The evolving role of PARP inhibitors in advanced ovarian cancer

Research Article

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Abstract: The field of ovarian cancer has been revolutionized with the use of poly (ADP-ribose) polymerase (PARP) inhibitors, which present greater inhibition effect in epithelial subtype due to high rates of homologous recombination deficiency. PARP inhibition exploits this cancer pitfall by disrupting DNA repair, leading to genomic instability and apoptosis. Three PARP inhibitors (olaparib, niraparib, and rucaparib) are now approved for use in women with epithelial ovarian cancer, while others are under development. Among women with *BRCA1/2* mutations, maintenance PARP therapy has led to a nearly fourfold prolongation of PFS, while those without *BRCA1/2* mutations experience an approximately twofold increase in PFS. Differences in trial design, patient selection and primary analysis population affect the conclusions on PARP inhibitors. Limited OS data have been published and there is also limited experience regarding long-term safety. With regard to toxicity profile, there are no differences in serious adverse events between the experimental and control groups. However, combining adverse event data from maintenance phases, a trend towards more events in the experimental group, compared with controls, has been shown. The mechanisms of PARP-inhibitor resistance include restoration of HR through reversion mutations in HR genes, leading to resumed HR function. Other mechanisms that sustain sufficient DNA repair are discussed as well. PARP inhibitors play a pivotal role in the management of ovarian cancer, affecting the future treatment choices. Defining exactly which patients will benefit from them is a challenge and the need for HRD testing to define 'BRCA-ness' will add additional costs to treatment.

Keywords: ovarian cancer • PARP inhibitors • BRCA mutation • maintenance treatment • resistance mechanisms • homologous recombination deficiency

Abbreviations

PFS	Progression Free Survival
OS	Overall Survival
OC	Ovarian Cancer
PARPi	PARP inhibitor
DDR	DNA damage response
SSBs	single strand breaks
HR	Homologous Recombination
DSB	double strand breaks
HRD	Homologous Recombination Deficiency

LOH	Loss Of Heterozygosity
HGSOC	High Grade Serous Ovarian Cancer
EMA	European Medicines Agency
FDA	Food and Drug Administration
ORR	Objective Response Rate
BCS	Biopharmaceuticals Classification System
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
VEGF	Vascular Endothelial Growth Factor
ORF	Open reading frame
ABC	ATP-binding cassette

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AE	Adverse event
PPI's	Proton pump inhibitors
MDS/AML	Myelodysplastic Syndrome / Acute Myeloid Leukemia

1. Background

Despite recent advances in cancer diagnosis and treatment, ovarian cancer (OC) remains the fifth most common cause of death from cancer in women in the United States and Europe^[1, 2]. This is mainly attributed to the fact that the majority of patients are diagnosed at advanced stage, mainly stage III disease^[3]. Therefore, effective treatment options at these stages of disease are of urgent need. The clinical application of PARP inhibitors (PARPi) has drastically changed OC therapy during the last decade. Early hints of activities, shown in the first clinical trials, had led to anticipatory excitement for this class of agents. Undeniably, the magnitude of benefit of PARP inhibitor (PARPi) therapy is considerable. However, treatment resistance is inevitable resulting in progress of disease and modest survival benefit^[4]. Ongoing clinical trials are testing new treatment strategies including new molecules and combination treatments to overcome resistance. Moreover, several PARPi have been approved the last two years, while treatment indications have changed, resulting in a variety of therapeutic options. In this comprehensive review we will discuss all the new available data with regard to the use of PARPi in OC treatment.

2. Mechanism of action

Unlike normal cells, cancer cells are characterized by their continuous proliferation, driven either by activation of oncogenic genes or inactivation of tumor suppressor genes, resulting in inadequate repair of DNA replication errors and a higher susceptibility to genomic instability^[5, 6]. The family of poly (ADP-ribose) polymerases (PARPs) consists of at least 18 enzymes, mainly represented by the DNA-binding PARP1 and PARP2, and exerts a multitude of actions, ranging from mediation of cardiac and inflammatory disease to their activity in DNA repair mechanisms^[7]. PARPs have a central role in the DNA damage response (DDR) system which is comprised of various pathways that contribute to preserving the genome^[8]. Upon activation by DNA damage, PARP1 binds to loci of single strand breaks (SSBs) and triggers a repair complex by attracting repair proteins and promoting chromatin remodeling, ultimately leading to the repair of DNA

lesions^[7]. This posttranslational process is named PARylation [Poly(ADP-ribosyl)ation] and is mainly activated under stressing conditions^[9].

The initially proposed mechanism of action of PARP inhibition was based on the potential synergistic effect of PARPi with chemotherapeutic agents and radiotherapy, which were known to cause DNA damage in cancer cells^[6]. However, this treatment approach was limited by several factors, including the increased toxicity and difficulty in patient selection and optimal treatment combination^[10]. Current knowledge of PARPi's mechanism of action is focused on the concept of "synthetic lethality", a term used to describe the effects of PARP inhibition when combined with defective homologous repair (HR) system that was attributed to BRCA1 and BRCA2 mutations^[11, 12]. PARP inhibition results in failure to repair SSBs, which in turn accumulate and ultimately lead to the formation of double strand breaks (DSB); in HR deficient cells DSBs remain unrepaired leading the cells to high genomic instability and death^[8]. More recent findings show that PARPi have 2 distinct mechanisms of action; they can act as catalytic inhibitors of PARylation, but also promote structural changes and the trapping of PARP1 in a PARP-DNA complex, leading to delays of the SSB repair replication fork and final DSB formation^[13].

Clinical trials have revealed that PARP inhibition is effective in wild type BRCA1,2 ovarian cancer cells as well. This has led to the recognition of the pivotal role that the HR system has in DNA damage repair and the inclusion of a number of HR gene deficiencies that predict responsiveness to PARPi (RCC2, XRCC3, RAD54, and H2A) and comprise the BRCAness phenotype^[13, 14]. Further analysis of these BRCA-like ovarian cancers revealed that homologous repair deficiency (HRD) may be attributed to various genomic alterations, mainly loss of heterozygosity (LOH), telomeric allelic imbalance and large-scale transitions. These alterations are considered surrogates that can be combined to provide an assessment of the tumor's HRD score that has emerged as a possible biomarker of sensitivity to PARPi^[15, 71, 76].

The model of a delay in replication fork has recently been challenged by a study, showing that in BRCA1 deficient cells, PARPi actually induces an increase in fork replication speed above a specified threshold, which results in a reduced cell capacity to recognize and repair DNA brakes^[16]. These data show that PARPi in fact trigger the replication stress that would normally be regulated with PARylation; this in turn leads the tumor cells to replication fork collapse, DNA double-strand breaks and a proclivity to undergo abnormal DNA synthesis. DNA damage is further accumulated and

compromises cancer cells' viability ultimately leading to cell death^[17].

3. PARP inhibitors in ovarian cancer

Up to the present, more than ten PARP inhibitors have been developed and tested, not only for ovarian cancer but also for other solid tumors, BRCA related or not. The first study to confirm efficacy of a PARP inhibitor in germline *BRCA* mutation carriers was conducted over a decade ago, pointing out the way to a novel therapeutic approach^[18]. Initially, most trials of PARPi in OC clinical settings, included patients with germline *BRCA* mutations. Since then, the clinical relevance of PARPis has been confirmed in a number of studies including a larger group of patients, namely patients with somatic *BRCA1/2* mutations, HRD and genetic or epigenetic aberrations that result in a "BRCAness" profile^[19, 20]. This broad group of patients appears to respond better to platinum-based chemotherapies, as well as to PARPis, ultimately demonstrating improved progression-free and overall survival rates^[21–24].

Approximately 15% of epithelial ovarian carcinomas are known to harbor germline mutations in *BRCA1/2* genes, while 6% present *BRCA1/2* somatic mutations^[21, 23, 25]. Another 20% has been associated with a mutation or epigenetic silencing of other genes in the HR pathway, such as *ATM*, *CHEK1*, *CHEK2*, *RAD51C*, *RAD51D*, *BRIP1*, *MRE11A* and *PALB2*^[23, 25, 26]. In addition, other epigenetic processes, such as aberrant promoter hypermethylation, lead to significant disruption of this mechanism and can cause genomic instability^[27]. Another example is the *EMSY* gene amplification or overexpression, which interferes with *BRCA2* protein activity in 20% of high-grade serous OC (HGSOC)^[28–30].

Incidence of germline and somatic mutations in ovarian cancer seems to be histology dependent. Around 50% of HGSOC exhibit a defect in the HR repair mechanism, whereas low-grade serous carcinomas harbor HR defects less frequently (3–11%)^[23, 25]. As far as endometrioid and clear-cell carcinomas is concerned, incidence of HR defects varies widely, ranging between 8–37.6% and 3–26% respectively^[22, 23, 31–33]. Endometrioid histology, instead, has been strongly associated with Lynch syndrome^[21, 34, 35]. Even rarer, HR defects can be found in mucinous OC and carcinosarcomas.

Currently, there is marketing approval in ovarian cancer for olaparib, rucaparib and niraparib. Investigated or under investigation are talazoparib, veliparib, fluzoparib, pamiparib, E7449, IMP4927, NMS-P515, while iniparib (INN, previously known as BSI 201) is no longer considered as a PARP inhibitor.

The basic biochemical characteristics of the most known PARPis are presented in Table 1^[14, 36–45]. Although PARPi main target is PARP 1 protein, trapping potency is differentiated among them. The leading position belongs to talazoparib, which differs up to 200 -fold than the others in its capacity to trap its target. Olaparib and rucaparib, almost equivalent to each other, come after, followed by veliparib and niraparib. The potency of catalytic inhibition follows the same rank order but with substantially smaller variance^[46]. However, both in vitro and in vivo models show, that trapping potency does not correlate with the therapeutic efficacy in monotherapy treatment with PARPi^[13, 46]. Contrariwise, trapping potency plays an important role in clinical outcome and tolerability when these drugs are combined with other agents, most often with alkylating agents^[47].

3.1. Olaparib (AZD2281 or KU-0059436) (Lynparza, AstraZeneca)

Olaparib is the first polyADP-ribose polymerase inhibitor approved for ovarian cancer both by EMA and FDA in 2014^[36]. It blockades in a reversible way PARP-1, -2 and -3 isoforms of the PARP family enzymes. The trapping of PARP1 is stronger and it constitutes the main mechanism of olaparib cytotoxic activity^[13]. Olaparib has low aqueous solubility characteristics and no lipophilic compound, which is translated in low membrane permeability. This may not affect the drug absorption but it impedes its penetration in the brain, so that the final tumor tissue exposure is about 60% less of the plasma concentration^[37, 38]. A fat or high calorie meal may cause delay in drug absorption and peak plasma concentration, but the final bioavailability remains intact, so that patients can receive the drug regardless of food^[48]. A steady state situation in plasma occurs within 3–5 days of drug initiation and it is almost 0.8 times higher when olaparib is taken as a tablet^[49]. It is metabolized in the liver, primarily mediated by CYP3A4 and CYP3A5, whilst its metabolites are excreted in feces (12–60%) and urine (35–60%). A dosage adjustment is necessary in severe liver and renal insufficiency, as well as with concomitant use of a CYP3A inhibitor^[48].

Olaparib is available for oral administration, initially only as capsule of 50mg and now as a tablet of 100mg and 150mg, as well. The new dose is 300mg twice daily. The need for another pharmaceutical form arose in an attempt to improve drug bioavailability. As capsules and tablets are not bioequivalent, the one formulation cannot be changed or replaced by the other one in any indication and time of treatment. Since 2017, based on SOLO-2 results, the tablet is the indicated pharmaceutical form

Table 1: Biochemical Characteristics of PARP inhibitors.

	Molecular formula	Molecular weight (g/mol)	Route	Peak plasma concentration	Potency	IC ₅₀ * Nmol PARP1/2	Max tolerated dose	Half-life
Olaparib	C ₂₄ H ₂₃ FN ₄₃	434.5	oral	1-3hr	PARP1 > PARP2 >> PARP3	5/1	Tb 300mg BID Cap 400mg BID	5-11hr
Rucaparib	C ₁₉ H ₁₈ FN ₃₀	323.4	oral	1.9hr	PARP1 > PARP2 >> PARP3 And tanyrase inhibitor	1.4	Tb 600mg BID	17-19hr
Niraparib	C ₁₉ H ₂₀ N ₄₀	320.4	oral	3hr	PARP1 = PARP2	3.2/ 4	300mg once daily	36hr
Veliparib	C ₁₃ H ₁₆ N ₄₀	244.29	oral	0.5 – 1.5hr	PARP1 PARP2	5.2/2.9	Tb 400mg BID	5.2hr
Talazoparib	C ₁₉ H ₁₄ F ₂ N ₆₀	380.4	oral	1-2hr		1.2/0.9	Cap 1mg daily	90hr

*IC₅₀: half maximal inhibitory concentration

°BID: bis in die, twice daily

for every clinical practice^[36, 50]. In fact, all phase III trials published, used the tablet formulation and FDA has permanently discontinued the capsule since 2018.

The efficacy and safety of olaparib in patients with germline *BRCA1/2* mutations and recurrent ovarian cancer have been assessed in a number of trials, both in platinum resistant disease in comparison with chemotherapy, and in platinum sensitive disease as maintenance treatment^[14, 51-54]. Olaparib was initially granted FDA approval as monotherapy for patients with advanced OC and germline *BRCA* mutations, who had been previously treated with three or more chemotherapy regimens, following the results of a phase 2 study^[55, 56]. Benefit from olaparib monotherapy in terms of tumor objective response rate (ORR) (31.1%), duration of response (median, 225 days), PFS (median, 7 months) and OS (median, 16.6 months) was reported. Differences regarding the RR between *BRCA1* and *BRCA2* mutation carriers were not considered of note^[55, 56].

The first indication of PARPi efficacy in OC patients without germline *BRCA* mutations was introduced after a multicenter, phase 2 trial, in patients with advanced, high-grade serous or poorly differentiated OC, as well as breast cancer^[57]. Objective responses were observed in all women with HGSOc, both with and without *BRCA* mutations, particularly in those with platinum-sensitive carcinomas, supporting the hypothesis that factors implicated in the HR repair mechanism, besides germline *BRCA* mutations, may predict sensitivity to PARPi treatment. Furthermore, the reported data of Study 19, confirmed PFS benefit in women with platinum-sensitive HGSOc and suggested that further investigation is required regarding the efficacy of PARPi in women with BRCAness phenotype^[14]. The prearranged

analysis according to *BRCA* status indicated that the origin of *BRCA* mutations was not associated with the response to PARPi treatment, as women with somatic *BRCA* mutations gained similar benefit^[53]. A further updated analysis of these patients revealed statistically significant improvement regarding PFS (HR 0.23) and OS (HR 0.15)^[58].

Since then, more robust evidence for the efficacy of olaparib has been aggregated from phase 3 trials in various treatment settings. SOLO2 was designed to determine the efficacy of olaparib versus placebo, as maintenance therapy in platinum-sensitive, relapsed, *BRCA*-associated OC patients^[50]. Germline *BRCA* mutations were confirmed in all patients and deemed pathogenic or likely pathogenic in 97% of cases. Maintenance olaparib extended median PFS by 13.6 months with an HR of 0.30. Furthermore, improvement was observed regarding time to first subsequent therapy (median, 27.9 vs 7.1 months), time to second subsequent therapy (HR 0.37), as well as time to second progression or death (HR 0.50). As a result, the indications were expanded by both the FDA and the EMA in the maintenance therapy setting, to include relapsed OC patients, with response to previous platinum-based chemotherapy, irrespective of their *BRCA* status^[45, 59]. Very recently, final impressive overall survival data was announced, with a median OS improvement of nearly 13 months^[60]. Regarding first-line maintenance therapy, the results of the SOLO1, confirmed the efficacy of olaparib in this additional setting^[61]. The vast majority of participants was germline *BRCA* mutant (388/391 patients); two patients had somatic *BRCA* mutations and one had a *BRCA* variant of uncertain significance. Olaparib maintenance offered 36 months median PFS benefit, compared to placebo. Similar significant

improvements were observed in time to first subsequent therapy and time to second disease progression, while OS did not appear to differ substantially at that point. Safety profile was as expected.

SOLO3 trial tested whether olaparib was more effective than physician-selected chemotherapy in women with germline BRCA-associated, platinum-sensitive, relapsed HGSOc treated with at least 2 prior platinum-based chemotherapy lines. ORR proved to be significantly higher (72.2% vs 51.4%) and PFS was further improved in favor of the olaparib group (median, 13.4 vs 9.2 months)^[62]. The clinical relevance of these findings remains debatable, since at present most of the patients receive olaparib as first-line maintenance therapy. Until new evidence surfaces regarding the role of olaparib in heavily pretreated patients, including PARPi as prior therapy, this question stands unanswered. On the other hand, olaparib monotherapy may be more relevant in patients with relapsed, platinum-resistant OC, as it is indicated by the preliminary results of the ongoing CLIO trial^[63]. ORR for olaparib monotherapy proved superior against standard-of-care chemotherapy (18% vs 6%, respectively), especially in patients with germline mutations. Further analyses of patients with somatic BRCA mutations are ongoing. Finally, the efficacy of olaparib has been tested in combination with other antitumor agents, which is discussed in another section.

3.2. Rucaparib (AG-14447) (Rubraca, Clovis Oncology)

Rucaparib is a small molecule inhibitor of PARP-1, -2 and -3 and of tankyrase-1 and -2. It is considered the less selective PARPi and its strongest trapping target is PARP-1. Its efficacy is increased by blocking both PARPs and hexose-6-phosphate dehydrogenase (H6PD)^[64]. Rucaparib's full name is rucaparib camsylate and it belongs to camphorsulfonate salts. Its water solubility is low, irrespective of the pH range, while its permeability is low- to moderate^[45]. Rucaparib was tested both intravenously and orally, whereas oral rucaparib achieved better results with regard to ORR and disease stabilization^[65]. It is available as an oral tablet and can be administered with or without food, though there is a moderate effect of food in the drug pharmacokinetics^[66]. Its average bioavailability is 36% and the maximum concentration is reached in 1.9 hours. Rucaparib succeeds a steady state in 1 week following the indicated dose of 600mg twice daily^[39, 66]. The drug is metabolized in liver via oxidation and glucuronidation, primarily by CYP2D6 and to a lesser extent by CYP1A2

and CYP3A4. The major metabolite is named M324 and it is inactive. The drug is excreted both intact and through its metabolites through feces (>72%) and urine (~17%). In cases of mild to moderate renal disease or in mild liver insufficiency no dose adjustments are required. There are no data for more severe impairments^[39, 45]. Rucaparib distribution in the brain is limited and this is potentially due to its interaction with p-glycoproteins, implying a drug resistance mechanism^[67, 68]. Regarding interactions with other drugs, two factors should be taken under consideration when rucaparib is administered: first that rucaparib inhibits p-glycoproteins and second its relationship with the CYP-enzymes.

Rucaparib, has shown acceptable toxicity profile and antitumor activity in patients with germline and somatic *BRCA* mutations and HRD^[69-72]. ARIEL2 was designed to determine whether rucaparib would maintain its efficacy across three subgroups of women with platinum-sensitive, relapsed HGSOc, based on *BRCA* mutation status and LOH; *BRCA* mutant, *BRCA* wild-type with high LOH and *BRCA* wild-type with low LOH^[71]. PFS was significantly improved in women with *BRCA* mutations as compared to the other subgroups, irrespective of mutation's origin (germline or somatic)^[71, 72]. Proceeding to the maintenance clinical setting, ARIEL3 recruited 564 patients with platinum-sensitive, recurrent HGSOc, with complete or partial response to their previous platinum-based therapy. PFS advantage was consistent across all prespecified subgroups, regardless of parameters such as LOH, *BRCA* status, disease at baseline or response to previous treatment. With regard to the HRD cohort, significant PFS prolongation was also noted for the patients on rucaparib and this overall benefit was consistent, regardless of the presence of *BRCA* mutations^[73]. However, the presence of mutations in other HR genes, both in LOH high and low subgroups, suggests that more sensitive biomarkers, predictive of the PARPi response, are required. Based on the results of Study 10, ARIEL2 and ARIEL3, rucaparib, initially approved by the FDA in 2016 for advanced high grade serous ovarian cancer with germline *BRCA* mutations as a third or later line treatment, was also approved in 2018 by the FDA as a maintenance treatment for the platinum sensitive disease irrespective of *BRCA* status^[71, 73]. With regard to maintenance treatment setting, its role is going to be elucidated by the MAMOC trial (NCT04227522), which is going to be initiated soon. Patients will be randomized to receive rucaparib vs. placebo, until disease progression and/or death, or unacceptable toxicity, after receiving bevacizumab maintenance for 12 to 15 months.

3.3. Niraparib (MK-4827) (Zejula, GlaxoSmithKline)

Niraparib is the first PARPi to show PFS benefit as maintenance treatment in both BRCA mutant and wild type women with platinum sensitive recurrent OC. It equally and selectively blockades PARP-1 and -2, which is a common characteristic with veliparib. They are both carboxamides, so their carboxyl terminal domain interacts via hydrogen bonds with the α -helical domain of the PARP-1 and -2 enzymes, a subdomain which does not exist in other PARPis^[40]. Niraparib has a crystal structure and is classified according to BCS as class II. Its solubility is independent of the pH conditions. It is disposable only as capsule of 100mg and the standard dose of any clinically relevant indication is 300mg once daily. Niraparib is very rapidly absorbed irrespective of time or quality of meals intervals, having a bioavailability of 73% in humans, and reaching the peak plasma concentration in about 3 hours. Due to its high membrane permeability, it can cross the blood-cerebrospinal barrier, leading to brain concentration of 0.9-fold the concentration in plasma. Regarding tumor exposure to niraparib, both preclinical models and phase I trials have shown that tumor concentration ratio is 3-fold higher of that of the plasma^[37, 38]. It is metabolized in the liver primarily by carboxypeptidases (CEs) in a diphasic process^[41, 74]. The P450 enzymes have a minor role in niraparib metabolism, thus the risk of drug-to-drug interaction is uncommon, as are high aminotransferase levels. Niraparib is metabolized in more than ten non-active metabolites and it is excreted both in its initial formation and its metabolites, in feces (~39%) and in urine (~47%)^[74]. Its half life time is 36 hours. No dosage adjustments are needed in mild-to-moderate liver and renal impairment, while there are no pharmacokinetics data and consequently no accurate guidelines for its administration in severe impairments.

Niraparib was initially tested in HRD solid tumors in 2013 and gained approval by both the EMA and the FDA in 2017, based on the results of the ENGOT-OV16/NOVA trial^[75-77]. Among 553 patients with platinum-sensitive recurrent OC, 203 were germline *BRCA* mutation carriers, 138 of whom were assigned to 300 mg niraparib. This group performed significantly better in terms of PFS compared to those on placebo (median 21.0 vs 5.5 months), irrespective of their best achieved response to the last platinum-based therapy. Among the non-germline *BRCA* mutation cohort, further subgroups were created according to HRD status. Niraparib proved beneficial in almost every subgroup in terms of PFS, chemotherapy-free interval and time to first subsequent treatment. Women with HRD positive

tumors experienced significantly prolonged PFS when treated with niraparib compared to placebo (median, 12.9 vs 3.8 months; HR 0.38). It is noteworthy that the favorable outcomes of niraparib were retained across subgroups with HRD positive and *BRCA*-wild type tumors, but also in HRD-negative patients^[75-77]. In 2019 FDA approved also its use as fourth line treatment in women with HRD ovarian cancer^[78].

PRIMA trial consolidated niraparib's pivotal position in patients with HRD^[80]. HRD status was defined as one of the stratification parameters and 373 women (50.9%) with response to first-line chemotherapy were categorized as deficient. In patients with HRD, significant PFS benefit of 21.9 months was reported with niraparib versus 10.4 months compared with placebo (HR:0.43). The risk of progression or death was generally lower in women regardless of HR deficiency or proficiency, but the greater effect was displayed in patients with *BRCA*-associated tumors^[79]. The antitumor activity of niraparib has been further illustrated in QUADRA trial, in heavily pretreated platinum-sensitive HRD-positive HGSC patients with no prior exposure to PARPi^[80]. The following analysis of the primary efficacy group yielded an ORR of 28% and a median PFS of 5.5 months. The strongest effect with regard to OS was 26 months observed in *BRCA*-mutant patients, followed by 19 months in the HRD-positive women. Despite the broad range of patient populations in this study, as no restrictions to mutational status or platinum-response were applied, the requirement for PARPi-naïve patients and the subsequent per-protocol analysis of results raise concerns regarding the role of PARPi in this line of treatment. Finally, niraparib is about to be tested in the neoadjuvant treatment of ovarian cancer in the phase II NEOPRIMA trial.

3.4. Talazoparib (BMN 673) (Talzenna, Pfizer)

Talazoparib targets PARP1, -2, -3 and tankyrases 1 and 2. It is unclear where talazoparib owes its unique properties regarding trapping. The theory of the allosteric effects in PARP proteins is questionable, whereas crystalized chiral-center structure could play a role^[40, 46, 81]. The phenomenon is even more obvious in populations with *BRCA1/2* and *PTEN* dysfunctions. Although potency seems to be associated with bone marrow toxicity in both in vitro and in vivo data, it remains unclear if it is indicative of a better therapeutic result^[47].

Talazoparib is available as an oral capsule and the indicated dose for its clinical use as monotherapy is 1g daily. After every dose administration it reaches its maximum plasma concentration in 2 hours while it

needs 2 to 3 weeks from the starting dose to succeed a steady state situation. Food intake has a moderate effect in talazoparib bioavailability, which in general ranges between 55% - 65%. Thus, patients can take the drug regardless of meals. It has a low solubility, which is pH dependent, and moderate permeability, a fact that restricts the delivery of talazoparib in the central nervous system^[82]. Most of the drug (>65%) is eliminated unchanged through urine, while it is a potent p-glycoprotein inhibitor, so co-administration with similar drugs should be avoided^[44]. No dose adjustments are recommended for mild or moderate renal or hepatic dysfunction, while there are no data for its safety in more severe impairments.

Talazoparib has been mostly investigated in patients with *BRCA1/2* mutations and *PTEN* mutated models, mainly in breast cancer populations, where it has an official treatment approval. As far as ovarian cancer is concerned, the field of investigation is limited in small pilot and phase I/II trials, which test talazoparib as monotherapy with optimistic results, but are still not adequate to forward its further investigation in phase III trials^[44, 83]. Of special interest was the attempt, that tried to find out if the drug could be active after a prior exposure to other PARP inhibitor, which was nevertheless, early terminated (NCT02326844)^[84].

3.5. Veliparib (ABT-888) (AbbVie)

Veliparib is the smallest PARPi and weakest, with regard to its trapping efficacy, whereas it is the most selective together with niraparib. It is orally available and the indicated dose is 400mg twice daily continuously. It is very rapidly absorbed and food only moderately affects the C_{max} and T_{max} time, so its administration is independent of meals^[42]. It is a very soluble molecule, categorized as class I in the BCS, having the ability to penetrate the central nervous system. Veliparib's bioavailability is high and reaches at least 73%^[85]. The majority of the drug is excreted unchanged in urine, while 20% is metabolized in the liver, mainly by CYP2DA. In renal or liver dysfunction, and potentially in CYP2DA insufficiency, drug exposure is increased, however it is not well-documented if a dose adjustment under these circumstances is necessary^[43, 86]. The ongoing trial NCT01366144 which combines veliparib with paclitaxel and carboplatin in solid tumors in patients with liver and renal impairment may elucidate this question. As it does not induce or inhibit the major Cytochromes P450 and it does not seem to significantly interact with P-gp, it is considered safe when co-administered with other drugs^[43].

Veliparib's efficacy was established in early phase trials, demonstrating promising antitumor activity^[87, 88]. In another phase 2 study, the results of 50 enrolled patients with germline *BRCA* mutations and recurrent OC were not as remarkable^[89]. Responses were reported in 35% of patients with platinum-sensitive, as compared to 20% of those with platinum-resistant disease; however, this difference did not reach statistical significance. Veliparib has still not managed to gain an approval in the treatment of ovarian cancer in any setting of disease, neither in USA nor in Europe. Combination treatment with veliparib will be discussed below.

3.6. Novel PARP inhibitors

Fluzoparib (SHR-3162) is a new PARP1 inhibitor, orally bioavailable, with favorable pharmacokinetic properties and tolerability in phase I trials. It has shown efficacy in HRD tumors, especially in platinum sensitive ovarian carcinomas^[90, 91]. Currently, ongoing phase III trials investigate the potent efficacy of fluzoparib as maintenance treatment in platinum-sensitive recurrent ovarian cancer (NCT03863860), and furthermore its combination with apatinib (VEGFR2 inhibitor) in the 1st line maintenance setting (NCT04229615).

Pamiparib (BGB-290) is another new PARP 1/2 inhibitor with high selectivity and capability to penetrate the central nervous system^[92]. As all other PARPis, pamiparib is orally disposable. It is currently under investigation as maintenance treatment in platinum-sensitive ovarian cancer (NCT03519230), and in *BRCA1/2* mutated ovarian cancer (NCT03933761)^[93, 94].

E7449 (2X-121) is also an oral PARP 1/2 and tankyrases 1/2 inhibitor, which can enter the blood-brain barrier. Its action seems to be independent of p-glycoprotein expression. As many of the already known PARP inhibitors, it has been tested in preclinical *BRCA* 1/2 mutated models alone or with alkylating drugs, proving its antitumor activity and its capacity to potentiate DNA-damaging^[95]. At the moment, it is being tested within a phase II trial (NCT03878849) as a 3rd line treatment in recurrent ovarian cancer, regardless of *BRCA* or HR status^[96].

4. PARP inhibitors and treatment combinations

Overall, treatment with PARPis offers a modest survival benefit and furthermore is characterized by primary and secondary resistance. A selection of PARPi combinations can lead to a promising outcome. It would have been

Table 2: Completed clinical trials of olaparib combinations with other agents in ovarian cancer.

Study	Combination	Year	Phase	Cancer type	Olaparib dosage	Outcome
NCT00516438	Topotecan	2009	I	Solid tumors	Starting with cap 50mg BID ^a continuously, escalating	Unacceptable toxicity
NCT00572364	Dacarbazine	2009	I	Solid tumors	Cap 10mg BID continuously	Tolerated, no clinical benefit
NCT00710268	Bevacizumab	2015	I	Solid tumors	Cap 400mg BID	Well tolerated
NCT00819221	Lip-doxorubicin	2017	I	Ovarian cancer	Cap 150mg BID, continuously	Tolerated and clinical benefit
NCT02430311, Chinese population	Paclitaxel	2019	I	Solid tumors	Tb 100mb BID	Reduce of olaparib bioavailability
NCT01650376	Carboplatin and weekly paclitaxel	2019	Ib	Ovarian cancer	Tb 150mg BID continuously	Tolerated- clinical benefit in BRCAm
GEICO1601-ROLANDO trial	Lip-doxorubicin	2019	II	Ovarian cancer, Platinum-resistant	Tb 300mg BID continuously	Not recruiting, waiting for results
NCT01081951	Carboplatin and paclitaxel	2020	II	Ovarian cancer-relapsed, platinum-sensitive	Cap 200mg BID continuously	PFS: 12.2 months (combo) vs 9.6 months (carboplatin/paclitaxel), HR : 0.51 (p=0.0012) OS: data not yet available

^aBID: bis in die, twice daily

expected that such combinations would have been tried mostly with chemotherapeutic agents (platinum salts, alkylating agents, topoisomerase inhibitors), as PARP inhibition potentiate their cytotoxic activity. Instead, many different categories of antitumor-drugs in combination with PARPis have been investigated in OC, namely antiangiogenetic agents, immunotherapy (immune checkpoint inhibitors) and DNA damage repair targets. Furthermore, they can be combined as a component of a triplet, such as the addition of immunotherapy and bevacizumab to PARP inhibitor therapies^[97].

4.1. Combination with chemotherapy

Several trials have been conducted combining PARPis with chemotherapy in different types of cancer. Table 2 shows olaparib's combinations with chemotherapy agents. Regarding Olaparib's combination treatment with the classic chemotherapeutic drugs, namely carboplatin and paclitaxel in the platinum-sensitive setting and liposomic doxorubicin in the platinum-resistant setting, have been attempted. Both treatment strategies had promising clinical responses in terms of ORR and PFS benefit, especially for the subgroup of BRCA mutant patients^[98-101]. In spite of this, no phase III trials have been conducted to investigate if this is an effective treatment strategy, maybe due to overlapping myelosuppression, modifying treatment strategies to metronomic schedules. Moreover, paclitaxel and carboplatin combination with olaparib are now

investigated in the neoadjuvant treatment of BRCA mutant ovarian cancer (germline and/or somatic) in the active, phase II NUVOLA trial.

Rucaparib is now under investigation as a combination treatment with many other therapeutic agents. Table 3 demonstrates all the currently ongoing rucaparib's combination trials. Combination treatment of rucaparib with chemotherapy has been reported only within phase 1 trials, and proved to be safe^[65]. According to our knowledge, there are no clinical trials which combine niraparib with alkylating agents. Talazoparib, is another PARPi which has been combined with other agents in early phase trials, especially with alkylating drugs (carboplatin and temozolamide) and the topoisomerase 1 inhibitor irinotecan, playing the role of the chemosensitizer^[82, 102, 103]. Limited data exist regarding its safety and efficacy in combination with chemotherapeutic agents in OC.

Veliparib's unique characteristic to act as a sensitizing factor for radiotherapy and chemotherapy increases its DNA-damaging efficacy^[92], making veliparib perhaps the ideal PARP inhibitor for potential combinations. It has been combined with many different chemotherapy agents such as alkylating agents, paclitaxel, liposomic doxorubicin, and topoisomerase inhibitors, proving to be tolerable in phase I trials and sometimes also effective (Table 4)^[104-108]. It has been also investigated as a radiosensitizer in peritoneal carcinomatosis, in a small phase I trial which included only 4 patients with ovarian cancer. The combination was tolerable, while only one gBRCA

Table 3: Recruiting clinical trials of olaparib combinations with other agents in ovarian cancer.

Study	Combination	Year	Phase	Cancer type
NCT03772561	Durvalumab	2018	I	Solid tumors
NCT03682289	ATR kinase inhibitor AZD6738	2019	II	Solid tumors
NCT02485990	Tremelimumab	2020	I	Recurrent or persistent ovarian cancer
NCT02953457	Durvalumab and tremelimumab	2016	II	Recurrent or resistant Mbrca Ovarian cancer
NCT04123366	Pebrolizumab	2020	II	Solid tumors, mHRD, dHRD
NCT03162627	Selumetinib	2017	I/II	Endometrial, Ovarian cancer and other solid tumors
NCT03462342 (CAPRI Trial)	Ceralasertib (AZD6738)	2018	II	Recurrent Ovarian cancer
NCT03579316	Adavosertib	2018	II	Ovarian cancer

Table 4: Clinical trials of veliparib combinations with other agents in ovarian cancer.

Study	Combination	Year	Phase	Cancer type	Rucaparib dosage	Status / Outcome
NCT02470585	Topotecan	2017	I/II	Resistant/Partially Sensitive Ovarian cancer	30 mg BID ^a , on D1-3 and 8-10, q28	Well tolerated, Best response – SD in 37%
NCT01113957	Temozolamide	2018	II	Recurrent Ovarian cancer	NA	Completed No Results yet
NCT02470585 - VELIA trial	Carboplatin and Paclitaxel	2019	III	Newly diagnosed Ovarian cancer	Induction: 150 mg BID q21 Maintenance: 300 BID for 2 weeks, escalating to 400 mg BID	PFS 23.5 vs 17.3 months (HR = 0.68; P < .001)
Japanese trial	Paclitaxel- carboplatin	2016	I	Newly diagnosed Ovarian cancer	100mg – 150mg BID q21	Well tolerated/ potential clinical benefit
NCT01459380	Pegylated Liposomal Doxorubicin and carboplatin +/- bevacizumab	2015	I	Recurrent, platinum-sensitive ovarian cancer	50mg or 80mg Or 120mg	Well tolerated in low doses of veliparib
NCT01233505	Capecitabine and oxaliplatin	2014	I	Solid tumors	40mg BID days 1-7, 15-21, q28	Well tolerated
NCT01306032	Cyclophosphamide	2016	II	Refractory BRCA-Positive Ovarian Cancer and Breast cancer	60mg daily	Well tolerated/ no PFS benefit
NCT00989651	Bevacizumab and Paclitaxel plus either carboplatin or IP cisplatin	2009	I	Ovarian cancer	N/A	Active-not recruiting

^aBID: bis in die, twice daily

mutated patient with platinum sensitive disease achieved a response^[109]. Recently, results of VELIA trial, which tested the addition of veliparib to the standard neoadjuvant therapy and its continuation as maintenance therapy, were announced^[90]. Of the 1140 patients randomized, 214 had a germline *BRCA* mutation, while 84 had a *BRCA* mutation of somatic origin. Three nested cohorts of *BRCA* mutation, HRD and intention-to-treat population were prespecified. In general, substantial PFS benefit was demonstrated across all cohorts for the veliparib-throughout group.

In the intention-to-treat cohort, median PFS was 23.5 versus 17.3 months for the veliparib-throughout and control group respectively (HR 0.68). Similarly, in the *BRCA* mutant population, a median PFS of 34.7 months was achieved in the veliparib-throughout group compared to 22.0 months in the control group (HR 0.44). The HRD cohort population achieved significantly longer PFS in comparison with the control group (median, 31.9 vs 20.5 months; HR 0.57). Women with *BRCA* mutations appeared to derive the greatest advantage from PARPi therapy, while those with HRD

carcinomas had a borderline significant reduction in risk of progression or death. Interestingly, these differences were not observed during comparisons of the veliparib-combination-only with the control group, in either cohort^[91]. Therefore, the role of veliparib as an addition to induction chemotherapy, remains questionable.

4.2. Combination with antiangiogenic agents

The inhibition of PARP enzymes in parallel with the VEGF pathways seems also an effective strategy. The addition of cediranib, an anti-VEGFR inhibitor, to olaparib vs. olaparib alone demonstrated clinical activity not only in women with recurrent, platinum-sensitive OC, but also in platinum resistant disease^[110-112]. Surprisingly, subgroup analysis revealed that patients without germline *BRCA* mutations performed better with the combination, compared to *BRCA* mutant patients, in terms of both PFS and RR^[111]. Updated analysis revealed no OS benefit for the combination in the overall population, though OS was significantly increased by the cediranib/olaparib combination in the *BRCA* wild-type patients^[113]. The same combination when tested in the phase III GY004 trial, failed to meet its primary PFS endpoint in platinum-sensitive relapsed ovarian cancer, compared to standard of care chemotherapy^[114].

While most olaparib trials referred to patients with germline *BRCA*-associated OC, PAOLA-1 trial was designed to assess olaparib and bevacizumab as first-line maintenance treatment combination in high-grade OC patients, irrespective of *BRCA* status^[115]. Women were randomized to receive maintenance bevacizumab with either olaparib or placebo for a maximum of two years. The intention was to determine whether there would be synergistic benefit in combining bevacizumab with olaparib. In the intention-to-treat population there was a 6-month improvement in PFS with the combination (HR: 0.59). Impressively, in the HRD-positive patient population the HR was 0.33. However, the trial has been criticized for not including an olaparib monotherapy arm, meaning adding a third arm that would have been placebo plus olaparib, so that we can really define the relative contribution of the addition of bevacizumab to olaparib in the *BRCA*-mutated and HRD population.

Many ongoing trials investigate tolerability and efficacy of different niraparib combinations with other agents (Table 5). Thus far, niraparib has been examined as definitive treatment with bevacizumab, compared to niraparib alone, in women with platinum-

sensitive, relapsed HGSOc in AVANOVA2 phase 2 study^[116]. Stratification was based on HRD status and chemotherapy-free interval following previous therapy. In general, PFS was significantly prolonged for the combination group, regardless of HRD status (median, 11.9 months vs 5.5; HR 0.35) and origin of *BRCA* mutation (germline or somatic).

4.3. Combination with immunotherapy

Based on preclinical studies that suggested PARP inhibition may create a more immunogenic tumor milieu in OC, combination of PARPis with immune checkpoint inhibitors proceeded to early phase clinical trials. Olaparib and durvalumab, initially tested in germline-mutated (gBRCAm) platinum-sensitive OC, showed modest clinical activity in recurrent OC^[117, 118]. Combination of pembrolizumab with niraparib has been tested in women with relapsed, platinum-resistant, *BRCA*-mutant and HRD OC, in the phase 1/2 TOPACIO/KEYNOTE-162 trial^[119]. ORR was estimated at 18% for somatic *BRCA*-mutant and 14% for the HRD-positive women, respectively. Although antitumor effect was reported in all subgroups regardless of their biomarker status, intriguingly, long-term responses appeared to especially favor women with platinum-refractory or resistant disease and *BRCA* wild type or HRD-negative tumors. Another combination trial which did not meet its primary endpoint of improving PFS in patients with OC and has since been discontinued, is JAVELIN Ovarian PARP 100 trial, in which talazoparib was tested together with avelumab, an anti-PDL1 agent^[120]. The decision upon discontinuation, also made due to the modest benefit observed with avelumab in frontline OC in JAVELIN Ovarian 100. Translational research studies indicate that VEGF/VEGFR pathway blockade would be necessary for improved efficacy of this combination. As a consequence, triplet combinations are already being tested in early phase clinical trials.

4.4. Combination with other targeted agents

Future is focused on combinations with the before mentioned effective therapies in phase II and III trials, trying to overcome resistance and improve patient outcomes. At the same time, into play come new target agents, such as the MEK and PI3K inhibitors, most of the times in the recurrence phase of ovarian cancer. Selumetinib, a novel MEKi, having shown antitumor activity in recurrent low grade serous ovarian cancer

Table 5: Clinical trials of niraparib combinations with other agents in ovarian cancer.

Study	Combination	Year	Phase	Cancer type	Niraparib dosage	Statuts / Outcome
NCT04217798	Etoposide	2020	II	Resistant/Refractory Ovarian cancer	200mg daily	To be initiated
NCT04149145	M4344 – ATR inhibitor	2020	I/II	Resistant/Recurrent Ovarian cancer	Starting with 100mg, escalating to 200mg	To be initiated
NCT03895788	Brivanib	2019	I	Recurrent Ovarian cancer	100mg or 200 mg, daily	Recruiting
NCT03602859-ENGOT-OV44 /FIRST study	Dostarlimab – anti-PD-1	2018	III	1 st line non-mucinous Ovarian cancer	300mg daily	Recruiting
NCT03695380	Cobimetinib +/- Atezolizumab	2018	Ib	Platinum sensitive ovarian cancer	200mg daily	Recruiting
NCT03955471 – MOONSTONE trial	TSR-042 anti-PD-1	2019	II	Recurrent platinum-resistant Ovarian cancer	N/A	Recruiting
ENGOT-OV24-NSGO/AVANOVA trial	Bevacizumab	2019	I/II	Ovarian cancer, Platinum-sensitive	300mg D1-21	PFS benefit with the combination [11,9 months (95% CI 8,5-16,7) vs 5,5 months (3,8 - 6,3)], HR 0,35 (95% CI 0,21-0,57), p<0,00,1+
NCT04267939	BAY1895344 ATR inhibitor	2020	Ib	PARPi naïve and with a platinum-resistant/refractory disease or PD after PARPi maintenance	N/A	Recruiting
NCT03574779 OPAL trial	Dostarlimab and bevacizumab	2018	II	Recurrent Ovarian cancer	200mg or 300mg daily	Active – not recruiting- no results yet
NCT03326193 - OVARIO trial	bevacizumab	2018	II	Platinum sensitive Ovarian cancer	300mg daily	Active – not recruiting- no results yet
NCT03598270 - ANITA trial	Atezolizumab	2018	III	Platinum sensitive relapse	200mg or 300mg daily	Recruiting
NCT02657889 - TOPACIO/ KEYNOTE-162 trial	Pembrolizumab		I/II	Triple negative Breast cancer or recurrent ovarian cancer	200mg	ORR of 25% in all PROC and ORR of 45% in tBRCAmut patients, well tolerated*
NCT03154281	Everolimus	2017	I	Recurrent ovarian or breast cancer	100mg or 200mg or 300mg daily	Recruiting
NCT03586661	Copanlisib	2018	I	Endometrial and Ovarian cancer	Escalating dose	Recruiting

+ Mirza MR, Lundqvist EA, Birrer MJ, Christensen RP, Nyvang GB, Malander S, et al. Niraparib Plus Bevacizumab Versus Niraparib Alone for Platinum-Sensitive Recurrent Ovarian Cancer (NSGO-AVANOVA2/ENGOT-ov24): A Randomised, Phase 2, Superiority Trial. *Lancet Oncol* 2019;20(10):1409-19.

* Konstantinopoulos PA, Waggoner S, Vidal GA, Mita M, Moroney JW, Holloway R, et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. *JAMA oncol* 2019;5(8):1141-9.

and ER positive HGSOc^[121, 122], it is now tested in early phase clinical trials in combination with olaparib (NCT03162627). On the other hand, preliminary clinical evidence of synergism between olaparib and alpelisib has paved the way to further investigation^[123]. Furthermore, targeting more than one DNA repair pathway, including *ATR*, *ATM*, *Chk1*, *Wee1* and *DNA-PK*, has the potential to enhance responses to PARP inhibitors. Other agents having shown activity in combination with PARPis, particularly in preclinical studies and early phase trials, are HDAC inhibitors and hypomethylating agents^[124, 125]. Table 6 shows olaparib's combination trials with immunotherapy, HDAC inhibitors and hypomethylating agents.

5. Mechanisms of PARP inhibitor resistance in HR deficient tumor cells

The BRCA1/2 proteins function in two characteristic cellular processes, the execution of HR repair and the protection of the stalled replication fork. Tumor cells can become resistant to PARPi by two general mechanisms. The first is that the tumor cells can find a way to restore HR repair, most likely by producing a somatic reversion of the mutated *BRCA1/2* allele^[126]. A second mechanism involves that the tumor cell develops a bypassing process for protecting its replication fork. In this second case, the PARPi resistant tumor may still have an HR defect, but will not respond to PARPi exposure^[126]. In

Table 6: Clinical trials of rucaparib combinations with other agents in ovarian cancer.

Study	Combination	Year	Phase	Cancer type	Rucaparib dosage	Statuts / Outcome
NCT03462212 (MITO25)	Carboplatin/Paclitaxel +/- Bevacizumab	2018	II	Resistant/Refractory Ovarian cancer	400mg or 500mg Or 600mg BID*	Recruiting
ATHENA trial	Nivolumab	2018	I/II	Platinum Sensitive Ovarian cancer	600mg BID	Recruiting
NCT03840200	Ipatasertib (Akt inhibitor)	2019	Ib	Breast, Prostate and Ovarian cancer	600mg BID	Recruiting
NCT02873962	Nivolumab and bevacizumab	2016	II	2 nd line Ovarian cancer	600mg BID	Recruiting
NCT03992131 (SEASTAR trial)	Lucitanib (VEGF 1-3 inhibitor) or Sacituzumab (anti-Trop-2 monoclonal antibody linked with SN-38)	2019	I/ II	Solid tumors	600mg BID	Recruiting
NCT03824704 – ARIES trial	Nivolumab	2019	II	Platinum sensitive recurrent Ovarian cancer	N/A	Active/ not Recruiting
NCT03552471	Mirvetuximab Soravtansine (olate receptor alpha targeting antibody-drug conjugate)	2018	I	Recurrent Ovarian cancer	600mg BID	Recruiting
NCT04267939	BAY1895344 ATR inhibitor	2020	Ib	PARPi naive and with a platinum-resistant/refractory disease or PD after PARPi maintenance	N/A	Recruiting
NCT03574779 OPAL trial	Dostarlimab and bevacizumab	2018	II	Recurrent Ovarian cancer	200mg or 300mg daily	Active – not recruiting- no results yet
NCT03326193 – OVARIO trial	bevacizumab	2018	II	Platinum sensitive Ovarian cancer	300mg daily	Active – not recruiting- no results yet

*BID: bis in die, twice daily

this setting, there is often an upregulation of the ATR/CHK1 pathway, thereby activating the phosphorylation of multiple proteins contributing to fork stability^[126].

5.1. Hypomorphic BRCA1 or BRCA2 allele

Analysis of *BRCA1* missense mutations suggests that the conserved N- and C-terminal domains are most important for the response to HR-deficiency targeted therapies. Specifically, tumors carrying the *BRCA1*-C61G mutation which disrupts the N-terminal RING domain respond poorly to PARPis, and rapidly develop resistance^[127]. Interestingly, mutations in the BRCA1-terminal (BRCT) domain of *BRCA1* commonly create protein products that are subject to protease-mediated the BRCT domain of these mutant *BRCA1* proteins under PARP inhibitor selection pressure^[128]. The HSP90-stabilized mutant *BRCA1* proteins can efficiently interact with PALB2-*BRCA2*-RAD51, form RAD51 foci, and confer PARP inhibitor and cisplatin resistance. Treatment of resistant cells with an HSP90 inhibitor may reduce the mutant *BRCA1* protein level and restore their sensitivity to PARP inhibition^[128].

5.2. Somatic reversion or restoration of open reading frame (ORF)

In *BRCA1/2*-mutated tumors, the most common acquired mechanism of resistance to PARPis is secondary intragenic mutations restoring the *BRCA1* or *BRCA2* protein functionality^[129, 130]. Restoration of *BRCA1/2* function occurs either by genetic events that cancel the frameshift caused by the original mutation and restore ORF leading to expression of a functional nearly full length protein which can be similar to the full length wild-type protein. These genetic events were originally observed in *BRCA1*- and *BRCA2*-mutated cancer cells under in vitro selective pressure, due to exposure to cisplatin or PARPis and as a result would eventually cause platinum and PARPi resistance^[126]. This mechanism of resistance is highly clinically relevant for patients with *BRCA*-mutated cancers who are treated with platinum-based therapy; 46% of platinum resistant *BRCA*-mutated HGSOc exhibit tumor-specific secondary mutations that restore the ORF of either *BRCA1* or *BRCA2*^[126]. Lastly, multiple somatically-reverted *BRCA1/2* alleles have been detected from patients undergoing PARPi or platinum therapy through analysis of circulating free DNA (cfDNA)^[131].

5.3. Epigenetic reversion of BRCA1 promoter hypermethylation

HR repair can be restored by reversal of *BRCA1* promoter methylation. The primary sensitive sample may show extensive promoter methylation and low *BRCA1* expression, while the sample from the relapsed disease has lost *BRCA1* methylation and the *BRCA1* gene is expressed at comparable levels to homologous recombination proficient tumors^[126]. The loss of *BRCA1* promoter methylation may result from an active demethylation event but more likely from a heterogeneous tumor from which the tumor cells with less promoter methylation undergo positive selection in PARPi^[126].

5.4. Loss of PARP expression

Since PARPi function by blocking the enzymatic action of PARP enzymes, another possible mechanism of PARPi resistance may be decreased expression of PARP enzymes. This mechanism of resistance may be particularly relevant to the PARP-trapping mechanism of action of PARPi. Interestingly, a recent study identified a PARP1 mutation (1771C > T) in an ovarian cancer patient who demonstrated de novo resistance to PARP inhibitor^[132].

5.5. Loss of end resection regulation 53BP1 or REV7

Several mechanisms of resistance involving reacquisition of DNA end resection capacities have also been described. There are several proteins which are known to working a pathway which suppresses end resection and thereby inhibits HR repair. These proteins include 53BP1, REV7, PTIP, and RIF1. Discovery of this mechanism came from the observation that the requirement of *BRCA1* for HR can be alleviated by concomitant loss of 53BP1. 53BP1 blocks CtIP-mediated DNA end resection via downstream effectors like Rif1 and PTIP and thus commits DNA repair to CNHEJ^[134]. Loss of 53BP1 partially restores the HR defect and their hypersensitivity to DNA-damaging agents in knockout mice for *BRCA-1*^[134].

In *BRCA1*-mutant cells, loss of 53BP1 confers resistance to PARPi. More recently, a set of new proteins which bind to REV7, including RINN1, -2, -3 have been identified^[135]. Knockdown of these proteins also results in PARP inhibitor resistance.

5.6. Resistance due to limited drug uptake or increased drug export

Pharmacological effects that alter the cellular response to PARPi may also be relevant. Several studies have shown that PARPi responses may be modified by ATP-binding cassette (ABC) transporters^[136]. Increased expression in tumor cells of ABC transporters, such as the P-glycoprotein (PgP) efflux pump (also known as multidrug resistance protein 1) have been implicated in reducing the efficacy of many compounds by enhancing their extracellular translocation.

Importantly, *BRCA1/2* deficient tumor cells can acquire resistance to PARPi by finding independent mechanisms for protecting their replication forks. Research has demonstrated how the study of drug resistance can uncover novel principles of DNA repair and replication fork biochemistry. Multiple studies have previously demonstrated the role of *BRCA1*, *BRCA2*, and other FA proteins in the protection of RFs^[137, 138]. It has been demonstrated that different nucleases are necessary for fork protection. The first study showed that *BRCA1* cells were shown to become resistant to PARPi by reducing the recruitment of the nuclease, MRE11 (required for the RF stability), to the stalled fork, thereby resulting in fork protection through reduced expression of the protein, PTIP^[139]. In a second study it was demonstrated that *BRCA2* deficient tumors cells can become resistant to PARPi by reducing the recruitment of a different nuclease, MUS81, to the stalled fork^[140]. As a mechanism of PARPi resistance, these tumors downregulate EZH2 activity at the fork and downregulate MUS81 recruitment^[140]. Interestingly, through both of these mechanisms, the tumors achieve PARPi resistance without restoring HR repair.

5.7. PARP Inhibition Induced Akt Activation resistance

Recently it has been suggested from in vitro trials that inhibition of nuclear protein PolyADP-ribosylation reaction catalyzed by PARP1 somehow triggers the activation of cytoplasmically localized Akt. PARP1 activated by DNA strand breaks PolyADP-ribosylation itself, thereby creating a scaffold that recruits a complex of proteins^[141]. If excess PARP activation is prevented by a pharmacological inhibitor or genetic manipulation, one of the complex proteins does not undergo ribosylation it translocates to the cytoplasm and in part associates with the mitochondrial outer membrane^[142]. There, the complex recruits Akt and mTOR, and together with them forms a signalosome that activates Akt, leading to

activation of downstream pro-survival pathways^[143].

6. PARP inhibitors and adverse events

PARPis are associated with a variety of adverse events, the type and the severity of which may lead to dose adjustments and modifications or even to the discontinuation of therapy. PARP inhibition is not selective. By interfering with the DNA repair ability of cancer and normal cells, treatment with PARPis can lead to both target specific and non-target specific side effects. Blood toxicity is one of the most common non target specific adverse effects related to PARP inhibition treatment.

Adverse events (AEs) related to PARP inhibition may be class related or drug specific. Class related are the AEs that are observed among all the drugs of the PARP family, while those which are unique to each drug are called drug specific. A meta-analysis examining the differences in class related toxicity between olaparib, niraparib and rucaparib showed that olaparib was related mainly to diarrhea, niraparib to blood toxicity and rucaparib to abdominal pain^[144]. Close monitoring of patients is necessary, as AEs may affect their health and safety.

6.1. General and Nutrition Disorders

Fatigue is the most common AE, presented in 50% to 70% of patients receiving PARPis. It is mainly grade 1-2 and most common with rucaparib, niraparib and olaparib^[145]. According to Coleman et al, the incidence of fatigue with veliparib is about 26% (88). When not related to hematological toxicity as anemia or thrombocytopenia, activity and physical exercise may be helpful to manage this adverse event. Another class related AE is anorexia and decrease in appetite. This appears to be a common side effect observed in about 20-25% of patients, to whom nutritional consultation may be necessary^[145].

6.2. Gastrointestinal Toxicity

A recent meta-analysis has shown that the risk of high grade gastrointestinal toxicities associated with PARPis is significantly increased in ovarian cancer patients, with the exception of constipation^[146]. Of these, nausea and vomiting seem to appear early on treatment with a tendency to decline later on. According to the SOLO-2

trial, the incidence of all – grade nausea with olaparib was 76% and of vomiting 37%. Lower incidence rates were reported with diarrhea and stomatitis, 33% and 20% respectively (50). Nausea and vomiting related to PARP inhibition usually subside with medication and treatment often involves drugs as metoclopramide, benzodiazepines or 5-HT₃ receptor antagonists. Last but not least, dyspepsia (10-20%) and dysgeusia (10-40%) have frequently occurred in patients treated with PARP inhibitor maintenance, the later more commonly noted with rucaparib. Prescription of PPI's and certain dietary and oral hygiene measures may be helpful to control these AEs^[145].

6.3. Hematologic Toxicity

Hematologic AEs are very common during treatment with PARPis and require complete blood counts regularly to exclude enhancing blood toxicity. According to a meta-analysis from Zhou et al including 2479 patients from 12 randomized controlled trials treated with PARPis, the incidence of severe neutropenia, thrombocytopenia and anemia were 32.9%, 15.9% and 9.1% respectively^[147]. Hematologic toxicity is more common with niraparib and talazoparib and less with rucaparib, olaparib and veliparib^[144]. According to one trial, the incidence of neutropenia of any grade in patients on treatment with PARPis is about 20%^[145]. On the other hand, febrile neutropenia is extremely rare when the PARP inhibitor is used a single agent^[60, 73, 79]. In general, the use of granulocyte growth factors during treatment with PARP inhibitors is not recommended. MDS/AML has been reported as an AE related to PARPi therapy although in a very small percent (approximately 1%). Exposure to DNA-damaging agents is demonstrated to be a significant risk factor for developing MDS/AML especially in the presence of *BRCA* mutations^[78].

Anemia with hemoglobin levels <8g/dL generally require interruption of treatment until hemoglobin recovers to 9 g/dL. Blood transfusions are often required and dose modifications with lower doses are necessary after persistent occurrence of anemia with treatment. PARPis should be withheld when platelet counts are <100x10⁹ cells/L. Treatment adjustment is required when platelet count reduces <75x10⁹ cells/L or at a second occurrence with the exception of talazoparib, where treatment may be continued if platelet counts are >50x10⁹ cells/L. Severe thrombocytopenia with platelet counts <10x10⁹ cells/L require emergency platelet transfusions^[145].

6.4. Respiratory Disorders

The most common respiratory symptoms noted on treatment with PARP inhibitors are dyspnea, cough and nasopharyngitis. Usually mild, they affect 10-20% of patients and may relate to infectious conditions. Clinical and radiographic assessment may be necessary to exclude olaparib related pneumonitis which is reported in <1%^[145].

6.5. Nervous System Disorders

Insomnia and headache are frequently related with PARP inhibition. Headache is common with both olaparib and niraparib at a rate of 26% while insomnia is observed in 27% of patients who are treated with niraparib. Dizziness is related to niraparib too with an incidence rate of 18%. Pharmacological measures may appear necessary to control refractory cases of drug related neurological adverse events^[145].

6.6. Laboratory Abnormalities

Transient transaminase elevations have been described mainly with rucaparib. All grade incidences have been reported to be approximately 34% and usually transaminase normalization occurs after a few weeks from initiation of treatment. Olaparib and niraparib can cause transaminase elevations too, but to a lesser extent than rucaparib^[145]. Elevations in creatinine have been described in approximately 10-12% of patients across different PARPis^[145]. A retrospective trial by Zibetti et al. showed that elevation of blood creatinine levels in patients receiving PARPis was not related to a decrease in the GFR measured by renal scan^[146]. In the event of persistent blood creatinine rise, other causes should be ruled out before withholding treatment.

6.7. Cardiac Disorders

Among cardiac adverse events, hypertension and palpitations occurrence have been related mainly to niraparib. In the NOVA trial, all grade hypertension

was noted in 20% of patients, while palpitations in 10% respectively (77). This potential may be due to the drug's off-target pharmacologic activity on the dopamine, the norepinephrine and the serotonin transporters^[149]. Accordingly, thorough investigation is needed to exclude other causes of tachycardia and palpitations, and medication to be used when necessary.

6.8. Skin Disorders

Skin disorders related to treatment with PARP inhibitors include rash, pruritus and photosensitivity. In the ARIEL3 clinical trial, 17% of the patients receiving rucaparib reported photosensitivity, 13% pruritus and 12% rash (73). Sun protection and Dermatologic consultation may be indicated.

7. Conclusions

Advanced ovarian cancer treatment landscape has changed dramatically since the introduction of PARP inhibitors in clinical practice. Although survival benefit has been shown in clinical trials, treatment resistance remains inevitable. Ongoing clinical trials are testing multiple combinations of PARPis with several agents, trying to discover the appropriate combination, as well as, the treatment setting they should be indicated for.

Author Contributions

Sofia Levva conceived and designed the study. Sofia Levva, Aglaia Skolariki, Eleni Sogka, Alexandros Bokas, Avraam Assi, Marianna Pispirigkou and Panagiotis Koliou provided the study material, collected and assembled the data, analyzed and interpreted the data, and wrote the manuscript. All authors approved the manuscript.

Disclosures

The authors reported no financial relationships.

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