status (germline and somatic) showed a significant benefit in median PFS in the olaparib group compared to the placebo group (11.2 *vs* 4.3 months respectively; HR 0.18; p<0·0001)

[27]. Adverse events were mostly grade 1-2. This study led to the EMA and FDA registration of olaparib for EOC [16,17].

However, despite a large difference in PFS, there was no benefit shown in overall survival (OS) [26,27]. Nonetheless, [28] did an exploratory post hoc analysis to investigate if OS was confounded due to switching to a PARP inhibitor after progression by 23% of the patients receiving placebo. They concluded that post progression PARP inhibitor therapy had a confounding influence on the OS analyse and therefore patients with BRCA mutated recurrent EOC treated with olaparib might actually have longer OS. The phase III SOLO2/ENGOT-Ov21 trial, investigated the efficacy of olaparib maintenance therapy in platinum-sensitive recurrent EOC. They confirmed the findings from Study 19 in the BRCA1/2 mutation subgroup using the olaparib tablet, 300 mg BID, formulation [29]. Furthermore, the SOLO-1 trial [30] is currently investigating the efficacy of olaparib maintenance therapy compared to placebo in primary BRCAm EOC after first line platinum-based chemotherapy. Olaparib is also investigated in breast cancer both in metastatic and adjuvant settings in the OlympiA [31] and OlympiAD [32] trial, respectively. Presented data from the OlympiAD trial showed that patients treated with olaparib had a 42% risk reduction of disease worsening or death as compared to standard chemotherapy (HR 0.58; p=0.0009) [33]. Based on these results olaparib was registered by the FDA for the treatment of patients with gBRCAm, HER2-negative metastatic breast cancer who have previously been treated with chemotherapy [17].

Veliparib (Abbvie)

Veliparib is another PARP inhibitor of which clinical trials show promising results in recurrent EOC. The first phase I trial by Puhalla et al. [34] recommended a phase 2 dose (RP2D) of 400 mg BID for the treatment of platinum-resistant or -refractory EOC or basal-like breast cancer. 60 out of 88 patients had a gBRCAm. Nausea, fatigue, and lymphopenia were the most common all-grade toxicities. In the phase II study by Coleman et al. [35] veliparib monotherapy was administered in 50 patients with persistent or recurrent EOC carrying a BRCAm. Results showed an ORR of 26% with acceptable toxicity. No data on OS with veliparib are available yet.

Niraparib (Tesaro)

Another potent PARP inhibitor is niraparib. This PARP inhibitor was first clinically tested in the phase I trial by Sandhu et al. [36] The RP2D was 300 mg/day with adverse events of anaemia, anorexia, fatigue, neutropenia, nausea, thrombocytopenia, constipation and vomiting (mostly grade 1-2). Efficacy evaluation revealed that 40% of patients with BRCAm recurrent EOC and 50% of patients with metastatic breast cancer had a partial response. Recently, the placebo-controlled phase III NOVA trial [37], with niraparib as maintenance therapy after completing or near complete response to platinum-based chemotherapy in patients with platinum-sensitive recurrent EOC, revealed a higher PFS in the niraparib group than in the placebo group. Patients with a gBRCAm had the largest benefit with an increase in PFS of 21.0 *vs.* 5.5 months (HR: 0.27), followed by a subgroup with HDR deficiency as defined by the MyChoice HDR deficiency test (Myriad Genetics) (see section 6) with an increase in PFS of 12.9 *vs* 3.8 months (HR: 0.38). Surprisingly, even in the HDR proficient group a PFS benefit of 6.9 vs 3.8 months was observed (HR: 0.58). OS data were not mature. It was concluded that niraparib is beneficial in all patients with platinum-sensitive recurrent EOC in response to platinum-based chemotherapy regardless of the BRCA mutation or HDR deficiency status. Furthermore, [38] concluded that patients treated with niraparib after complete or partial response can maintain their quality of life.

Because of these results, the FDA and EMA have accepted niraparib for the treatment of platinum-sensitive recurrent EOC irrespective of BRCA status [20,21]. For patients with anthracycline and taxanes resistant metastatic breast cancer the efficacy of niraparib monotherapy is currently being tested in the BRAVO trial (NCT01905592) [39]. Moreover, the efficacy of niraparib maintenance therapy for patients with primary EOC after first line platinum-based chemotherapy is investigated in the ongoing PRIMA trial [40].

Rucaparib (Clovis oncology)

One of the first phase I trials investigating rucaparib was done by Kristeleit et al. [41]. Results showed a RP2D of 600 mg BID [42] subsequently investigated the efficacy of intravenous (IV) intermittent and oral continuous dosing schedules of rucaparib in gBRCAm recurrent ovarian and metastatic breast cancer. The IV intermittent dosing schedule resulted in an ORR of 2%, which was 15% for oral rucaparib. 41% of the patients receiving the IV intermittent dosing schedule achieved stable disease (SD) for ≥ 12 weeks. In the oral continuous dosing cohort 81% achieved RECIST complete response, partial response or SD for ≥ 12 weeks. They concluded that oral continuous rucaparib dosing is required for best results. Furthermore, the ARIEL2 trial investigated the efficacy of rucaparib in 3 groups with relapsed EOC; patients with a BRCA mutation, patients with high loss of heterozygosity (LOH) as a definition for HDR deficiency and patients with low LOH [43]. Results showed a median PFS of 12.8, 5.7 and 5.2 months, respectively. PFS was significantly higher in the BRCAm (HR: 0.27 p<0.001) and LOH high group (HR:0.62, p=0.011) compared to the LOH low group.

Finally, the ARIEL3 trial investigated the efficacy of rucaparib maintenance treatment for recurrent EOC after response to platinum-based chemotherapy [44]. For BRCAm patients this phase III trial showed a median PFS of 16.6 months in the rucaparib group compared to 5.4 months in the placebo group (HR:0.23; p<0.0001). For patients with a HDR deficiency (defined as high LOH) EOC the median PFS was 13.6 months in the rucaparib group versus 5.4 months in the placebo group (HR:0.32; p<0.0001).

Based on these results rucaparib was registered in 2016 as monotherapy for the treatment of patients with BRCAm recurrent EOC who have received two or more lines of chemotherapy [18] and in 2018 rucaparib was registered as maintenance treatment for patients with recurrent EOC who are in complete or partial response to platinum-based chemotherapy [19].

Combination Therapy

Chemotherapy and PARP inhibitors

Olaparib in combination with chemotherapy: In order to achieve synergy and improve clinical efficacy, PARP inhibitors have been combined with chemotherapy. However, this combination is challenging due to overlapping bone marrow toxicity. [45] designed a phase I trial to determine the safety of olaparib plus cisplatin in patients with advanced breast cancer, EOC and other solid tumours. The MTD could not be established because none of the cohorts reached dose-limiting toxicity and therefore the authors concluded that the scheme of cisplatin 60 mg/m^2 (day 1, q21 days) in combination with intermittent 50 mg olaparib capsules (days 1-5) was tolerable. Subsequently, Oza [46] investigated, in a randomized phase II trial, the combination of olaparib (200 mg BID) with carboplatin (AUC4)

and paclitaxel (175 mg/m^2) followed by olaparib maintenance therapy, compared to standard carboplatin (AUC6) and paclitaxel (175 mg/m^2) in patients with platinum-sensitive, recurrent, high-grade serous EOC. The PFS was 12.2 months (95% CI, 9.7-15.0) versus 9.6 months (95% CI, 9.1-9.7) in favour of the olaparib arm (HR 0.51; p=0.0012). In patients with BRCA mutations, this difference was even greater (HR 0.21; p=0.0015). They concluded that the combination cohort had an acceptable and manageable tolerability profile but required upfront dose reduction of chemotherapy. However, the question arises whether this PFS benefit is a result of the simultaneous olaparib, carboplatin, paclitaxel combination or rather a result of olaparib maintenance therapy [27,28]. Dent [47] investigated the tolerability and toxicity of olaparib in combination with weekly paclitaxel (90 mg/m^2) in 19 patients with metastatic triple negative breast cancer. Preliminary data did not reach a MTD.

Veliparib in combination with chemotherapy: Veliparib is also investigated in combination with chemotherapy. For EOC, Bell-McGuinn [48] compared three arms of veliparib plus chemotherapy and bevacizumab in a phase I trial in patients with previously untreated EOC. The first arm received veliparib plus carboplatin (AUC6), paclitaxel (175 mg/m^2) and bevacizumab (15 mg/kg), the second arm received veliparib plus carboplatin, a lower dose of paclitaxel (80 mg/m^2) and bevacizumab and the third arm received veliparib plus cisplatin (75 mg/m^2), paclitaxel (60 mg/m^2) and bevacizumab. Preliminary results showed a RP2D of veliparib of 150 mg BID for all schedules. Veliparib has also been investigated in combination with cyclophosphamide in patients with BRCAm or high-grade serous EOC [49]. However, this combination did not result in an improved ORR (PR: 11.8% *vs* 19.4%; CR: 2.9% vs 2.7%) or PFS (2.3 *vs* 2.1 months; p=0.68) when compared to cyclophosphamide alone. Gray [50] investigated the effect of veliparib plus carboplatin and gemcitabine in advanced solid tumors in a phase I study. Results showed a RP2D of 250 mg veliparib with carboplatin (AUC 4) and gemcitabine (800 mg/m^2) and responses were seen in 69% of the patients with BRCAm EOC. The efficacy of veliparib with carboplatin and paclitaxel is currently further investigated. NCT02470585 is a phase III trial by the Gynaecologic Oncology Group (GOG), which is currently investigating veliparib with carboplatin and paclitaxel followed by maintenance therapy in patients with primary EOC [51] (Tables 1 and 2).

For breast cancer, Loibl [52] investigated the combination of veliparib (50 mg), carboplatin (AUC6) and paclitaxel (80 mg/m^2) for stage II-III triple negative early breast cancer as neoadjuvant therapy in the BrighTNess trial. Three arms were compared: veliparib, carboplatin and paclitaxel versus carboplatin and paclitaxel versus paclitaxel. BRCA1 or BRCA2 mutations were found in 14% of the veliparib, carboplatin and paclitaxel group, 16% in the carboplatin and paclitaxel group and in 15% of the paclitaxel group. Results showed a significantly higher pathological complete response for veliparib, carboplatin and paclitaxel group in comparison with paclitaxel alone (53% vs 31% p<0.0001), but a similar pathological complete response in comparison with the carboplatin plus paclitaxel group (53% vs 58% p=0.36). A phase I trial by Rodler [53] investigated the combination of veliparib (300 mg BID) with cisplatin (75 mg/m^2) and vinorelbine (25 mg/m^2) in patients with advanced triple negative and/or BRCAm breast cancer. The combination showed an ORR of 35% (95% CI 23-50%) with a tolerable safety profile. Currently investigations on the efficacy of veliparib plus temozolomide [54] and of veliparib plus carboplatin in patients with breast cancer [55,56] are ongoing. Preliminary results of these trials are depicted in Table 1.

Niraparib in combination with chemotherapy: A study investigating niraparib in combination with carboplatin, carboplatin and paclitaxel or carboplatin and pegylated liposomal doxorubicin (NCT01110603 [57]) and another study with niraparib in combination with pegylated liposomal doxorubicin (PLD) (NCT01227941 [58]) in solid tumours and EOC have been stopped prematurely without explanation.

Rucaparib in combination with chemotherapy: Plummer [59] first investigated pharmacodynamics and pharmacokinetics of rucaparib in combination with temozolomide in patients with advanced solid tumours. Results showed a PARP inhibitory dose of 12 mg/m^2. Currently phase II/III trials with PARP inhibitors in combination with chemotherapy are ongoing and results are awaited (Table 2).

Immunotherapy

There are multiple immune checkpoint inhibitors; pembrolizumab and nivolumab target the programmed death protein-1 (PD-1), avelumab, atezolizumab and durvalumab target the programmed-death ligand-1 (PD-L1) and ipilimumab and tremelimumab target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These immune checkpoint inhibitors have shown to be beneficial in treating several malignancies and are currently studied in female cancers. The combination of PARP inhibition and immune checkpoint inhibition seem especially promising in patients with EOC and HDR deficiency [60]. In fact, tumors with a BRCAm typically harbour TP53 mutations and have a higher mutational load [61,62]. Hence, they also harbour a greater number of neoantigens that enhance the recruitment of tumor infiltrating lymphocytes (TILs); in BRCAm tumors a significantly increased expression of CD3+ and CD8+ TILs have been shown [63], as well as increased expression of PD-1 and PD-L1 compared to wild type EOC [63,64]. Furthermore, PARP inhibition can modulate immune signalling pathways through various mechanisms [65,66], both activating and non-activating. *In vitro* a CTLA-4 antibody, but not PD-1/PD-L1 blockade, synergized therapeutically with veliparib [67]. On the other hand, the PARP inhibitor talazoparib increased the number of peritoneal CD8+ T-cells and natural killer cells and increased production of interferon (IFN)-$_\gamma$ and tumor necrosis factor-α in a BRCA1-mutated ovarian cancer xenograft model [68]. The exact immune-modulating effects of checkpoint inhibitor plus PARP inhibitor combinations are currently unknown and needs further research. Currently, multiple trials are therefore investigating these combinations [69-73] (Table 3).

Moreover, it is still uncertain in which clinical setting the use of immune checkpoint inhibitors in EOC is most favourable. PARP inhibitors in combination with immune checkpoint inhibitors might be most beneficial in primary disease or early recurrence due to a lower tumor burden. Future trials will test these combinations in first-line treatment of breast and EOC.

Anti-angiogenic therapy

Preclinical and clinical evidence suggests that interactions exist between the VEGF pathway and PARP inhibition. Several groups have reported that PARP inhibition reduces VEGF-induced angiogenesis. A preclinical study from Bindra [74] showed that hypoxia is associated with impaired HDR and therefore a state of BRCAness. They also hypothesized that in a hypoxic state the cells are pushed toward NHEJ because of impaired HDR and thus show increased genetic instability and cell death. Liu [75] designed a phase I trial with olaparib BID and cediranib, a tyrosine kinase inhibitor directed against VEGF. The RP2D was cediranib 30 mg daily with olaparib 200 mg BID. Subsequently, Liu

Investigators	Phase	Cancer type	No of patients (BRCAm)	Investigational arm	Control arm	Primary endpoint	Overall result	Previous treatment
Olaparib								
Fong et al. [22]	1	ST	60(22)	Olaparib (100-600 BID)	--	PK, PD, safety and tolerability	MAD=600 mg BID MTD=400 mg BID	53% ≥ 4 prior treatment regimens
Tutt et al. [23]	2	BC	54(54)	Olaparib (400 mg BID)	Olaparib 100 mg BID	ORR	ORR: 41% (400 BID) *vs* 22% (100 BID)	Median of 3 regimens
Audeh et al. [24]	2	EOC	58(58)	Olaparib (400 mg BID)	Olaparib 100 mg BID	ORR	ORR: 33%(400 BID) *vs* 13% (100 BID)	Median of 3 regimens
Kaufman et al. [25]	2	ST	298(298)	Olaparib (400 mg BID)	--	TRR	TRR in BC: 12.9% TRR in OC: 31.1% Overall TRR: 26.2%	Median of 4 regimens
Ledermann et al. [27,28]	2	EOC	265(136)	Olaparib (400 mg BID)	Placebo 400 mg BID	PFS	PFS in BRCAm 11.2 *vs* 4.3 months OS no difference	Median of 3 regimens
Robson et al. (Olympiad) [33]	3	BC	302(302)	Olaparib (300 mg BID)	Prespecified chemotherapy regimens	PFS	Median PFS: 7.0 *vs* 4.2 months HR for disease progression or death: 0.58 (p<0.001)	≤2 regimens
Balmaña et al. [45]	1	BC, EOC, PC	54(29)	Olaparib (50-200 mg BID) continuous *vs* intermittent + CDDP (60-75 mg/m^2 IV)		safety and tolerability	Intermittent olaparib (50 BID) + cisplatin (60 mg/m^2) ORR: 41%	Median of 3 regimens
Oza et al. [46]	2	EOC	162 (41 out of 107)	Olaparib (200 BID) + PTX (175 mg/m^2) + CBDCA (AUC 4 mg/ml per min)	PTC (175 mg/m^2)+CBDCA (AUC 4 mg/ml per min)	PFS	PFS 12.3 months *vs* 9.6 months	72% 1 regimen
Dent et al. [47]	1	TNBC	19	Olaparib (200 mg BID)+PTX (90 mg/m^2 weekly)	--	Safety and tolerability	37% PR 5% SD	≤1 regimen
Gelmon et al. [91]	2	EOC, BC	90 (27)	Olaparib (400 mg BID)	--	ORR	ORR in BRCAm OC: 41% ORR in BRCA+ OC: 24% ORR in BC: 0%	Median of 3 regimens
Veliparib								
Puhalla et al. [34]	1	EOC, BC	80 (60)	Veliparib (50-500 mg BID)	--	PK, PD, safety and tolerability	RP2D=400 mg BID	Unknown
Coleman et al. [35]	2	EOC	50(50)	Veliparib (400 mg BID)	--	ORR	ORR: 26%	28% 1 prior regimen, 36% 2 prior regimens, 36% 3 prior regimens
Bell-McGuinn et al. [48]	1	EOC	189	Veliparib (150-200 mg) + CBDC(AUC 6)+PTX (ranging doses) +bevacizumab (15 mg/kg)	Veliparib (150-200 mg) + CDDP(75 mg/m^2)+PTX (ranging doses) +bevacizumab (15 mg/kg	PK, PD, safety and tolerability	RP2D= 150 mg BID for all regiments	Unknown
Kummar et al. [49]	2	EOC	72 (31)	CYC 50 (mg OD) + Veliparib(60 mg OD)	CYC (50 mg OD)	PFS, ORR	No difference in PFS or ORR	Median of 4 regimens
Loibl et al. [52] (BrighTNess)	2	BC	116(15)	Veliparib (50 mg) + CBDCA (AUC 6) + PTX (80 mg/m^2)	CBDCA (AUC 6) + PTX (80 mg/m^2) versus PTX (80 mg/m^2)	Pathological CR	Pathological CR 53% (V+CBDCA+PTX) vs 58%(CBDCA+PTX) vs 31%(PTX)	Unknown
Gray et al. [50]	1	EOC + BC	66(36)	Veliparib + CBCDA (AUC 4)+ gemcitabine (800 mg/m^2)	-	RP2D	RP2D: veliparib 250 mg + CBCDA (AUC 4)+ gemcitabine (800 mg/m^2) Responses 69% in BRCAm EOC	≤ 2 prior chemotherapu regimens
Rodler et al. [53]	1	BC	45 (11)	Veliparib dose-escalating + cisplatin (75 mg/m^2) + vinorelbine (25 mg/m$^{2)}$	--	PK, PD, Safety and toxicity	Veliparib 300 mg BID is well tolerated	Unknown
Isakoff et al. [54]	2	BC	41	Veliparib (40 mg BID days 1-7) and TMZ (150 mg/m^2 days 1-5)	--	efficacy	1CR, 2 PR, 7 SD (all unconfirmed), and 14 PrD	Unknown
Somlo et al. [55]	2	BC	26(26)	Veliparib	Veliparib + carboplatin	ORR	3 CR (12%), 9 PR (35%)	1 prior chemotherapy regimen
Wesolowski et al. [56]	1	BC	44(16)	Veliparib +CBDCA in different regimens	--	Safety and toxicity	18.6% PR; 48.8% SD	Unknown

Niraparib								
Sandhu et al. [36]	1	ST	100 (29)	Niraparib (30-400 mg OD)	--	PK, PD, safety and tolerability	RP2D 300 mg/day	Median of 5 regimens
Mirza et al. [37]	3	EOC	553 (203)	Niraparib (300 mg OD)	Placebo (300 mg OD)	PFS	PFS 21.0 vs. 5.5 months in BRCAm group PFS 12.0 vs 3.9 months in BRCA+ group	Olaparib group: 0.7% 1 regimen, 50,7% 2 regimens, 48.6% 3 regimens Placebo group: 0% 1 regimen, 46.2% 2 regimens, 53.8% 3 regimens
Rucaparib								
Kristeleit et al. [41]	1	ST	56	Rucaparib 40 QD-840 mg BID	--	MTD, RP2D	RP2D of 600 mg BID	Unclear
Drew et al. [42]	2	EOC, BC	78 (78)	Rucaparib (4-18 mg/ m^2)	Rucaparib (92 mg OD-600 mg BID)	ORR	ORR of 2% 41% SD of ≥12 weeks	--
Swisher et al. (ARIEL 2) [43]	2	EOC	204(40)	Rucaparib (600 mg BID)	--	PFS	PFS HR: 0.27, p<0.001 BRCAm and LOH high vs LOH low	3-4 prior chemotherapy regiments
Coleman et al. (ARIEL3) [44]	3	EOC	564(196)	Rucaparib (600 mg BID)	Placebo	PFS	PFS BRCAm HR: 0.23; p<0.0001	≥ 2 regimens
Plummer et al. [59]	1	ST	33	Rucaparib (1-18 mg/ m^2)+TMZ (100 mg/m^2)	--	PK, PD, safety and tolerability	PID of 12 mg/m^2	Unclear
Talazoparib								
De Bono et al. [92]	1	EOC, BC, PC, CC, PrC, ST	39(24)	Talazoparib (25-1100 μg OD)	--	PK, PD, safety and tolerability	MTD 1000 μg/d	--

BC Breast Cancer, BID Bi-Daily, CBDCA Carboplatin, CDDP Cisplatin CR Complete Response, CYC Cyclophosphamide, EOC Epithelial Ovarian Cancer Including Primary Peritoneal and Fallopian Tube Cancer, MAD maximum Administered Dose, MTD Maximum Tolerated Dose, OD Omni Die, ORR Overall Response Rate, OS Overall Survival, PC Pancreatic Cancer, PD Pharmacodynamics, PrD Progressive Disease, PFS Progression Free Survival, PID PARP Inhibitory Dose, PK Pharmacokinetics, PR Partial Response, PrC Prostate Cancer, PTX Paclitaxel, RP2D Recommended Phase II Dose, SD Stabile Disease, ST Solid Tumors, TMZ Temozolomide, TRR Tumor Response rate

Table 1: Summarizing finished trials.

[76] investigated the efficacy of olaparib in combination with cediranib in a phase II trial in 90 patients with recurrent platinum-sensitive EOC. Results showed a PFS of 17.7 months for treatment with olaparib and cediranib versus 9.0 months for olaparib monotherapy. A post-hoc analysis showed that median PFS was even greater for patients with a g BRCA1/2m: 19.4 months in the combination arm compared to 16.5 months in the olaparib monotherapy group respectively. Most common grade 3 toxicities in the olaparib plus cediranib group were fatigue, diarrhoea and hypertension. Dose reductions were necessary in 77% and 24% of patients respectively. Zimmer [77] performed a phase I study investigating the RP2D for durvalumab+olaparib+cediranib in recurrent female cancers. They concluded a RP2D of 1500 mg q28d durvalumab +300 mg BID olaparib +20 mg 5 days on/2 days off cediranib is tolerable and active.

Overall, anti-angiogenetic therapy in combination with PARP inhibition seems promising due its efficacy and potential synergism. Currently many trials are investigating the combination of bevacizumab or cediranib with PARP inhibitors in ovarian or breast cancer, some of which are listed in Table 3.

Resistance to PARP inhibitors: Clinical trials have shown promising results. However, many studies have described disease progression. Also, thus far PARP inhibitors have failed to show OS benefit. The lack of OS proven benefit can be partly explained by treatment effects of post-progression therapy. Another explanation is resistance to PARP inhibitors. Lord and Ashworth describe four pathways that lead to resistance against PARP inhibitors [78]. Most of the studies that have been done *in vitro*, with mice with different kind of knock-out genes. The first mechanism is the occurrence of a secondary mutation in the affected BRCA gene that would lead to the restoration of the BRCA open reading frame. Due to this restoration, the BRCA gene can be translated and lead to (partial) functional protein to repair DSBs. Several studies have reported this phenomenon in patients who had developed resistance to PARP inhibitors [78]. The second mechanism depends on the (partial) restoration of HDR due to the somatic loss of expression of genes involved in the regulation of DSB repair pathway choice, such as the tumor suppressor p53-binding protein 1 (53BP1) [78] or REV7 [79]. This mechanism is shown *in vivo* in mice [78,79]. A very recent publication describes the identification of shieldin, a complex of REV7, RINN1, RINN2 and RINN3 proteins. This complex restrains DNA end resection and thereby promotes NHEJ. Deletion of one of the shield in components leads to resistance to PARP inhibitors in BRCA-1 depleted cells [80]. Thirdly, the upregulation of the P-glycoprotein efflux pump, which pumps PARP inhibitors out of the cell resulting in a decreased inhibition of PARP [78]. The fourth mechanism is the hypothesis that poses that acquired PARP1 loss-of-function mutations or down-regulation of transcription can result in PARP inhibitor resistance [78].

Another mechanism explaining resistance is replication fork stabilization. Deficiencies in PAX-interacting protein 1(PTIP), Chromodomain-helicase-DNA-binding protein 4 (CHD4) and PARP1 limit the action of MRE11 to single-strand DNA at stalled replication forks. MRE11 is involved in the degradation of stalled replication forks. When MRE11 dependent replication fork degradation is absent due to deficiencies in PTIP, CHD4 or PARP1, nascent DNA strands will be protected from degradation and therefore the cell will be resistant to PARP inhibition [81]. BRCA-deficient cells become resistant to

Trial Nr	Phase	Cancer type	Investigational arm	Second arm	Third arm	Primary endpoint
Olaparib						
NCT02032823 (OlympiA) [31]	3	BC	Olaparib (300 mg BID)	Placebo	--	IDFS
NCT01844986 (SOLO-1) [30]	3	EOC	Olaparib (300 mg BID)	Placebo	--	PFS
NCT01874353 [93]	3	EOC (after CR or PR)	Olaparib (300 mg BID)	Placebo	--	PFS
NCT01081951 [94]	2	EOC	Olaparib (200-400 mg BID) + PTX (175 mg/m^2) + CBDCA (AUC 4)	PTX (175 mg/m^2) + CBDCA (AUC 4)	--	PFS
NCT01445418 [95]	1	EOC/BC	Olaparib +CBDCA dose escalation	--	--	Safety and toxicity
NCT02418624 (REVIVAL) [96]	1	BC/EOC/advanced cancer	Olaparib + CBDCA dose escalation	--	--	MTD
NCT02561832 [97]	1	BC	Olaparib + CBDCA + amtharacycline + cyclophosphamide dose escalation	--	--	AE. pCR
NCT00707707 [98]	01-Feb	BC/TNBC	Olaparib + PTX	--	--	AE
NCT00782574 [99]	1	ST	Olaparib + CDDP			Safety and toxicity
NCT00516724 [100]	1	BC/EOC	Olaparib+ CBDCA	Olaparib+ PTX	Olaparib + CBDCA +PTX	MTD
Veliparib						
NCT01472783 (Veli-BRCA) [101]	01-Feb	EOC	Veliparib (300 mg BID)	--	--	MTD, RP2D, ORR
NCT01690598 [102]	01-Feb	EOC	Veliparib (30 mg BID)+ Topotecan (2 mg/m^2)	--	--	MTD, ORR
NCT01506609 [103]	2	BC	Veliparb (40 mg BID)+ temozolomide (150-200mg/m^2)	Veliparib (120 mg BID)+ CBDCA (AUC 6)+ PTX (175 mg/m^2)	placebo (120 mg BID)+ CBDCA (AUC 6)+ PTX (175 mg/m^2)	PFS
NCT02163694 [104]	3	BC	Veliparib+ CBDCA +PTX	Placebo + CBDCA + PTX		PFS
NCT02032277 [105]	3	TNBC	Veliparib+CBDCA + PTX + AC	Placebo+ CBDCA + PTX + AC	Placebo + PTX + AC	pCR
NCT01149083 [106]	2	BC	Veliparib	Veliparib + CBDCA		RR
NCT02470585 [51]	3	EOC	Veliparib +PTX +CBDCA with veliparib maintenance	Veliparib + PTX +CBDCA with placebo maintenance	placebo + PTX +CBDCA with placebo maintenance	PFS
Niraparib						
NCT01905592 (BRAVO) [39]	3	BC	Niraparib (3 x 100 mg OD)	Physician's choice	--	PFS
NCT02826512 [107]	2	BC	Niraparib (300 mg OD)	--	--	PFS
NCT02354586 (QUADRA) [108]	2	EOC	Niraparib	--	--	Anti-tumour activity
NCT02655016 (PRIMA) [40]	3	EOC	Niraparib	Placebo	--	PFS
Rucaparib						
NCT02855944 (ARIEL4) [109]	3	EOC	Rucaparib (600 mg BID)	CT	--	PFS
NCT01482715 [110]	1	EOC/ST	Rucaparib dose escalating	--	--	PK, PD, safety and tolerability
NCT01074970 [111]	2	TNBC	Rucaparib (24-30 mg)+CDDP(75 mg/m^2)	CDDP(75 mg/m^2)	--	2y-DFS
Talazoparib						
NCT01945775 (EMBRACA) [112]	3	BC	Talazoparib (1 mg OD)	Physician's choice CT		PFS
NCT02034916 (ABRAZO) [113]	2	BC	Talazoparib (1 mg OD)	--	--	ORR
NCT02282345 [114]	2	BC	Talazoparib (1 mg OD)	--	--	Toxicity
NCT02401347 [115]	2	BC	Talazoparib (1 mg OD)	--	--	ORR
NCT02836028 [116]	2	EOC	Talazoparib (1 mg OD)	Talazoparib(1 mg/ OD) + temozolomide (37.5 mg/m^2)	--	ORR

AC doxorubicin/cyclophosphamide, AE Adverse Events, BC Breast Cancer, BID bi-daily , CBDCA Carboplatin, CDDP Cisplatin, CT Chemotherapy, CR Complete response, EOC Epithelial Ovarian Cancer Including Primary Peritoneal and Fallopian Tube Cancer, IDFS Interval Disease-Free Survival, MAD Maximum Administered Dose, OD Omni Die, ORR Overall Response Rate, pCR Pathologic Complete Response, PFS Progression Free Survival, PTX Paclitaxel, PR Partial Response, RR Response Rate (RECIST), ST Solid Tumours, TNBC Triple Negative Breast Cancer, 2y-DFS 2 Year Disease Free Survival.

Table 2: Summarizing ongoing trials of PARP inhibitor monotherapy or in combination with chemotherapy (last updated: 20-12-2017).

various of DNA-damaging agents through the loss of PTIP, PARP1 and CHD4. Furthermore, Survival analysis of patients with EOC with a BRCA2 mutation treated with platinum chemotherapy showed that high PTIP expression has a correlation with a longer PFS [81]. Furthermore, increased phosphorylation of ribosomal protein S6 leading to upregulation of the mTOR pathway [82] and upregulation of NF-kB signalling [83] can also lead to PARP inhibitor resistance. Based on these mechanisms it was hypothesized that PARP inhibitor resistant

Trial Nr	Phase	Cancer type	Investigational arm	Second arm	Third arm	Primary endpoint
Immunotherapy						
NCT02571725 [69]	01-Feb	EOC	Olaparib (300 mg BID) + tremelimumab escalation dose	--	--	RP2D, ORR
NCT02734004 (MEDIOLA) [70]	01-Feb	EOC/BC/GC/ SCLC	Olaparib (300 mg BID) +durvalumab (1.5 g/4 weeks)	--	--	DCR
NCT02953457 [71]	01-Feb	EOC	Olaparib +tremlimumab+ durvalumab	--	--	DLT, PFS
NCT02657889 (TOPACIO) [73]	01-Feb	BC/TNBC/EOC	Olaparib (dose escalation up to 300 mg/day) + pembrolizumab (200 mg)	--	--	RP2D, ORR
Anti-angiogenic therapy						
NCT02345265 [117]	2	EOC	Olaparib + cediranib maleate	--	--	Biomarker signature development, ORR, PFS
NCT01116648 [118]	01-Feb	EOC/TNBC	Olaparib +cediranib maleate	Olaparib	--	DLT, MTD, PFS
NCT02354131 (AVANOVA) [119]	01-Feb	EOC	Niraparib + bevacizumab	Niraparib monotherapy	--	PFS
NCT02498613 [120]	2	Advanced ST	Olaparib + cediranib maleate	--	--	ORR
NCT03278717 (ICON9) [121]	3	EOC	Olaparib (300 mg BID) + cediranib (20 mg/day)	Olaparib (300 mg BID)	--	PFS, OS
NCT02446600 [122]	3	EOC	Platinum-based chemotherapy	Olaparib	Olaparib + cediranib maleate	PFS
NCT02477644 (PAOLA-1)	3	EOC	Olaparib (300 mg BID) + bevacizumab (15 mg/kg every 3 weeks)	Placebo + bevacizumab (15 mg/kg every 3 weeks)	--	--
Anti-angiogenic therapy and immunotherapy						
NCT02484404 [72]	01-Feb	ST/EOC/ TNBC/LC/PrC/ CC	Olaparib (200-300 mg BID) + durvalumab (3-10 mg/kg)	Cediranib (15-30 mg) + durvalumab (10 mg/kg)	Olaparib (200-300 mg BID)+Cediranib (15-30 mg)+durvalumab (10 mg/kg)	RP2D, ORR

AE Adverse Events, AC doxorubicin/cyclophosphamide, BC Breast Cancer, BID Bi-Daily, CC Colorectal Cancer, CT Chemotherapy, DCR, Disease Control Rate, EOC Epithelial Ovarian Cancer Including Primary Peritoneal and Fallopian Tube Cancer, GC Gastric Cancer, IDFS Interval Disease-Free Survival, MAD Maximum Administered Dose, ORR Overall Response Rate, pCR Pathologic Complete Response, PFS Progression Free Survival, PrC Prostate Cancer, RP2D Recommended Phase 2 Dose, RR Response Rate (RECIST), ST Solid Tumours, TNBC Triple Negative Breast Cancer, 2y-DFS 2-Year Disease Free Survival

Table 3: Summarizing current running trials of PARP inhibitor in combination with immunotherapy or anti-angiogenic treatment.

tumors should be treated with rapamycin (an mTOR inhibitor) or with bortezomib (a proteasome inhibitor). The combination of PARP inhibition and rapamycin effectively suppressed tumor growth in mice [82] and the combination of PARP inhibition plus bortezomib led to increased cell death in PARP inhibitor resistant cells [83]. Further investigations (both preclinical and clinical) of mechanisms of PARP inhibitor resistance will direct us to strategies that will optimally use PARP inhibitors in the clinic.

Biomarkers: Considering the application of PARP inhibitors beyond BRCAm tumors, it is essential to identify those patients that benefit most from PARP inhibitors to maximize treatment effect, prevent futile therapy, toxicity and limit health care costs. Several studies have already shown that there is an additional group of tumors with HDR deficiency that also respond to PARP inhibitors [37,84]. These tumours have a so called 'BRCAness' phenotype, a deficiency in HR in the absence of a BRCA mutation, which makes them responsive to PARP inhibitors.

Currently, different approaches have been used to identify HDR deficiency or BRCAness. The first way is to analyse tumours for loss of function mutations in genes that are involved in HDR. These genes include ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related (ATR), CHEK2, BRIP1, PALB2, RAD51C and RAD51D [84]. The second way to detect BRCAness is via transcriptional signatures. Larsen [85] analysed 55 familial germline BRCA1 or BRCA2 mutated breast cancer patients and 128 patients with sporadic breast cancer. They designed a transcriptional signature to distinguish BRCA1 tumors from sporadic tumors with an accuracy of 83% and BRCA2 tumors with 89%, which was validated in independent data sets. This transcriptional signature might also be used to identify BRCAness in non BRCA related tumors. The third way to detect BRCAness is through the detection of a genomic signature in a tumor. These signatures represent a pattern of mutations or genomic alterations which are characteristic for the use of error prone repair pathways in the absence of HDR [86]. These patterns consist of specific nucleotide substitutions (e.g. mutational signature 3) or sequence microhomology at breakpoints [87]. An algorithm based on the integration of six signatures associated with BRCA deficiency (including somatic nucleotide substitutions, insertion/deletion and rearrangement patterns), termed HRDetect was developed by Davies [88] Recently, also SNP based profiling has been used to define a so-called HDR deficiency score, based on the combination of three DNA-based measures of genomic instability (i.e. loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale transitions (LST)) [89]. This is the myChoice HDR deficiency test (Myriad Genetic) which was used in the NOVA trial as discussed earlier, but it could not discriminate between patients that showed a benefit from treatment niraparib or not [37]. A more recent approach to detect BRCAness is through functional biomarkers or a functional test for current HDR deficiency [15,90]. After the induction of DNA DSBs in fresh tumor tissue *ex-vivo*, RAD51 protein will accumulate at the sites of the breaks. This key step in the HDR pathway can be visualized by immunofluorescent staining as foci in the nucleus. The inability to form RAD51 foci after induction of DSBs in replicating tumor cells is a biomarker for BRCAness. However, this biomarker technique requires fresh tumor tissue before start of chemotherapy [91-100]. Finally, in the

ARIEL3 trial [44], the percentage of genome wide LOH quantification was used to compare effectiveness of rucaparib amongst groups with high or low genomic LOH levels. Tumors with high LOH appear to respond better to PARP inhibitor therapy and therefore genomic LOH quantification might be used to identify patients who might benefit from PARP inhibitors [101-122].

Concluding, it is essential to identify those patients that benefit most from PARP inhibitors. However, the most optimal test to identify BRCAness has not been determined yet.

Discussion

PARP inhibitors show promising results in the treatment of EOC, breast cancer as well as other HR related malignancies, but there are still some obstacles to overcome. All randomized phase II/III trials showed a benefit in PFS, but a statistically significant benefit in OS has not been shown yet. It should be further investigated whether this insignificant difference in OS is caused by confounding by later treatment with PARP inhibitors or subsequent therapy or whether there truly is no benefit in OS with PARP inhibitors. Moreover, results of phase III trials investigating the efficacy of PARP inhibitor as maintenance therapy are still awaiting OS data. Results from these trials may give us greater insight whether or not there is a benefit in OS with PARP inhibitors.

Conclusion

Recently, it was concluded that PARP inhibition is beneficial in the treatment of EOC regardless of the BRCA status [37]. However, the question might arise whether the biomarker was accurately enough to determine the HDR deficiency status of the tumor and therefore precisely define patients with BRCAness. Clearly, there is a need for a most optimal test identifying true HDR deficiency status. Future research should determine the role of PARP inhibition in the treatment of non- BRCAm EOC in respect to maintenance therapy in primary disease after first-line therapy, alone or in combination with immunotherapy or VEGF targeted therapy or combined with chemotherapy. Furthermore, ongoing trials will reveal further knowledge on the positioning as first-line or later line therapy and its role in combination with standard chemotherapy. Combinations with immunotherapy and anti-angiogenic therapy are also promising and need further clarification. Finally, the role of PARP inhibition after previous PARP inhibitor exposure needs to be elucidated. Improved knowledge on these questions will be key to improve the selection of patients that benefit most of (combination therapy with) PARP inhibition.

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