PARP Inhibitors in Ovarian Cancer

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Running title: Role of PARP inhibitors for the treatment of ovarian cancer: current status and future perspectives.

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Abstract

Background: Treatment of Epithelial Ovarian Cancer (EOC), historically based on surgery and platinum doublet chemotherapy, is associated with high risk of relapse and poor prognosis for recurrent disease. In this landscape, the innovative treatment with PARP inhibitors (PARPis) demonstrated an outstanding activity in EOC, and is currently changing clinical practice in BRCA mutant patients.

Objectives: To highlight the mechanism of action, pharmacokinetics, clinical activity, indications and current strategies of development of Olaparib, Niraparib, Rucaparib, Talazoparib and Veliparib, the 5 most relevant PARPis.

Methods: We performed a review on Pubmed using 'ovarian cancer' and the name of each PARPi (PARP inhibitor) discussed in the review as Medical Subject Headings (MeSH) keywords. The same search was performed on "clinicaltrial.gov" to identify ongoing clinical trials and on "google.com/patents" and "uspto.gov" for recent patents exploring PARPIs in ovarian cancer.

Results: Olaparib, Niraparib and Rucaparib are already approved for treatment of recurrent EOC and their indications are partially overlapping. Talazoparib and Veliparib are promising PARPis, but currently under investigation in early phase trials. Several studies are evaluating PARPis in monotherapy or in associations, in a wide range of settings (i.e. first line, neoadjuvant, platinum-sensitive and resistant disease).

Conclusion: PARPis are valuable options in patients with recurrent ovarian cancer with promising activity in different stages of this disease. Further studies are required to better define optimal clinical settings, predictors of response beyond BRCA mutations and strategies to overcome secondary resistance of PARPis therapy in EOC.

Keywords: ovarian cancer, PARP inhibitors, olaparib, niraparib, rucaparib, veliparib, talazoparib, recent patents.

1. INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy with 22440 estimated new cases and 14080 deaths in the United States in 2017 [1]. It is frequently diagnosed at advanced stage and standard therapeutic strategy consists of optimal debulking surgery (absence of residual disease) and platinum-based chemotherapy [2]. However, despite optimal surgery, about 70% of patients experience relapse [3]. Probability of response and prognosis of relapsed patients is related to progression/relapse free interval from last platinum therapy (Platinum free interval, PFI). Patients with platinum-refractory (PFI within 4 weeks) and platinum resistant (PFI within 6 months) disease would receive a single-agent chemotherapy (above all Pegylated Liposomal Doxorubicin-PLD, Taxanes, Gemcitabine, Etoposide or Topotecan) with low response rate and poor prognosis. On the other hand, patients that are platinum partially-sensitive (PFI between 6 and 12 months) and platinum sensitive (PFI longer than 12 months) could receive a platinum based therapy with a better prognosis and longer survival [2]. In this landscape, characterized by few therapeutic options and a narrow range of drugs that improve survival, inhibitors of poly (ADP-ribose) polymerases (PARPis) emerged as an exciting option [4]. Olaparib, Rucaparib, Niraparib, Veliparib and Talazoparib are the most studied PARPis and the first three have already been approved in different setting of relapsed EOC, determining a radical change in current practice.

1.1. DNA repair and Homologous Recombination Deficiency

DNA damage is a frequent event during cell life; it can be spontaneous (*e.g.* replication error) or caused by cell metabolism or by environmental agents[5]. It can result in single strand DNA breaks (SSBs) or double strand DNA breaks (DSBs) that cause loss of genome integrity and cell death, if not correctly repaired [6]. There are six main DNA repair pathways [7] [8]. Mismatch Repair (MMR), Nucleotide Excision Repair (NER), Base Excision Repair (BER), Trans-lesional Synthesis, Non Homologous end joining (NHEJ), and Homologous recombination (HR) [9]. The last two pathways are responsible for repairing DSBs; HR is a high fidelity repair mechanism, active during Phase G2-S of cell cycle[10, 11], whereas NHEJ is faster but error prone [12] [13]. If HR pathway is altered, leading to Homologous Recombination Deficiency (HRD), cells rely above all on NHEJ [14], with a less preserved genomic integrity and a higher risk to develop cancers [12] [13]. The first HR proteins that have been studied were Breast Related Cancer Antigen (BRCA) 1[15] [16] and 2 [17], whose germline mutations and, consequently, loss of function were correlated with an increased risk of breast cancer (ranging from 57% in BRCA1 mutation to 45% in BRCA2 mutation) and ovarian cancer (ranging from 11% in BRCA 1 mutation to 40 % in BRCA2 mutation) [18] [19].

BRCA mutated OC display distinctive biological and clinical features[20], being usually high grade cancers (G2-G3), with serous or undifferentiated histology [21]. Moreover, they are frequently diagnosed at an advanced stage [22] and in young women but BRCA mutated patients have a better prognosis in comparison with BRCA wild type (BRCA WT) EOC. [21] [23] [24]. Until recent approval of the new drugs, PARPis, patients with gBRCAm EOC had the same treatment of BRCA wild type EOC [25] [26] [27] . Recently TCGA demonstrated that almost half of high grade serous ovarian cancer (HGSOC), the most frequent EOC histology, exhibits HRD [28]. Germline BRCA1 and 2 [22] [29] account for 22.6% of mutations in HGSOC, usually accompanied by loss of heterozygosis (LOH), while somatic mutations are present in 6-7% [30] and BRCA1 hypermethylation is found in about 10% of HGSOC [28] Other altered genes in HRD pattern are EMSY (8%), PTEN (Phosphatase and Tensin Homolog) (7%), RAD 51C (3%), ATM/ATR (Ataxia-telangiectasia mutated and ATM- and RAD3-related) (2%), Fanconi Anemia genes (5%) and RAD 50 (<1 %) [28]. Sporadic EOCs that exhibit HRD without BRCA 1 or BRCA 2 mutations have similar histology, biology and clinical features of BRCA mutated tumours (so called BRCAness phenotype [31] [32] [33]). Unfortunately, nowadays a standardized test that can optimally identify HRD EOCs does not exist, even if several strategies were attempted. Among them some have tried to identify directly the key mutations in HR pathway with gene expression profiles of DNA repair proteins using "targeted capture and massively parallel sequencing" (e.i. BROCA profile) [34] [35] [36]. Other tests used indirect 'scars' [37], such as mutational signatures [38] or structural variations of the genome, identified as genome variation larger than 100 kb, that result from DSB in cells with HRD [37]. The most important "scars" used in HRD tests are:

- Numerical chromosomal instability (CIN), an amplification or deletion of large fragments of chromosomes, usually interesting a whole chromosome arm [39] [40] [41];
- Somatic rearrangement pathways related to specific DNA-repair deficiency, for example tandem duplications (TDs) [42] ;
- Loss of Heterozygosis (LOH) of multiple megabasis fragments [43], used as marker of HRD in several trials as discussed below [26] [44].
- A combination of three variables: intermediate size LOH (>15 Mb) added to allelic imbalance that involve the telomerase (TAI) and number of chromosomal breaks longer than 10 Mb [45] [27].

1.2. PARP family and PARP inhibitors Mechanism of action

In the complex landscape of DNA repair mechanism, PARP family plays a central role [46]. PARPs are a group of enzymes that transfer polyADP-ribose from NAD+ to some target proteins in a post transcriptional process known as PARylation [47]. Among them, PARP-1, 2 and 3 are the most extensively studied. PARP-1, that accounts for up to 90 % of the entire PARP activity, recruits DNA repair complex in BER [48], detects disruptions in replication forks [49], PARylates essential proteins involved in HR [50] (e.i. BRCA1 recruitment to sites of DNA damage [51]) and acts as a negative regulator in NHEJ [52] [53], with the cooperation of PARP-2 and PARP-3 and plays a central role in microhomology-mediated end joining repair, an error-prone pathway involved in DSBs repair [52] [53]**.** Beyond DNA repair PARPs are also involved in transcriptional regulation, mitosis, cell death, telomere length and intracellular metabolism [54].

PARPis are generally benzamide or purine based analogues of nicotinamide that compete with NAD+ in the catalytic domain of PARPs [55] [56]. Their activity is historically based on the concept of "synthetic lethality", first introduced in 2005, according to which two genetic lesions, not lethal when individually present, become lethal if both occur in the same cell. For this reason cells that are HR deficient are more sensitive to PARP activity inhibition [50] [57] [58]. PARP inhibition reduces both HR and BER activity, thus SSBs remaining unrepaired [59], leading to a high number of DSBs that are not repaired in HRD cells during DNA duplication [59]. PARPis prevent also the inhibition of NHEJ, with a high load of mutations and cell apoptosis [60]. Figure 1 resumes the principal PARPis mechanisms of action above described.

All PARPis [54] [61] developed in EOC are PARP-1 and PARP-2 inhibitors, while Olaparib and Rucaparib inhibit also PARP-3 and Rucaparib inhibits also tankyrase-1, another member of PARP family[62] [63].

Recent studies show that PARP inhibition is more cytotoxic that genetic depletion of PARPs, finding that PARPis "stabilized" PARP-1 and PARP-2 DNA complexes. This activity, known as PARP trapping, prevents DNA repair, leading to cell death [62] [63]. Murai et al demonstrated that PARP trapping is strongly related to PARPis cytotoxic activity [62] [63] [64]. Despite of similar PARP catalytic inhibitory activities, Talazoparib shows the greatest in vitro cytotoxicity and PARP-trapping [63], followed by Niraparib. Olaparib and Rucaparib show a medium citotoxicty and PARP-trapping, whereas Veliparib is the weakest one [4] [62]. These differences are probably due to allosteric differences in NAD+ binding site; Niraparib and Olaparib are bulky inhibitors compared to Veliparib, while Talazoparib has a rigid structure if compared to the "flexible" Olaparib and Rucaparib [62] [63].

The aim of this review is to describe the rationale beyond development of PARPis, their mechanism of action and the most important clinical trial that led to their approval in clinical practice. Moreover, we report an overview and future perspectives of these new molecules summarizing the ongoing clinical trial with PARPis. To do this we operated a search on clinicaltrials.gov with "*ovarian cancer*" and the single name of each compound (Olaparib, Niraparib, Rucaparib, Veliparib and Talazoparib) as keywords.

2. OLAPARIB

2.1. Description

Olaparib (@Lynparza, Astra Zeneca), known as AZD2281, is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzymes 1, 2 and 3 (PARP 1, PARP2 and PARP 3 respectively). Its chemical name is 4-[(3-{[4-(cyclopropylcarbonyl) piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)] one and the chemical structure is showed in Figure 2. Olaparib molecular formula is C24H23FN43 and has a molecular mass of 434.46 amu. Lynparza has a low, pH-indipendent, solubility, with a value of nearly 0.1 mg/ml in the normal pH range.

The molecule is disposable for oral use as capsules since 2014, each one containing 50 mg of Olaparib associated with some excipients [65]. Since August 2017, after the publication of SOLO-2 study results (see below for the details), also a tablet formulation is available in two different dosages, containing respectively 100 mg and 150 mg of Olaparib

2.2. Pharmacokinetics

Comparing tablet and capsule formulation the bioavailability is higher for the tablets, with a steady state exposure (AUC) 77% higher after 300 mg tablet twice daily in comparison after 400mg capsule twice daily. After a single dose of 300 mg tablet the geometric mean AUC is 42 μg*h/ml, while C_{max} is 5.8 μg/ml, while the steady state data are 49 μg*h/ml and 7.7 μg/ml respectively. In the pharmacodynamics studies no clinically relevant alterations of cardiac repolarization neither modification in QT interval were reported[66].

Absorption

After oral intake the median peak plasma concentration is established after 1.5 hours. The co-administration of high fat meals prolonged that time, with a delay of 2.5 hours in the absorption, but

no significant alteration in the amount of absorption was reported, except an increased mean AUC of nearby 8%.

Distribution

The mean (±SD) apparent volume of distribution is 158±136 L after a single intake of 300 mg of Olaparib, with an in vitro protein binding nearly 82%.

Metabolism

The two enzymes mostly involved in Olaparib metabolism are CYP3A4 and CYP3A5. For that reason, concomitant use of strong or moderate CYP3A inhibitors should be avoided. Oxidation reactions are fundamental in the metabolism and the great part of metabolites are produced with glucuronide or sulfate conjugation.

Excretion

After a single 300 mg dose the mean (±SD) plasma half-life is 14.9 ±8.2 hours, with an apparent plasma clearance of 7.4 ± 3.9 L/h. In an experiment with ^{14}C-Olaparib, 86% of radioactivity is redeemed in 7 days, 44% through urine and 42% through feces, with the most of compound excreted as metabolites [67].

2.3. First evidence of clinical activity

Olaparib was the first small-molecule oral PARP inhibitor developed in ovarian cancer. Back in 2009 a phase I trial by Fong and colleagues reported a low side effect profile (fatigue, nausea and anaemia in 30%, 32% and 5% of patients respectively) associated with a clinical benefit of 63 % in BRCA 1/2 mutated population (19 patients) [68]. One year after the same study-group presented a single-stage expansion of the phase I trial exploring the drug in 50 ovarian cancer BRCA-mutated patients. Forty per cent of patients had a radiological or serological response, while the overall clinical benefit rate (CBR) was 46%. Interestingly, for the first time, a correlation was reported between CBR and PFI; moreover, a post hoc analysis pinpointed an association of platinum sensitivity with Olaparib response both at radiological and serological level ($p = 0.001$ and $p= 0.002$ respectively) [69]. Despite the achievement of responses at a dose of 100 mg twice daily, Audeh and colleagues conducted a proof-of concept phase II trial in order to compare objective response rate (ORR) of this dosage with the maximum tolerated dose of 400 mg twice daily in a population of 57 heavily pretreated germline BRCA mutated (gBRCAm) ovarian cancer patients. ORR was 33% in the cohort treated with 400 mg twice daily *vs* 13% in the cohort treated at the lower dose; the median progression free survival (PFS) was 5.8 months (95% confidence interval CI 2.8-10.6) *versus* 1.9 months (95% confidence interval CI 1.8-3.6) in favor of 400 mg twice daily. The

treatment at higher dose was well tolerated, with a slight increase in nausea, fatigue and anemia. Therefore 100 mg *bis in die* (bid) dose seems to be less effective than 400 mg bid. It must be noticed that allocation of patients was not randomized and the 100 mg bid group had worse prognostic characteristics [70].

The better efficacy of the higher dose of 400 mg bid was confirmed by the first randomized phase II trial, known as Study 12. The study enrolled 97 gBRCAm ovarian cancer patients relapsed within 12 months of previous platinum therapy and assigned them to receive Olaparib 200 mg or 400 mg continuously, both dose twice daily, or PLD 50 mg/m2 day 1/28. Neither median PFS or ORR between Olaparib groups and PLD group reached statistical significance [71].

Olaparib seems to be active also in BRCA wild type ovarian cancer, as demonstrated for the first time in 2011 by Gelmon in a phase II trial, with a ORR of 24% versus the 41% reported in the gBRCAm patients [72]. These data confirmed the hypothesis that HRD and consequent susceptibility to platinum compounds or other drugs that create DNA damage, like PLD, or prevent damage repair, like PARPis, depend on various gene alteration and not only on BRCA mutation [28].

2.4. Pivotal trials for Olaparib approval

Olaparib monotherapy efficacy as a maintenance treatment was ratified in two randomized clinical trials, with more than 500 patients enrolled worldwide, known as Study 19 and SOLO 2, at the dose of 400 mg twice daily (capsules) and 300 mg twice daily (tablets), respectively.

In 2012 Lederman and colleagues [73] presented the first results of a double-blind, placebo-controlled phase II trial that enrolled 265 platinum-sensitive ovarian cancer patients previously treated with two or more platinum based chemotherapies and a complete or partial response achieved to the last platinum therapy. Patients were randomized to receive @Lynparza capsules 400 mg twice daily or placebo and the stratifications were done by response to the last platinum compound (complete versus partial), time to progression on penultimate platinum line and ancestry (Jewish *versus* non-Jewish). The primary endpoint of this trial was investigator-assessed PFS. PFS was significantly prolonged in the Olaparib group, 8.4 *versus* 4.8 months and a hazard ratio (HR) 0.35 (95% CI 0.25-0.49, $p<0.00001$). The first analysis of overall survival (OS), a secondary endpoint, showed no difference, although a pre-planned subgroup analysis seemed to highlight an advantage for patients with a known BRCA mutation. These modest results led to a “dark period” for Olaparib development because no drugs authorities would approve it in absence of greater and certain benefit [74]. In order to develop a “target therapy” meanwhile data on germline BRCA mutation status were derived from a retrospective analysis and showed that 36% of the enrolled

population (96 patients) were mutated, 53 in the Olaparib group (39%) and 43 in the placebo group (33%). This new information opened a new lucky era for Olaparib two years later, with the results of a preplanned-subgroup efficacy analysis based on BRCA status. The effect of Olaparib in BRCA mutated patients was greater and lead to a PFS of 11.2 months *versus* 4.3 months observed in BRCA wild type (HR 0.18, 95% CI 0.10-0.31, p<0.00001). A significant, even if smaller, benefit was reported also for BRCA wild type treated with Olaparib compared to the placebo group (7.4 versus 5.5 months, HR 0·54, 95%IC 0.34-0.85, p=0.0075) [75]. Nor in the second [75] neither in the third interim analysis [76] a significant difference in OS was reported and this was probably due to the high rate of crossover (23%). In this phase II study Olaparib showed a good tolerability profile with a dose interruption rate of 36% versus 16% in the placebo group; the grade 3 or worse side effects reported were fatigue, nausea and anemia. In patients treated for two years or more 75% reported low-grade nausea, 56% experienced fatigue, 38% vomiting and 25% anaemia. 15% of the BRCA mutated patients continued Olaparib for at least 5 years.

Since preclinical data proved that Olaparib could increase the efficacy of DNA-damaging chemotherapy, in 2015 Oza and colleagues [77] investigated this hypothesis and published the results of a randomized, open-label, phase II study in which, 162 platinum-sensitive, recurrent ovarian cancer patients, pre-treated at least with three previous platinum based chemotherapy lines were randomized to receive a) Olaparib 200 mg capsules twice daily from day 1 to 10 of a 21-day cycle in association with carboplatin AUC 4mg/ml/min and paclitaxel 175 mg/m2 on day 1/21 followed by Olaparib monotherapy (400 mg capsules twice daily given every day until progression; or b) carboplatin AUC 6 mg/ml/min and paclitaxel 175 mg/m on day 1/21 followed by none maintenance therapy. BRCA status was known or retrospectively retrieved for 107 patients; 38% were mutated and equally divided between the two arms of treatment. PFS was greater in the Olaparib arm, with a median of 12.2 versus 9.6 months (HR 0.51, 95% CI 0.34-0.77, p=0.0012), with a highly regarded advantage in BRCA mutated patients (HR 0.21, 95% CI 0.08-0.55, p=0.0015). The most common grade 3 or higher side effects during the association phase were neutropenia (43% versus 35 % in the chemotherapy alone group) and anemia (9% versus 7%), whereas serious adverse events were more frequently reported in the chemotherapy alone group (21% versus 15%).

The endorsement of Olaparib primary role to prolong PFS and time to first and second subsequent chemotherapy arrived with the publication of the randomized, double-blind, phase III trial conducted by Pujade-Lauraine et al. The SOLO-2 trial enrolled 295 gBRCAm patients and randomized them to receive Olaparib tablets 300 mg twice daily versus placebo after a partial or complete response to the most recent platinum based chemotherapy. Also in this trial, all patients

were pre-treated with two or more platinum containing chemotherapy, with a nearly 40% of highly pretreated (three or more previous line) in the Olaparib group. Investigator assessed-PFS, the primary endpoint, was longer in patients treated with @Lynparza, with a median of 19.1 *versus* 5.5 months (HR 0.30, 95% CI 0.22-0.41, p<0.0001)[25]. The advantage was seen in all subgroups, also in the patients pretreated with bevacizumab. As reported in the poster session of ESMO 2017 Congress, the superiority is reported also in the most heavily pre-treated patients with no statistical significant interaction between number of prior lines of platinum-based therapy received and PFS benefit [78]. Olaparib met also two secondary endpoints, actually considered OS surrogates, the time to first and second subsequent therapy, with HR 0.28 (95% CI 0.21-0.38, p<0.0001) and HR 0.37 (95% CI 0.26-0.53, p<0.0001), respectively. Moreover, Olaparib had no significant detrimental effect on health-related quality of life (HRQoL) [25] [79]. The most frequently reported side effects of CTCAE were low grade nausea, asthenia, vomiting, abdominal pain and diarrhea in both groups. The most common adverse event of grade 3 or higher in the Olaparib group was anemia, with blood transfusion rate of 18% *versus* 1% in the placebo group, whereas neutropenia and thrombocytopenia of grade 3 or worse severity were similar in the two groups.

Olaparib demonstrated to be effective also as monotherapy in a single arm study conducted by Kaufman [80], well known as Study 42, where 298 patients with deleterious or suspected deleterious gBRCAm patients with different kind of tumors, including 193 ovarian cancer patients heavily pre-treated (median of prior chemotherapy lines was 5). The ORR was 34% with a median duration of response (DOR) of 7.9 months. Domchek et al. published additional data about EOC gBRCAm population of this trial, focusing on the 137 patients with measurable disease and pretreated with three or more chemotherapy lines. ORR in platinum-resistant tumors was 30%; interestingly, although the median DOR was similar for platinum-sensitive and platinum-resistant, the platinum sensitive population achieved better outcome across all the endpoints [81].

Efficacy of Olaparib treatment, considering both ORR and DOR, was confirmed also by a pooled analysis on 300 gBRCAm EOC patients conducted by Matulonis and colleagues, with a similar and manageable safety profile in more heavily pretreated patients (≥3 lines of prior chemotherapy) [82].

2.5. Indication and dosage

Olaparib (@Lynparza) has been approved by FDA and EMA as maintenance therapy for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer after the achievement of a complete or partial response to chemotherapy with a platinum compound in patients with a somatic or germline mutations in BRCA 1 or 2 genes. The results presented by Kauffman [80] in December

2014 led to faster FDA approval to use olaparib as monotherapy in gBRCAm patients after at least three prior lines by.

As reported previously Olaparib is available both as capsules and tablets. Based on the different pharmacokinetics and biovailability is not possible to change from one formulation to another on a milligram-to-milligram basis. The approved dose for oral intake of @Lynparza is 300 mg (two 150 mg tablets) twice daily, with or without food, for a total daily dose of 600 mg. If tablets formulation is not yet available, the recommended capsules dose is 400 mg (eight 50 mg capsules) twice daily [83]. The treatment should be carried on until disease progression or unacceptable toxicity [66].

2.6. Current strategies of development

The recruiting, or about to recruit, ongoing clinical trial summarized in Table 1 would answer to some fundamental still pending questions on PARPi, and consequently, on Olaparib use. First of all, since the outmost important aim is to increase the cure rate, we are looking for results of SOLO 1 trial, where Olaparib in BRCAm patients is administered after the first line chemotherapy. Secondly, while today maintenance seems to be the right way to use this compound, some ongoing trials would give us data about the best treatment sequence (chemotherapy upfront *versus* PARP-I followed by chemotherapy). Moreover, it is important to investigate efficacy and safety of the possible combinations with promising new therapies for EOC like immunotherapy and antiangiogenic agents. The first encouraging clinical data on association of Cediranib, an oral tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptor with Olaparib were reported by Liu et al. The combination arm (Olaparib 200 mg twice daily associated with Cediranib 30 mg daily) achieved longer PFS then the control arm with Olaparib monotherapy (17 months versus 9 months, p=0.005) [84]. Lastly, we do not have data on rechallenge role in Olaparib pre-treated patients.

3. NIRAPARIB

3.1. Description

Niraparib (@Zejula, TESARO Inc.), formerly known as MK-4827, is an orally active and potent PARP inhibitor. The chemical name of Niraparib is tosylate monohydrate is 2-{4-[85]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). The molecular formula is C26H30N4O5S and it has a molecular weight of 510.61 amu (Figure 3). Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1

mg/mL across the physiological pH range. Each @Zejula capsule contains 159.4 mg niraparib tosylate monohydrate equivalent to 100 mg Niraparib free base as the active ingredient [86].

3.2. Pharmacokinetics

Niraparib pharmacokinetics and first-in-humans activity was assessed in the phase I trial by Sandhu et al. [87]. 300 mg/day was established as the maximum tolerated dose.

Following a single-dose administration of 300 mg the mean (±SD) peak plasma concentration (Cmax) was 804 (± 403) ng/mL. The systemic exposures (Cmax and AUC) of Niraparib increased in a dose proportional manner, with daily doses ranging from 30 mg (0.1 times the approved recommended dosage) to 400 mg (1.3 times the approved recommended dosage).

Absorption

The absolute bioavailability of Niraparib is approximately 73%. Following oral administration of Niraparib, peak plasma concentration, Cmax, is reached within 3 hours. Concomitant administration of a high fat meal (800-1,000 calories) does not significantly affect the pharmacokinetics.

Distribution

Niraparib is 83.0% bound to human plasma proteins. The average (±SD) apparent volume of distribution (Vd/F) was 1220 (±1114) L.

Elimination

Following multiple daily doses of 300 mg Niraparib, the mean half-life (t1/2) is 36 hours. In a population pharmacokinetic analysis, the apparent total clearance (CL/F) was 16.2 L/h.

Metabolism

Niraparib is metabolized primarily by carboxilesterase (CEs) to form a major inactive metabolite, which subsequently undergoes glucuronidation.

Excretion

Following administration of a single oral 300 mg dose Niraparib, the average percent recovery of the administred dose over 21 days was 47.5% (range 33.4% to 60.2%) in urine, and 38.8% (range 28.3% to 47.0%) in feces.

3.3. Clinical activity

The activity and safety of Niraparib monotherapy 300 mg once daily was first explored in the phase I trial by Sandhu and colleagues. Dose-limiting toxic effects were grade 3 fatigue, grade 3 pneumonitis, and grade 4 thrombocytopenia. Common treatment-related toxic effects were anaemia (48%), nausea (42%), fatigue (42%), thrombocytopenia (35%), anorexia (26%), neutropenia (24%), constipation (23%), and vomiting (20%), and were predominantly grade 1 or 2. Pharmacodynamic analyses confirmed PARP inhibition exceeded 50% at doses greater than 80 mg/day and antitumour activity was documented beyond doses of 60 mg/day. Antitumor activity beyond HGSOC was also reported in non-small-cell lung cancer and prostate cancer [87]. Trial 1 (ENGOT-OV16/NOVA) was the first phase III trial designed and has studied Niraparib efficacy in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in [27]. The NOVA trial was a double-blind, placebo-controlled trial in which EOC patients (n=553) were randomized 2:1 to Niraparib 300 mg orally daily or matched placebo within 8 weeks of the last therapy. All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. Randomization was stratified by time to progression after the penultimate platinum therapy (6 to <12 months and ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no) and best response during the most recent platinum regimen (complete *versus* partial response). Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline *BRCA* mutations (gBRCAm) were assigned to the germline *BRCA* mutated (g*BRCA*mut) cohort (n=203), and those without germline *BRCA* mutations were assigned to the non-g*BRCA*mut cohort (n=350). The major efficacy outcome measure, PFS, was determined primarily by central independent assessment per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1). Results showed that PFS in the Niraparib group was significantly longer than in the placebo group in all three primary efficacy populations (P<0.001). In the g*BRCA* cohort, median PFS was 21.0 months in the Niraparib group and 5.5 months in the placebo group (HR 0.27). Moreover, Niraparib treatment resulted in significantly longer PFS in both the HRD-positive subgroup of the non-g*BRCA* cohort (median 12.9 months vs. 3.8 months) and in the overall non-g*BRCA* cohort (median 9.3 months vs. 3.9 months). Adverse reactions in the NOVA trial led to dose reduction or interruption in 69% of patients, most frequently for thrombocytopenia (41%) and anemia (20%). Analyses of patient-reported outcomes (PRO) indicated similar outcomes for those receiving Niraparib and those receiving placebo. The permanent discontinuation rate due to adverse reactions was about15%. The median exposure to Niraparib in this cohort was 250 days.

Following these results several post hoc and subgroups analyses have already been done. First of all, Matulonis and colleagues analyzed data from the NOVA trial to determine the long-term efficacy of Niraparib and its impact on subsequent therapy [88]. Results showed that Niraparib was associated with a superior estimated PFS probability at 12, 18, and 24 months, regardless of patient's *BRCA* mutation status, suggesting that patients who had received treatment with Niraparib were not resistant to subsequent therapy. Secondary, Mirza et al. presented results of a post hoc analysis of efficacy, safety, and PRO from a subset of patients in the NOVA trial who achieved a PR after their last platinum-based chemotherapy (n=272) [89]. A comparison of the PFS and Quality of life (QoL) HRs showed no difference between the overall population and patients who achieved a PR to their most recent platinum-based chemotherapy. Moreover, Dr. José Del Campo and colleagues evaluated platinum sensitivity and outcomes in patients assigned to the placebo arm in the NOVA trial [90]. Patients who experienced disease progression within 6 months after their last platinum-based regimen had received more prior lines of platinum-based therapy, as well as more lines of any chemotherapy, compared with patients whose remission lasted 6 months or longer. Among patients with germline BRCA1/2 mutation, 46% of those progressing within 6 months and 39% of those progressing at 6 months or later received 3 or more lines of platinum-based therapy, and 63% *vs* 45%, respectively, received 3 or more lines of any type of chemotherapy. Among BRCA1/2 wildtype patients, 29% of those who progressed within 6 months and 15% of those who progressed at 6 months or later received 3 or more lines of platinum-based therapy, and 43% *vs* 19%, respectively, received at least 3 lines of any chemotherapy, indicating that a substantial number of patients with platinum resistant ovarian cancer was included in the NOVA trial. Finally, more recently Mirza at the European Society of Gynecologic Oncology Meeting 2017 presented data showing how in the NOVA trial thrombocytopenia grade 3-4 correlated with patients weight (if <67kg) and myelosuppression during the prior chemotherapeutic regimen[91]. These data belong to a retrospective analysis, thus further investigations are required to better tailor Niraparib dosage in the real clinical practice setting.

3.4. Indication and dosage

Following the results of the NOVA trial [27] Niraparib (@Zeyula) received both FDA and EMA approval as maintenance treatment of adult patients with recurrent EOC, fallopian tube, or primary peritoneal cancer in a complete or partial response to platinum-based chemotherapy, regardless BRCA status and number of previous lines of treatment. The recommended dose is 300 mg once daily. Patients should start treatment within 8 weeks after their most recent platinum-containing regimen and treatment should be continued until disease progression or unacceptable toxicity [86].

3.5. Current strategies of development

Niraparib combinations with molecular-targeted agents and cytotoxic agents are under investigation and in some cases have moved to the clinical trial phase. Several clinical trials are actually ongoing both in platinum-sensitive and platinum-resistant setting, investigating the activity of Niraparib single agent as first line therapy or Niraparib in association with anti-PD1 and anti-VEGF agents (Table 2).

4. RUCAPARIB

4.1. Description

Rucaparib (@Rubraca, Clovis) also known as AG-014699 and PF-01367338 is an oral PARP-1, 2 and 3 inhibitor. Its molecular formula is C19H18FN3O and its chemical name is 8-fluoro-2-(4-((methylamino)methyl)phenyl)-4,5-dihydro -1h-azepino [5,4,3-cd]indol-6(3H)-one. The molecular mass of Rucaprib is 555.67 Daltons. As previously reported this drug differs by others PARP inhibitors because of its inhibitory activity also on other enzymes involved in homologous chromosomal recombination called tankyrases [63]. The chemical structure of Rucaparib is reported on Figure 4 [92].

4.2. Pharmacokinetics

The pharmacokinetics, safety and activity of oral Rucaparib were evaluated in 56 patients, primarily affected by breast or ovarian cancer, enrolled by Kristelet et al in a phase I/II trial (Study 1) [93].

Absorption The median time to reach maximum concentration (Cmax) is 1.9 hours at the approved dosage. The mean absolute bioavailability of Rucaparib immediate-release tablet is 36% with a range from 30% to 45%. Following a high-fat meal, the Cmax increases by 20%, and the time to reach C max is prolonged by 2.5 hours [92] [94].

Distribution The protein binding of Rucaparib observed in vitro was 70% in human plasma at therapeutic concentrations. Rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.83.

Elimination The mean terminal half-life after a single oral dose of Rucaparib ranges from 17 to 19 hours. The apparent clearance ranges from 15.3 to 79.2 L/hour with 600 mg Rucaparib twice daily.

Metabolism Rucaparib is metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4.

Excretion Rucaparib is excreted mainly through the faeces, accounting for >= 79% of the total dose.

4.3. Clinical activity

The efficacy of Rucaparib in monotherapy for the treatment of EOC was first assessed in two multicentre single arm trial, the phase I/II study, named Study 1 (NCT01482715) and the phase II trial Study 2 (ARIEL2). In the first part of study 1, as previously reported, 56 patients were enrolled and the 35,7% of them was affected by platinum sensitive or platinum resistant ovarian cancer. One patient with platinum sensitive EOC achieved a complete response and two patients with a platinum resistant EOC obtained a partial remission. No grade 4 adverse events were observed. The most common drug-related toxicities reported were fatigue, gastrointestinal disorders, myelotoxicity, hyporexia, and elevation of transaminase levels. In the second part of the trial authors evaluated the activity of Rucaparib in 42 patients with platinum sensitive ovarian cancer with BRCA1/2 germline mutations. This population reported an objective response rate of 59.5% and a median duration of response of 7.8 months (range 5.6-10.5) [93] [95].

In the first part of the phase II ARIEL 2 trial 204 patients with recurrent platinum sensitive EOC were enrolled and classified in three subgroups on the basis of HRD status (BRCA mutated (n=40), LOH high (n=82), LOH low (n=70). All patients were treated with 600 mg of oral Rucaparib twice daily. A median PFS of 12.8, 5.7 and 5.2 months was observed respectively in the three subgroups. The difference observed between patients harboring BRCA mutation or with LOH high was significantly greater than in the low LOH group. The most common grade 3 or worse toxicities observed were anemia and transaminase increase [26]. The second part of ARIEL 2 trial is still ongoing; 286 patients who have received at least 3 lines of chemotherapy with both platinum sensitive or platinum resistant disease have been enrolled to evaluate clinical activity of Rucaparib in this different setting based on HRD status. In another phase II trial Drew et al investigated intermittent and continuous schedules of intravenous or oral Rucaparib in 78 patients with advanced breast or ovarian cancer harbouring BRCA1/2 mutations. The ORR for oral Rucaparib (across all dose levels) was 15%. 12 out of 13 patients treated with continuous oral Rucaparib obtained a CR/PR or SD for more than12 weeks, with a median duration of response of 179 days. The intermittent intravenous Rucaparib resulted in an ORR of only 2%. However, 41% of patients achieved SD for longer than 12 weeks, with 3 patients maintaining disease stabilisation for more

than 52 weeks. All the 51 patients with ovarian cancer enrolled in this study have been previously treated with a platinum-based chemotherapy; authors observed a correlation between response rate to Rucaparib and PFI. No response was reported among breast cancer patients. The half-life of Rucaparib after oral dosing reported in this study was 9.1±2.7hours. The most common reported adverse events were fatigue and nausea [96].

The results of the phase III trial ARIEL 3 have been recently published. In this randomized, double-blind, study 564 patients with platinum sensitive EOC in response after their last platinum-based chemotherapy were treated with Rucaparib 600 mg twice daily or placebo. Authors reported a prolonged PFS in patients assigned to the experimental arm. For BRCA mutated patients median PFS was respectively of 16.6 months in the Rucaparib arm *versus* 5.4 months in the placebo group. A significant increase in PFS was also observed in patients without BRCA mutation, PFS reported for patients with a HRD carcinoma treated with Rucaparib was 13. 6 months vs 5.4 for the placebo group while in the intention to treat population was 10.8 versus 5.4 months. Grade 3-4 adverse events were more frequent in the experimental arm (56% vs 15%) and the most common were anaemia and transaminase elevation [44].

4.4. Indication and dosage

Rucaparib have been approved by the FDA as a single agent for the treatment of patients affected by relapsed ovarian cancer with germline or somatic BRCA mutations who have been treated with two or more lines of chemotherapy. The recommended phase II dose of single-agent oral Rucaparib is 600mg twice daily [93]. Based on the results of ARIEL 3 trial, Clovis Oncology have recently submitted a supplemental New Drug Application (sNDA) for a second-line and later maintenance treatment indication for patients with recurrent platinum-sensitive EOC in response to their most recent platinum therapy

4.5. Current strategies of development

Rucaparib is actually the only PARP inhibitor approved in monotherapy regardless of platinum sensitivity, following the publication of the results of Study 1 and ARIEL 2 demonstrating the efficacy in monotherapy in patients with recurrent BRCA mutated EOC. Considering the fewer available options of treatment for patients with platinum resistant disease NCCN guidelines recommends Rucaparib single agent also in this setting in presence of BRCA mutations [97]. As previously reported it is feasible that early Rucaparib will also be approved as maintenance therapy in patients with platinum sensitive relapsed EOC in response to their last platinum-based

chemotherapy. Several trials investigating the activity of Rucaparib, both as a single agent and after platinum based chemotherapy for treatment of ovarian cancer, are ongoing. A phase I study evaluating the association of Rucaparib and the anti-PD-L1 Atezolizumab is actually recruiting patients. The others ongoing clinical trials are summarized in Table 3.

5. TALAZOPARIB

5.1. Description

Talazoparib (also known as MDV3800 and BMN 673) is a selective inhibitor of PARP1 and2. The molecular formula of Talazoparib is C19H14F2N6O and its chemical name is (8S,9R)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one. The molecular weight is 380.359 g/mol. The chemical structure of Talazoparib is shown in Figure5.

5.2. Pharmacokinetics

The antitumor activity and pharmacokinetics of Talazoparib was evaluated for the first time by De Bono et al in a 2-stage dose-escalation trial [98]. In the first part of this study 39 patients with BRCA mutated tumors were enrolled in 9 cohorts from 25 to 1100 µg/d. The maximum tolerated dose was defined at 1000 µg/d. An inhibitory activity against PARP was reported at doses ≥ 100 µg/day in PBMCs. Steady state plasma concentrations were reached by the end of the second week of daily dosing; the maximum plasma concentration was reached within 2 hours after all evaluated doses .

Absorption

In a subsequent dose-escalation phase I study [99] conducted in patients with BRCA 1 or 2 mutations Talazoparib has shown to have a rapid absorption. The maximum plasma concentration (Cmax) was reached within 2 hours after all evaluated doses.

Distribution

Talazoparib has demonstrated to be well distributed into tissues, and its volume of distribution seems to be in excess of the volume of the systemic circulatory space.

Elimination

The half-life observed at the MTD dose of 1.0 mg/day was nearly 48 hours.

Excretion

Results for urinary elimination of the parent compound suggest linear urinary elimination kinetics after daily Talazoparib dosing between the 0.025 and 1.1 mg dose levels

5.3. Clinical activity

The evaluation of Talazoparib activity in the treatment of ovarian cancer is still at an early stage. In 2016 Dhawan et al. presented the results of a phase I/II trial evaluating Talazoparib in combination with carboplatin in patients with solid tumors with or without germline mutations. Among the 24 patients enrolled, 2 patients (8%) were affected by EOC and 20% were BRCA1/2 mutant cases. Other grade 3/4 toxicities reported were fatigue (13%), neutropenia (63%), thrombocytopenia (29%), and anemia (38%). A deeper decrease of the neutrophil count was observed in patients with germline BRCA mutations. Authors reported 1 CR and 2 PR among BRCA mutated patients. Four patients maintained a stable disease beyond 4 months; 3 of them had a somatic BRCA mutation and the fourth had a BRIP germline [100].

De Bono et al investigated the safety pharmacokinetics and activity of Talazoparib in a phase I/II dose-escalation trial enrolling patients with germline BRCA1 or 2 mutated tumors or selected patients with sporadic cancers. A sustained PARP inhibition was observed at doses ≥0.60 mg/day. The most common possibly related adverse event observed were fatigue; nausea; anemia; neutropenia; thrombocytopenia and grade 1 alopecia. A dose-limiting thrombocytopenia was observed respectively in 1/6 and 2/5 patients at 900 and 1100 μg/d. In this trial 34 EOC patients were enrolled, 25 of them with germline BRCA mutated, all previously treated with platinum based chemotherapy were enrolled, 12 of them with measureable disease. Among them 42% had an objective response rate and 67% add a clinical benefit rate with a median PFS of 36.4 weeks [99].

Results from phase II or III in patients with EOC are not available. However regarding patients with BRCA mutations encouraging signs about the efficacy of Talazoparib came from a phase II study conducted in patients with BRCA positive breast cancer (ABRAZO) in which an ORR of 24% and 34% respectively was reported for BRCA 1 and BRCA 2 mutations carriers [101].

5.4. Current strategies of development

Evidences supporting the use of Talazoparib in the treatment of EOC are few in comparison with other PARPis. However some studies evaluating the activity of Talazoparib in ovarian carcinoma are ongoing (Table 4), including a phase 1 study in association with a checkpoint inhibitor and a

phase II study exploring Talazoparib activity in advanced cancers with BRCA1/2 germline or somatic alterations, PTEN mutations or PTEN loss and HRD defect.

6. VELIPARIB

6.1. Description

Veliparib, also called ABT-888, is a poly(ADP-ribose) polymerase (PARP) -1 and -2 inhibitor with chemosensitizing and antitumor activities. Veliparib has no antiproliferative effects as a single agent. The molecular formula of Veliparib is C13H16N4O and its IUPAC name is 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide. The chemical structure of Veliparib is reported in Figure 6.

6.2. Pharmacokinetics

The pharmacokinetics of Veliparib was assessed by Kummar et al in phase 0 trial. They observed that the absorption peak occurs after 0.5–1.5 hours with a single dose of 50 mg [102]. In a phase I trial presented by Puhalla et al in 2014 the half-life of Veliparib was assessed at 5.2 hours [103].

Absorption

Veliparib demonstrated to have a good oral bioavailability, and a peak absorption between 0.5 and 1.5 hours, with a C max of 0.45 µM after a single dose of 50 mg.

Distribution

Significant inhibition of PARP levels in both tumor tissue and peripheral blood mononuclear cells was observed 3–6 hours after administration

Metabolism and Excretion

Veliparib is excreted previously in the urine; however, in a lower percentage (nearly 13%) Veliparib undergoes hepatic metabolism by the activity of cytochrome CYP2D6.

6.3. Clinical activity

In 2014 Puhalla et al. presented the results of a phase I trial aimed at assessing maximum tolerated dose, dose-limiting toxicities, pharmacokinetic and pharmacodynamic properties, and preliminary efficacy of Veliparib. Eighty-eight patients, mainly affected by ovarian or breast cancer, were enrolled; 60 were BRCA positive and 28 BRCA wild type. The recommended phase 2 dose was 400 mg BID. The most common toxicities reported were nausea, fatigue, and lymphopenia. The half-life was established at 5.2 hours. BRCA mutated patients had an ORR of 23% and a clinical benefit rate (CBR; CR + PR + stable disease) of 58% across all dose levels. Among BRCA-wild type patients the ORR was 4% with a CBR of 38%. Coleman et al. evaluated the activity of Veliparib in a phase II trial in 52 BRCA mutated patients with persistent or recurrent ovarian cancer. Sixty percent of patients was platinum resistant. Veliparib was administered at 400 mg orally twice a day. No drug related deaths were reported. The most common toxicities observed were mielotoxicity and gastrointestinal toxicity. Authors reported a median PFS of 8.11 months (ranging from 0.43 to 19.55 months) and a median OS of 19.7 months (ranging from 2.3 to 19.7 months) [104].

Recently, the results of a phase I/II trial have been published exploring the role of Veliparib monotherapy in patients with germline BRCA mutations platinum sensitive or resistant ovarian cancer. Sixteen patients were enrolled in the phase I study, and 32 in the second part of the study. The maximum tolerated dose was established at 300 mg twice daily. Median PFS and OS for the intention to treat population were respectively 5.6 and 13.7 months. The most common toxicities observed were fatigue, nausea and vomiting [105]. In another phase I study Nishio et al evaluated the safety, tolerability, pharmacokinetics and efficacy of Veliparib (100 or 150 twice a day) in association with Carboplatin and weekly Paclitaxel in 9 Japanese patients with newly diagnosed EOC. The most frequent toxicities were neutropenia, alopecia, neurotoxicity, anemia and nausea. Authors reported an ORR of 100% in the 5 patients evaluated (the other 4 had no measurable lesions). After this study the dose of Veliparib in association with Carboplatin and Paclitaxel was established at 150 mg twice a day [106].

The safety of this PARP inhibitor was also assessed in association with chemotherapy (PLD, Carboplatin and Bevacizumab) in a phase I trial enrolling patients with platinum sensitive ovarian cancer. DLTs reported in the dose escalation part included grade 4 thrombocytopenia and prolonged neutropenia. With the addiction of bevacizumab, a DLT was observed in 9 out of 12 patients and these included grade 4 thrombocytopenia, prolonged neutropenia, hypertension and sepsis. The maximum tolerated dose of Veliparib in association with carboplatin was established at 80 mg twice a day [107]. Kummar et al conducted a phase II study comparing low dose Cyclophosphamide

alone or in association with Veliparib in patients with ovarian cancer. Seventy two patients were enrolled; no differences were reported for the two arms of treatment in terms of response rate [108].

In a phase I trial Reiss et al. evaluated the activity of Veliparib combined with low-dose fractionated whole abdominal radiation therapy in 32 patients with carcinomatosis due to advanced solid tumors. Eighteen patients were affected by EOC, 5 of them were BRCA mutations carriers. One objective response was observed, and stable disease was reported in 33% of patients. Patients with BRCA mutated EOC had a PFS of 4.47 months compared to PFS 3.58 months in the non-BRCA carriers and an OS of 10.15 months compared to 7.89 months in non-BRCA carriers. Patients whit platinum-sensitive disease had a PFS of 7.92 months compared to 3.58 months in platinum-resistant EOC. The most frequently observed toxicity was myelosuppression [109].

6.4. Current strategies of development

As discussed above, Veliparib alone has no anti-proliferative effect. However, there are several preclinical and clinical evidences of its activity as sensitizing agents for DNA-damaging treatments, such as chemotherapy and radiotherapy. As previously reported for Talazoparib, evidences supporting the use of Veliparib in the treatment of EOC are fewer compared to those for other PARP inhibitors, however several studies are ongoing, both with Veliparib as a single agent and in association with chemotherapy, including a phase III trial evaluating Veliparib as first line treatment in association with carboplatin and paclitaxel (Table 5). This randomized study includes three treatment arms: one with chemotherapy only, the second with chemotherapy followed by Veliparib in maintenance and the third with Veliparib associated with chemotherapy followed by Veliparib as a maintenance. Considering as primary outcome PFS, an enrolment of 1100 patients is estimated. There is also a phase II trial evaluating Veliparib as a single agent for the treatment of relapsed EOC (Table 5). Fifty-one patients are expected to be enrolled in this trial, patients with both platinum sensitive and platinum resistant disease are eligible but they must have a germline BRCA1/2 mutation.

7. CURRENT AND FUTURE DEVELOPMENTS

The development of PARPis is certainly the most important breakthrough in the treatment of ovarian cancer. Both FDA and EMA have already changed clinical practice after Olaparib and Niraparib approvals, but several questions regarding their use, strongly connected each other, still need an answer.

1) Which is the optimal clinical setting?
2) How can we choose among different PARPis?
3) How can we better identify HRD patients?
4) How much do we know about resistance to PARPis?
5) Is it better to use PARPis alone or in association with other agents?

1) Even thought the activity of PARPis as maintenance therapy has been demonstrated [25] [27] [44] ongoing trials are seeking to clarify the ideal time for these agents to be used in the course of ovarian cancer. Results from SOLO-1, ARIEL-4, PRIMA and QUADRA trials will help to answer this question (for the details see Table 1, 2 and 3). The first three trials aim to demonstrate that an early maintenance with PARPis after the frontline treatment could improve the outcome, while QUADRA trial is investigating chemotherapy free-regimen in heavily pretreated patients. Indeed, even if Olaparib activity has already been investigated in the above mentioned setting by Kaufman et al. [80], only FDA has recognized this indication. Moreover, as reported above, during the poster session of ESMO 2017 Congress, Olaparib superiority in SOLO-2 study is reported also in heavily pre-treated patients, with no difference of efficacy regarding number of prior lines of platinum-based therapy received [78]. Further data, regardless the BRCA status, are looked-for in Europe, in order to potentially extend the use of PARPis, first of all Niraparib, in poor setting as platinum resistant disease. Moreover Olaparib is currently under investigation in the neoadjuvant setting in the NEO trial.

2) At first relapse, BRCA mutated platinum sensitive recurrence ovarian cancer should go for secondary cytoreductive surgery, if a complete resection is expected [110]. If patients are not eligible for surgery, they should receive a platinum doublet followed by maintenance therapy, either with Bevacizumab, or with any PARPis, in case of CR or PR. However the difference in terms of PFS is strongly in favor of PARPis. On the contrary, in BRCA WT, PFS results from Bevacizumab and Niraparib (the only PARPi for relapsed BRCA WT patients) are similar, and therefore, the choice should be based on toxicities and disease characteristics. For example Bevacizumab seems more active, in patients with bulky disease, ascites and high Ca125 [111], but it may lead to hemorrhage and thrombosis more frequently than Niraparib. Beyond their activity, each PARPi shows different toxicities that can drive clinical choices, particularly in a maintenance setting. Nausea and fatigue were the most common side effects, reported in about 50% of patients with 10% of G3 or G4 regardless of the type of PARPi [112]. Instead, 3% of patients treated with Olaparib reported G3-G4 abdominal pain, while 8% of patients treated with Niraparib developed severe

hypertension [113]. The percentage of hematologic adverse events varied depending on which PARPis were used. Indeed, while anemia is common in patients treated with Olaparib, Niraparib and Rucaparib, neutropenia and thrombocytopenia are typical side effect of Niraparib (with rate of 20% and 33% respectively), while Rucaparib is characterized by 10% of asymptomatic increase of AST and ALT that normalizes over time [25] [27] [44]. Niraparib required a dose reduction in 66% of patients, while Olaparib in 54% and Rucaparib in 25% of patients nevertheless adverse events apparently do not affect quality of life neither in SOLO 2 nor in NOVA trial [114]. Thanks to these data, we can actually choose the best PARPi for each patient, considering residual toxicities, disease burden and BRCA status. Beside acute toxicities, potential long term toxicities are not clear and need careful surveillance. Preclinical model suggests a role of PARP-1 in cardiovascular diseases and long-term memory formation [112]. but, above all, an increased risk of MDS /AML was reported in patients treated with PARPis. It could be related to the high genomic instability of HRD patients (above all BRCA mutated patients) for whom further drugs induce DNA damage could raise this risk [112]. Currently, only few data are available on long-term exposure to Olaparib, that reported no warning on long-term toxicities [76], but further information, especially on Rucaparib and Niraparib, is needed. Moreover, we have no long term benefit predictors to PARPis, although an observational and sample collection study (A Study of Long-Term Responders on Olaparib, OLALA NCT02489058) is trying to identify them.

3) Even though germline BRCA mutations are the best predictors of PARPis activity in EOC, their efficacy has been observed also in patients without this alteration. Niraparib and Rucaparib have proved their activity also in HRD positive [27] [44], but different test to examine HRD status were used, as summarized in the introduction. While testing for BRCA mutations have already been incorporated into everyday clinical practice, a well recognized test to identify BRCAness phenotype due to a homologous recombination impairment does not exist yet [115]. Numerous patents have been registered regarding new methods trying to determinate HRD status (WO 2016138574 A1)[116], DNA sequences defects (WO 2017008912 A1)[117] or LOH (9388472)[118].

In the near future, the systematic evaluation of RAD51, γH2AX and Fanconi family of genes foci together with genomic instability might help to identify patient populations who can be classified as responders or non-responders to PARPis (for discussion of resistance mechanism see point 4 below)[119]. Early data in breast cancer have demonstrated a correlation between cytoplasmic PARP expression, detected by immunohistochemistry, a procedure sustainable and reproducible also in peripheral hospital, and high sensitivity to treatment [120]. Identification of responders is useful to optimize cost-benefit rate. Waiting for the genome profiling, actually the only parameters

significantly associated with PARPis response, except BRCA status, is PFI, firstly identified by Fong in 2010 [69] and confirmed in a Cochrane's review including nearly 600 patients [121].

4) It is well known that even if a patient is BRCA mutant, after a long-term exposure to PARPis, develops drug resistance through different mechanisms [122] . The first mechanism studied has been the recovery of HRR ability, through secondary mutations restoring BRCA activity, as demonstrated by Norquist in a group of 46 recurred EOC. This retrospective analysis showed mutations were higher in platinum-resistant patients than in the sensitive ones (46% *versus* 5%, p=0.003) [123]. Dhillon proposed the restoration of BRCA activity begins from BRCA-deficient and chemosensitive cells as a consequence of numerous mutations induced by platinum agents. This initial restored clone will expand during drug exposure-related selective pressure [124]. A recent patent by Yen et al. (US20170035737)[125] proposed a new method by administering COH29 and a DNA-damaging agent in a combined synergistic amount. In ARIEL 2 trial PARPis resistance seems to be related with secondary mutation of RAD51, one of the gene causing HRD when defective. If secondary mutations occur in RAD51C and RAD51D and their activity is recovered PARPis resistance arises [126]. Rottenberg and colleagues demonstrated in an *in vivo* model a possible resistance mechanism due to an increased expression of P-Glycoprotein (multi-drug resistance protein), a drug efflux pump responsible of a decrease intracellular drug concentration [127]. In 2015 Patch performed whole genome sequencing of nearly 100 ovarian cancers and reported various other acquired resistance mechanisms such as loss of BRCA1 promoter methylation and ABCB1 rearrangement, but their clinical impact are already unknown [128].

5) As already described several PARPis associations with molecular-targeted agents, standard cytotoxic agents and/or immunotherapy are currently under investigation and in some cases have already moved to the clinical trial phase (for complete list of ongoing trials see the above tables). While Olaparib and Niraparib have been approved as single-agents maintenance therapy, Veliparib seems to be the best candidate for chemotherapy-associations due to its toxicity profile. Several patents have recently been published exploring PARPIs combinationations with chemotherapy, immune-agents, TKIs or small nucleic acid molecule (e.i patents n. WO/2017/029517A1, US20170035737, US20170049767, WO/2017/151554A1, US20170100368, WO 2016209935 A1, US20170049767, 9707302, WO/2017/151554A1, WO/2017/013237A1, WO/2017/029517A1)[125, 129-131]. Interestingly, Blanchette et al. registered the combination between PARPI, a topoisomerase-1 inhibition and irinotecan (WO/2017/031442A1)[132]; the topoisomerase-1 inhibitor can be delivered as a liposomal formulation resulting in an increased efficacy of the PARP inhibitor and reduced toxicity of the irinotecan.

Moreover, a phase I study of Veliparib + whole abdomen radiotherapy has already shown efficacy with a 33% rate of stable disease [109] suggesting its potential role also as chemo-sensitizer. On the other hand, no definitive data sustain a potential role of RT in increasing systemic PARPis response (the well-known abscopal effect) [133] [134]. A robust rationale exists instead on the association of PARPis with immunotherapy. BRCA mutant patients show a higher mutational load and number of neoantigens than BRCA WT, which reflects in an increased recruitment of tumor infiltrating lymphocytes (TILs) and potential response to checkpoints inhibitors[135] [136] [137]. In this field, Lambrechts et al. registered a patent (WO 2013153130 A1) [138]to detect mismatch repair (MMR) deficient tumors and exploring the synergism between PARPIs and MMR.

There is also strong pre-clinical evidence that support combination with anti-angiogenic agents. In fact the inhibition of VEGF induces chronic hypoxia leading to down-regulation of DNA repair mechanisms and creating an artificial HRD status which increase sensitivity to PARPis [84] [139]. AVANOVA, OCTOVA and CONCERTO are three examples of active trials exploring this setting.

For an exhaustive update on patents exploring PARPIs in ovarian cancer see Table 6.

Finally, a good opportunity to study new drugs and combinations as soon as they are developed is to create common bio-banks of tumor tissues as established in phase II ENGOT (NCT03267589) a cooperative innovative trial.

8. CONCLUSION

PARP inhibition has already proved to be an outstanding strategy for improving PFS in ovarian cancer, although a longer follow-up is needed to assess also OS benefit. The development of new combinations through clinical trials and new patents will provide a better understanding of PARPIs mechanisms of action and hopefully reflects in better clinical benefit for patients.

Ethics Approval and Consent to Participate

Not applicable.

Human and Animal Rights

No Animals/Humans were used for studies that are base of this research.

Consent for Publication

Not applicable.

Conflict of Interest

All authors have no conflict of interest to declare.

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Figure 1. Principal mechanisms of action of PARPIs

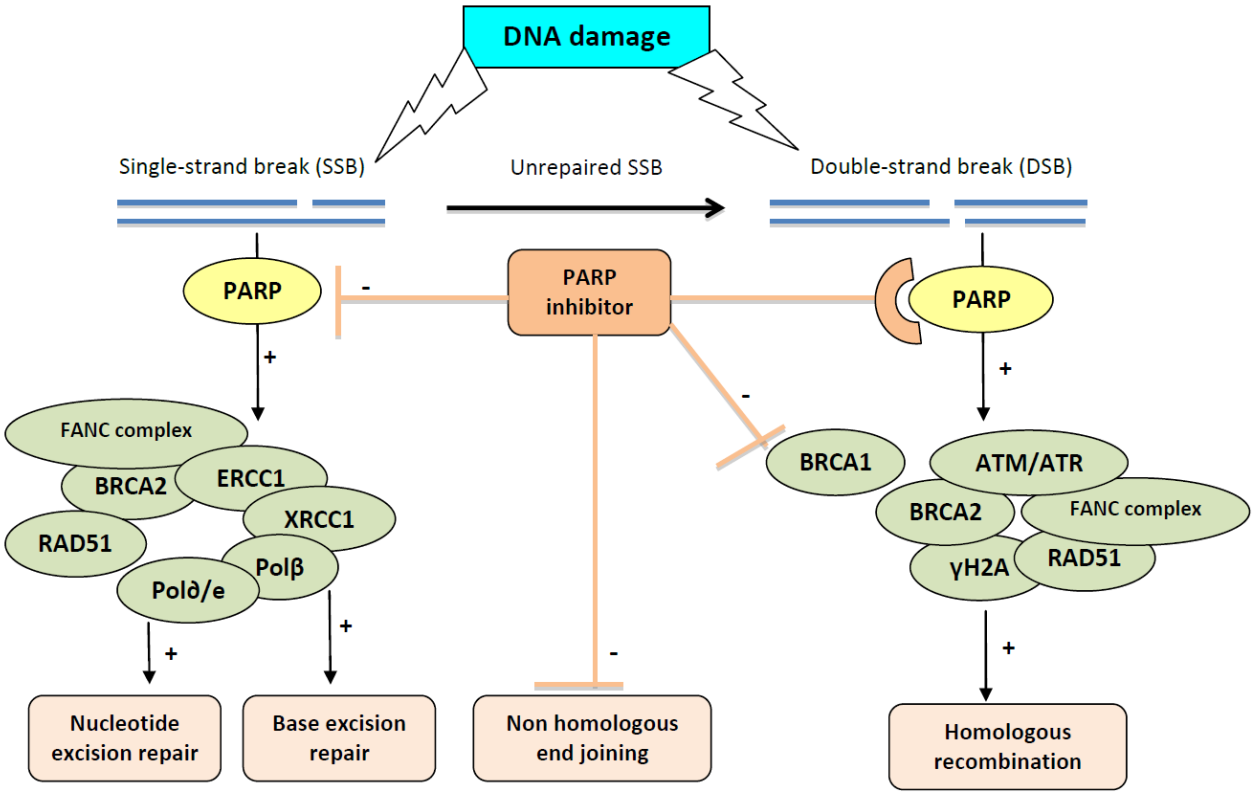

Figure 2. Olaparib chemical structure

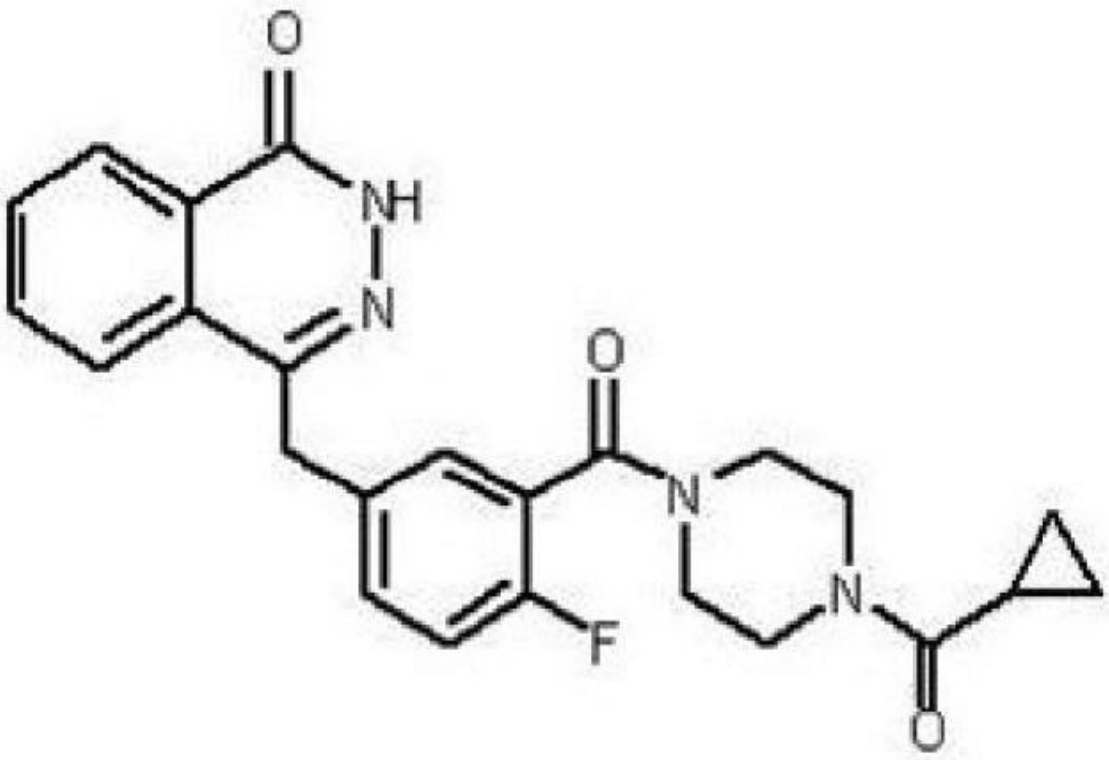

Figure 3. Niraparib chemical structure

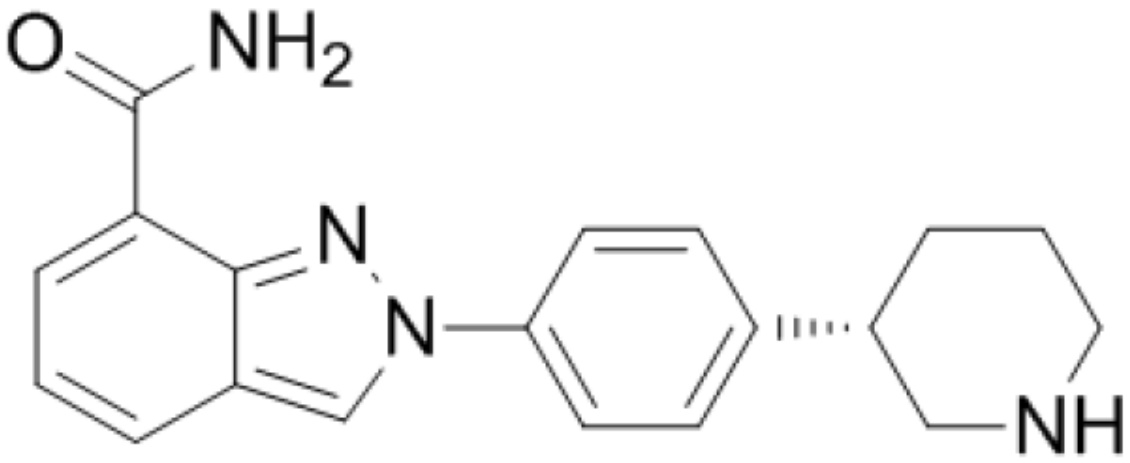

Figure 4. Rucaparib chemical structure

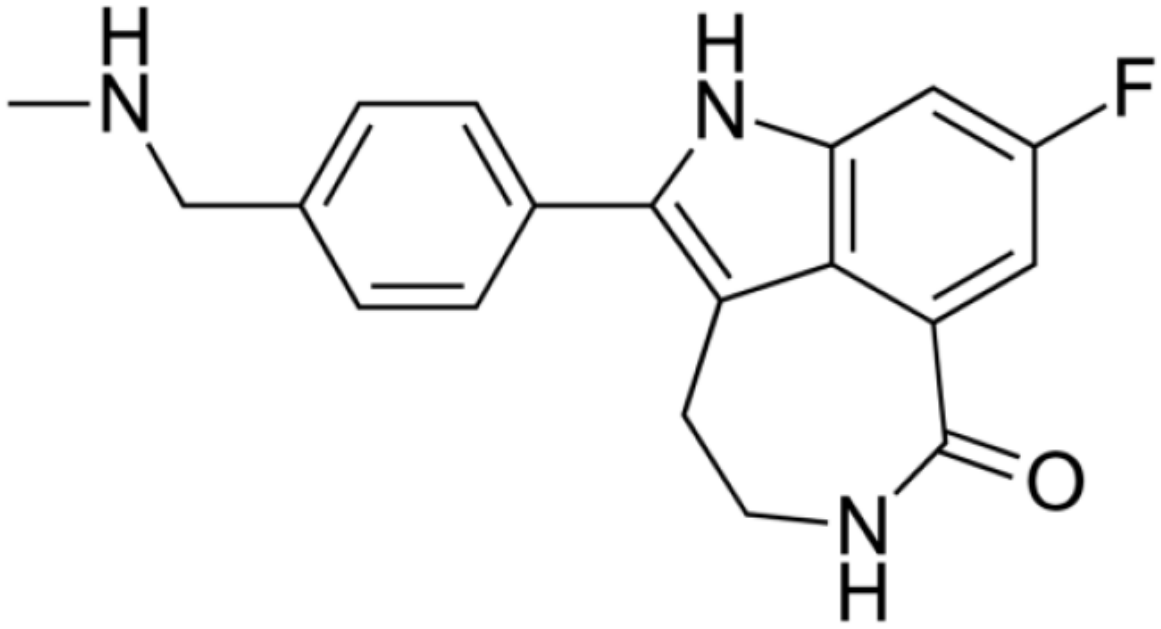

Figure 5. Talazoparib chemical structure

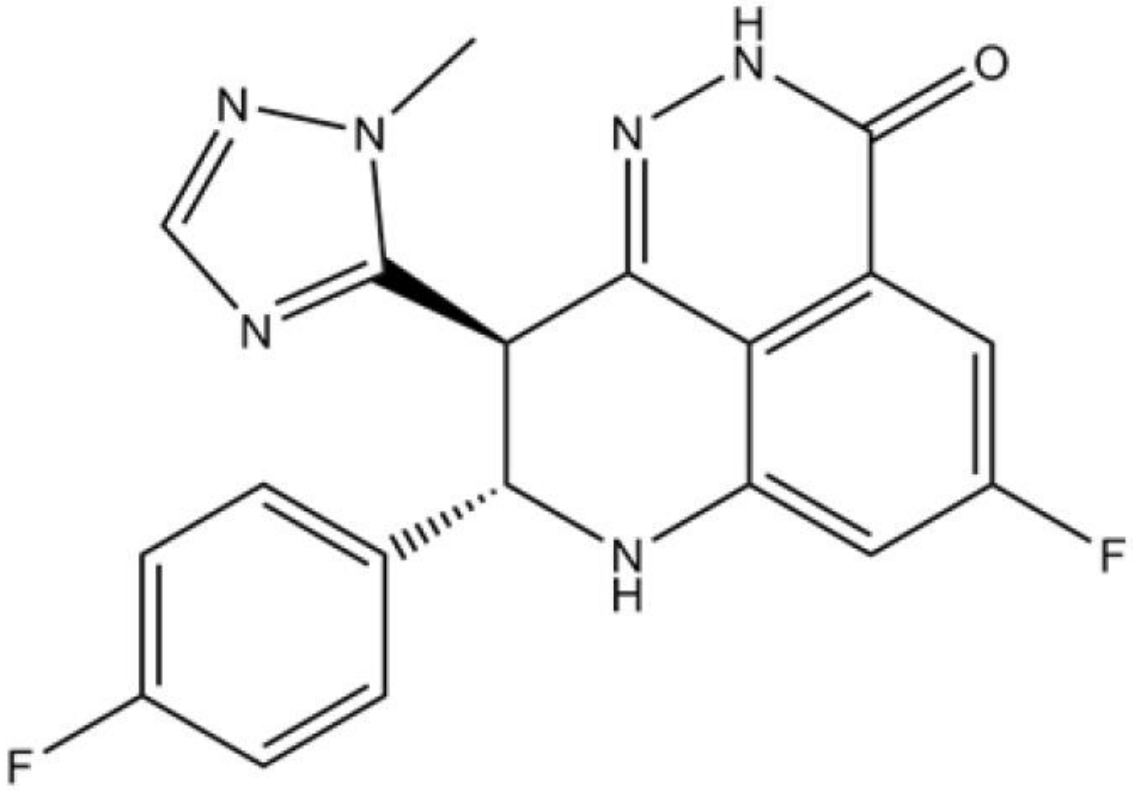

Figure 6. Veliparib chemical structure

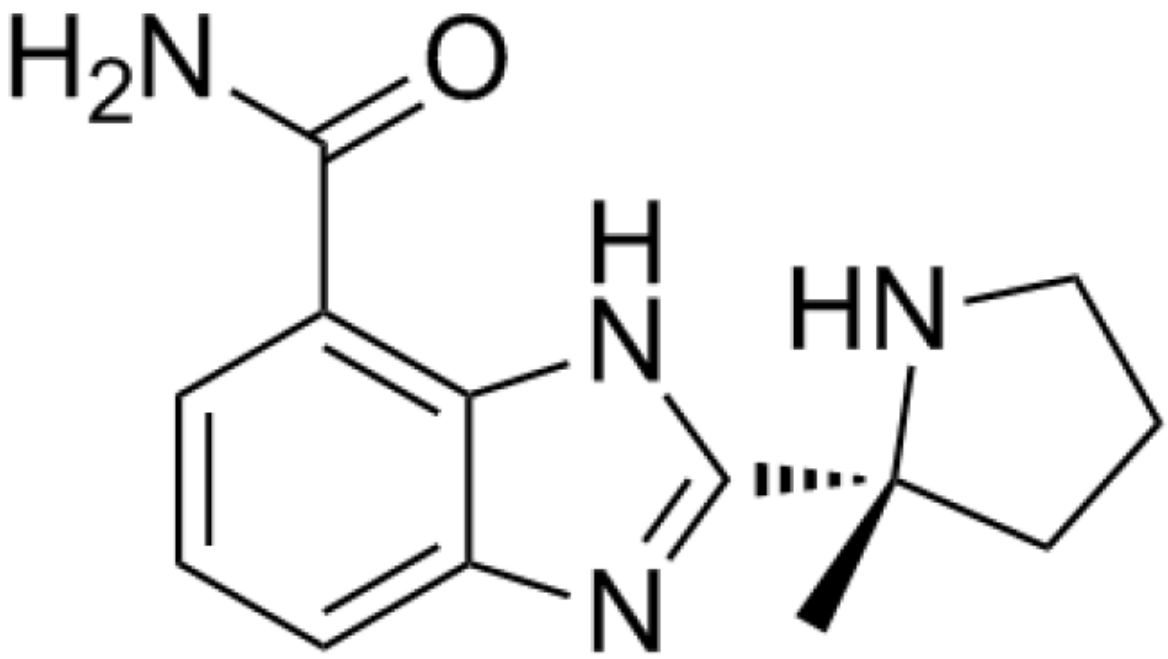

Table 1. Ongoing clinical trials involving Olaparib in EOC.

	Setting	Line of therapy	Phase	Status	Trial identifier
Olaparib	Newly diagnosed BRCAm	1L	3	Not yet recruiting	NCT01844986
Olaparib	Neoadjuvant	1L	2	Recruiting	NCT02489006
Olaparib+Bevacizumab	gBRCAm manteinance	1L	3	Recruiting	NCT02477644
Olaparib versus single agent chemotherapy	Platinum-sensitive gBRCAm	≥3	3	Recruiting	NCT02282020
Olaparib versus chemotherapy	Platinum-sensitive and resistant regardless BRCA status	≥2	2	Recruiting	NCT02822157
Olaparib+Cediranib	Relapsed after Olaparib treatment	≥2	2	Not yet recruiting	NCT02340611
Olaparib	Platinum-sensitive HRD positive	≥2	2	Recruiting	NCT02983799
Olaparib	EOC pretreated with Olaparib responding to platinum compound	≥2	3	Recruiting	NCT03106987
Olaparib+Cediranib	Platinum-sensitive and resistant relapsed after PARPi	≥2	2	Recruiting	NCT02681237
Olaparib+Cediranib after chemotherapy	Platinum-sensitive relapsed BRCAm pretreated with Olaparib	≥2	1	Recruiting	NCT02855697
Olaparib+Cediranib	Platinum-sensitive	≥2	3	Recruiting	NCT02446600

	BRCAm				
Olaparib+Cediranib	Platinum resistant BRCA WT	≥3	2	Recruiting	NCT02889900
Olaparib+Cediranib versus Paclitaxel	Platinum resistant/refractory	≥2	2	Recruiting	NCT03314740
Olaparib±Cediranib versus Paclitaxel	Platinum resistant BRCAm	≥2	2	Recruiting	NCT03117933
Olaparib±Cediranib	Maintenance after platinum response	2	3	Not yet Recruiting	NCT03278717
Olaparib and/or cediranib+anti-PD1	Platinum-sensitive or resistant	≥3	1/2	Recruiting	NCT02484404
Olaparib+tremelimumab	Platinum-sensitive or resistant BRCAm	≥2	1/2	Recruiting	NCT02571725
Olaparib+Tremelimumab+Durvalumab	Platinum-sensitive or resistant BRCAm	≤3	1/2	Recruiting	NCT02953457
Olaparib+PLD	Platinum resistant	≥2	2	Not yet recruiting	NCT03161132
Olaparib+PM01183	Platinum resistant	≥2	1/2	Recruiting	NCT02684318
Olaparib	Maintenance BRCAm/HRD+	2	4	Recruiting	NCT02476968
Olaparib+Onalespib	Platinum resistant	≥3	1	Recruiting	NCT02898207
Olaparib+AZD1775	Platinum resistant	≥3	1b	Recruiting	NCT02511975

Table 2. Ongoing clinical trials involving Niraparib in EOC

Combination	Setting	Line of therapy	Phase	Status	Trial identifier
Niraparib	Platinum-sensitive	1L	3	recruiting	NCT02655016
Niraparib	Platinum-resistant	>3L	2	recruiting	NCT02354586
Niraparib + Bevacizumab	Platinum-sensitive	>1L	2	recruiting	NCT02354131
Niraparib + Bevacizumab	Platinum-sensitive	1L maintenance	2	recruiting	NCT03326193
Niraparib + Pembrolizumab	Platinum-resistant	>2L	1-2	recruiting	NCT02657889
Niraparib + Everolimus	Platinum-sensitive and resistant	>1L	1	not yet recruiting	NCT03154281

Table 3 Ongoing clinical trials involving Rucaparib in EOC.

Combination	Setting	Line of therapy	Phase	Status	Trial identifier
Rucaparib	Platinum sensitive	>1	2	Ongoing not recruiting	NCT01891344
Rucaparib + Atetolizumab	Gynaecological neoplasms/Breast cancer	>1	1	Recruiting	NCT03101280
Rucaparib vs chemotherapy	Platinum sensitive/resistant	≥3	3	Recruiting	NCT02855944
Rucaparib	Ovarian cancer/other BRCA mutated tumors	≤4	1/2	Ongoing not recruiting	NCT01482715

Table 4. Ongoing clinical trials involving Talazoparib in EOC.

Combination	Setting	Line of therapy	Phase	Status	Trial identifier
Talazoparib	Neoadjuvant	1	1	Ongoing not recruiting	NCT02316834
Talazoparib + avelumab	Platinum sensitive EOC/other tumors	≥1	1/2	Recruiting	NCT03330405
Talazoparib	Platinum sensitive or platinum naive EOC/other tumors	≥1	1	Recruiting	NCT01989546
Talazoparib	Progression after another PARPis	≥1	2	Completed	
Talazoparib	EOC/other tumors	any	2	Ongoing not recruiting	NCT02286687

Table 5. Ongoing clinical trials involving Veliparib in EOC

Combination	Setting	Line of therapy	Phase	Status	Trial identifier
Veliparib + topotecan	Platinum resistant/partially resistant EOC	>1	1/2	Completed	NCT01690598
Veliparib + topotecan	Solid tumors/relapsed EOC	<4	1/2	Recruiting	NCT01012817
Veliparib+ Carboplatin + Paclitaxel	Newly diagnosed EOC	1	3	Ongoing not recruiting	NCT02470585
Veliparib	Recurrent EOC	>1	2	Ongoing not ecruiting	NCT01540565
Veliparib + Fluxuridine		>5	1	Recruiting	NCT01749397
Veliparib + PLD	Recurent ovarian/breast cancer	<2 pl based	1	Ongoing not recruiting	NCT01145430
Veliparib+ Carboplatin + Paclitaxel + Bevacizumab	Newly diagnosed EOC	1	1	Ongoing not recruiting	NCT00989651

Table 6. Recent patents exploring PARPIs in ovarian cancer.

Patent ID	Patent Title	Short Description	Date of registration	Reference number
WO 2013153130 A1	Novel markers for detecting microsatellite instability in cancer and determining synthetic lethality with inhibition of the DNA base excision repair pathway	New markers to detect Mismatch Repair (MMR) deficient tumors. Innovative treatment for MMR-deficient tumors based on the synthetic lethal interaction between MMR and PARP.	10 Apr 2013	[138]
WO/2016/018089A1	Novel biomarker for predicting sensitivity to parp Inhibitor, and use thereof	A novel biomarker to predict response to PARPis	9 Aug 2013	[140]
US20150290185 (EP2918292A1)	Polymeric Compound Having Camptothecin Compound And Anti-Cancer Effect Enhancer Bound Thereto, And Use of Same	A polymeric camptothecin compound + a PARP inhibitor	31 Oct 2013	[141]
US20160138114 (WO/2014/205105A1)	Biomarkers of Response to Inhibition of Poly-ADP Ribose Polymerase (PARP) in Cancer	Methods of identifying PARPis sensitive tumors	18 Jun 2014	[142]
9388472	Methods and materials for assessing loss of heterozygosity	Methods and materials used in assaying LOH signature in tumor cells	18 Jun 2014	[118]
JP2017504623A (WO/2015/108986A1)	Use of PARP inhibitor for treating the patient of a breast cancer or an ovarian cancer who shows loss of heterozygosis	Use of PARPis in subject with LOH	14 Jan 2015	[143]
US20170100368 (WO 2015184145 A1)	Use of eribulin and poly (adp ribose) polymerase (parp) inhibitors as combination therapy for the treatment of cancer	Eribulin mesylate + PARP inhibithors (e.g., E7449) +/- platinum based therapy	28 May 2015	[144]
US20150344968	Methods for determining PARP inhibitor and platinum resistance in cancer therapy	BRCA1 exon excision variant sequencing	01 Jun 2015	[145]
WO 2016138574 A1	Homologous recombination factors	Factors that act on homologous recombination, method to modulate it.	1 Mar 2016	[116]
WO 2016209935 A1	Platinum compounds, compositions, and uses thereof	Platinum compounds having at least one reacting group (e.g. that recognize a selected target cell population)	22 Jun 2016	[146]
9707302 (US20170274093)	Combining anti-HLA-DR or anti-Trop-2 antibodies with microtubule inhibitors, PARP inhibitors, bruton kinase inhibitors or phosphoinositide 3-kinase inhibitors significantly improves therapeutic outcome in	PARP inhibitors + adoptive cell therapy, bruton kinase inhibitors or PI3K inhibitors	23 Jun 2016	[147]

	cancer			
WO 2017008912 A1	Method for determining a mutation in genomic dna, use of the method and kit for carrying out said method	A mutation analysis is carried out using genomic DNA	15 Jul 2016	[117]
WO/2017/013237A1	Use of a combination of dbait molecule and PARP inhibitors to treat cancer	PARP inhibitor + nucleic acid molecule	22 Jul 2016	[148]
WO/2017/031442A1	Combination therapy using liposomal irinotecan and a PARP inhibitor for cancer treatment	Irinotecan liposomal formulation (MM-398) and Veliparib	19 Aug 2016	[132]
WO/2017/029517A1	Compositions comprising phosphoinositide 3-kinase inhibitors and a second antiproliferative agent	A composition of phosphoinositide 3-kinase inhibitors and a second agent (e.g. a PARPi)	19 Aug 2016	[149]
US20170035737	Treatment of BRCA1-defective cancer or resistant cancers	COH29 ((N-(4-(3,4-dihydroxyphenyl)-5-phenylthiazol-2-yl)-3,4-dihydroxybenzamide))	9 Feb 2017	[125]
US20170049767	Combination therapy for cancer treatment	Topoisomerase-1 inhibitor + PARPis	23 Feb 2017	[130]
WO/2017/151554A1	Combination therapy for treatment of ovarian cancer	Ganetespib + a DNA- damaging or repair-inhibiting agent	28 Feb 2017	[131]