Review

PARP Inhibitors in Epithelial Ovarian Cancer: State of Art and Perspectives of Clinical Research

ANGIOLO GADDUCCI and MARIA ELENA GUERRIERI

Department of Experimental and Clinical Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy

Abstract. *Homologous recombination (HR) and base excision repair (BER) are two of the major DNA-repair pathways. The proteins encoded by breast-related cancer antigen (BRCA) and poly(adenosine diphosphate-ribose) polymerases (PARP) are involved in HR and BER, respectively. Tumors with HR deficiency, including those in BRCA mutation carriers, are sensitive to BER blockade via PARP inhibitors. These represent novel therapeutic tools for HR-deficient ovarian cancer, able to improve progression-free survival of women with recurrent, platinum-sensitive disease in response to recent platinum-based chemotherapy. More research is needed to assesses whether inhibitors of PARP have any role as maintenance treatment after first-line chemotherapy and as palliative treatment of platinum-resistant disease. Germline BRCA testing should be offered to all patients with ovarian cancer, regardless of age and family history. HR deficiency has been observed not only in germline BRCA mutation carriers, but also in patients with somatic mutations or epigenetic silencing of BRCA, and with loss of function of other genes. Half of all high-grade ovarian carcinomas are HR-deficient, and additional biological and clinical investigations are strongly warranted to identify patients with this subset of tumors.*

Epithelial ovarian cancer (EOC) is the leading gynecological cause of death in Western countries (1, 2). Primary cytoreductive surgery followed by platinum- and paclitaxel- based chemotherapy is the standard treatment for advanced disease, able to achieve a clinical complete response (CR) rate of approximately 50%, a pathological CR rate of 25-50%, median progression-free survival (PFS) of 15.5-22 months and median overall survival (OS) of 31-44 months (3-8). Almost 75% of clinical CRs and 50% of pathological CRs will relapse after a median of 18-24 months (9). Although EOC is a chemosensitive disease, resistant clones develop in the majority of cases (10). The unsatisfactory results obtained with standard treatment have encouraged investigations addressing the detection of novel molecularly targeted agents that can also be used as maintenance therapy (11-18). Eight phase III randomized trials including anti-angiogenic agents have met their primary endpoint represented by PFS (11-14, 18). Four of these trials included bevacizumab and the other four used pazopanib, nintedanib, cediranib, and trebananib. Bevacizumab has gained European Medicines Agency approval for the first-line treatment of advanced EOC in combination with carboplatin and paclitaxel, and for the treatment of recurrent, platinum-sensitive EOC in combination with carboplatin and gemcitabine (16). Moreover, a phase III trial demonstrated a significant PFS advantage from the addition of bevacizumab to single-agent chemotherapy in recurrent, platinum-resistant disease (14). Besides bevacizumab, additional molecularly targeted agents, namely the inhibitors of the poly(adenosine diphosphate (ADP)-ribose) polymerases (PARPs), have been tested in EOC with promising results.

Five major DNA-repair pathways have been identified (19, 20). Base excision repair (BER), nucleotide excision repair, and mismatch repair are involved in the repair of single-stranded breaks (SSBs), whereas error-free homologous recombination (HR) and error-prone non homologous end-joining (NHEJ) are repair mechanisms for double-stranded breaks (DSBs). Nuclear proteins PARP play a major role in the BER pathway. In the present review, we analyzed the state of art and perspectives of clinical research on PARP inhibitor use in the management of EOC.

Correspondence to: Angiolo Gadducci, Department of Experimental and Clinical Medicine, Division of Gynecology and Obstetrics, University of Pisa, Via Roma 56, Pisa, 56127, Italy. Tel: +39 50992609, Fax: +39 50992354, e-.mail: a.gadducci@med.unipi.it

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Biological Data on PARP Inhibitors

The lifetime risk of developing EOC for women living in Western countries is about 1.4% (21). The large majority of these tumors are sporadic, and only 10% arise in families with a predisposing gene (21, 22). Breast-related cancer antigen *(BRCA)*$_1$ and *BRCA*$_2$ gene mutations are responsible for most hereditary EOCs. *BRCA*$_1$ and *BRCA*$_2$ mutation carriers have a 18-60% and 11-27% lifetime risk of developing this malignancy, respectively (23-28). The proteins encoded by these genes are involved in HR, the most important cell mechanism able to repair DSBs resulting from endogenous and exogenous genotoxic agents and radiotherapy (29-31). The central step in this process consists in the binding of multiple monomers of the RAD51 recombinase protein to 3'-ending single-stranded DNA overhangs created by nucleolytic resection (31, 32). The resulting nucleoprotein filament enhances the formation of a joint molecule between the processed broken DNA and the homologous repair template. Platinum forms intra- and interstrand adducts with DNA which generate DSBs, and therefore cells with compromised HR are highly sensitive to platinum and other DNA-damaging agents (33).

PARP1 is a member of the PARP enzyme family that functions as a DNA nick-sensor enzyme and plays a major role in the BER pathway (34). Activated PARP1 cleaves nicotinamide adenine dinucleotide into nicotinamide and ADP-ribose and polymerizes the latter onto nuclear acceptor proteins, such as histones and transcription factors, thus contributing to DNA repair and maintenance of genomic stability. Ionizing radiation and alkylating agents elicit higher lethality in *Parp1*-deficient mice when compared with wild-type animals, which confirms that PARP is a survival factor playing an essential role during DNA-damage recovery (35).

Tumors with HR deficiency, including those with *BRCA*$_1$ and *BRCA*$_2$ mutations, are highly sensitive to BER blockade *via* PARP inhibition (36). Such inhibition results in an excess of SSBs, which in turns causes accumulation of DSBs during replication. In HR-deficient tumors, DSBs are repaired by NHEJ, which is error-prone and causes genomic instability and cell death. This provides the basis for a novel synthetic lethal approach to cancer therapy. *In vitro* and *in vivo* experimental studies have confirmed that BRCA$_1$- and BRCA$_2$-deficient tumor cells are much more sensitive to PARP inhibitors than are wild-type tumor cells (37-39).

HR deficiency has been observed not only in patients with EOC with *BRCA*$_1$ or *BRCA*$_2$ germline mutations, but also in patients with EOC with somatic loss-of-function mutations of BRCA$_1$ or BRCA$_2$, epigenetic silencing of *BRCA*$_1$, and loss of function of other genes, such as *RAD51*, ataxia telangiectasia mutated protein (ATM), ataxia telangiectasia mutated and RAD3 related-protein (*ATR*) (40, 41). These patients have a 'BRCAness' phenotype that is similar to that of BRCA$_1$ or BRCA$_2$ germline mutation carriers, and includes serous histology, high response rates to first and subsequent lines of platinum-based chemotherapy treatment, long treatment-free interval between relapses, and improved OS (42-45). It is estimated that up to 50-60% of high-grade serous EOCs could be HR-deficient, and therefore biological and clinical investigations to identify this subset of tumors are strongly warranted (46, 47).

MicroRNA-506 (miR-506) has been found to increase the response to cisplatin and the PARP inhibitor olaparib through targeting RAD51 and suppressing HR in a panel of EOC cell lines *in vitro* and in an orthotopic ovarian cancer mouse model *in vivo* (48, 49). miR-506 expression was associated with better response to therapy and longer PFS and OS in patients with EOC (49).

One of the earliest cellular responses to DSB generation is phosphorylation of the core histone protein H2AX (termed γH2AX), which represents a molecular marker of DNA damage (50). *In vitro* studies on EOC cell lines showed that the histone deacetylase inhibitor (HDAC), suberoylanilide hydroxamic acid (SAHA) induced coordinated down-regulation of HR pathway genes, including *RAD5*$_1$ and *BRCA*$_1$, and that the combination of SAHA with olaparib induced apoptosis and γH2AX expression to a greater extent than either drug alone (51).

Using a bioinformatics approach, Choi *et al*. found that inhibitors of heat-shock protein 90 (HSP90) may suppress HR and thus convert HR-proficient to HR-deficient tumors (52). In HR-proficient EOC cell lines, the addition of the HSP90 inhibitor tanespimycin to olaparib down-regulated *BRCA*$_1$, RAD51 and induced significantly more γH2AX activation compared with olaparib alone (51). Sublethal concentrations of tanespimycin sensitized HR-proficient EOC cell lines to olaparib and carboplatin but did not affect sensitivity of the HR-deficient OVCAR8 cell line to these drugs, thus confirming that the tanespimycin-mediated sensitization is dependent on HR suppression.

In addition to catalytic inhibition of SSB repair, PARP inhibitors trap the PARP1 and PARP2 enzymes at damaged DNA (53). Trapped PARP–DNA complexes seem to be more cytotoxic than unrepaired SSBs, which suggests that PARP inhibitors act through a dual mechanism. Muray *et al*. showed that in the DT40 human cancer cell lines the potency in trapping PARP differed markedly among various inhibitors of PARP and it did not correlate with the catalytic inhibitory properties of these drugs (53). It is noteworthy that olaparib concentrations (<10 μM) needed to readily detect PARP1–and PARP2–DNA complexes were below the peak plasma concentrations of olaparib in clinical trials (54).

Possible mechanisms of therapeutic resistance to PARP inhibitors include secondary mutations that restore functional *BRCA*$_1$ or *BRCA*$_2$ genes, reduced expression of the NHEJ factor 53BP1, and increased cellular drug efflux *via*

increased expression of P-glycoprotein (55). Well-designed clinical trials that include blood and tumor sampling at the time of progression for comprehensive biomarker and genomic analyses are strongly recommended in order to elucidate the molecular mechanisms of resistance to PARP inhibitor.

Clinical Data on PARP Inhibitors

Single-agent olaparib. A phase I trial of oral olaparib, including 60 patients with different types of solid tumor refractory to standard therapies, showed that the maximum tolerated dose (MTD) was 400 mg *bid* and that the most common adverse effects were grade 1-2 nausea (32% of patients), fatigue (30%), vomiting (20%), taste alterations (13%),and anorexia(12%) (54). Objective antitumor activity was detected only in $BRCA_1$, and in $BRCA_2$ mutation carriers, all of whom had ovarian, breast, or prostate cancer. Pharmacokinetic analyses revealed that olaparib absorption was rapid, with peak plasma levels reached within 3 h. Afterwards, plasma concentrations declined biphasically with a terminal half-life of 5 to 7 h. Pharmacodynamic studies detected PARP inhibition of more than 90% in peripheral-blood mononuclear cells from patients treated with olaparib 60 mg or more *bid*. This phase I study was expanded to a cohort of 50 women with $BRCA_{1-2}$ mutated recurrent EOC (56). Twenty patients (40.0%) achieved an objective response (OR) and three maintained stable disease (SD) for more than 4 months, with an overall clinical benefit rate of 46% and a median response duration of 28 weeks. The clinical benefit rate was 69% for patients with platinum-sensitive, 45% for those with platinum-resistant, and 23% for those with platinum-refractory disease, respectively.

Several phase II studies of olaparib have been performed on recurrent EOC (57-65) (Table I). Audeh *et al*., who enrolled patients with *BRCA*-mutated EOC, reported OR rates of 33.3% and 12.5% in women who were given olaparib at doses of 400 mg *bid* and 100 mg *bid*, respectively (57). Nausea and fatigue were observed in 48% and 33%, respectively, of patients treated with high-dose drug, and in 37% and 38%, respectively, of those treated with low-dose drug. This study provided positive proof of concept of the efficacy and tolerability of olaparib in BRCA-mutated EOC.

In a phase II non- randomized study, including women with high-grade serous or undifferentiated EOC, olaparib achieved an OR in 41.2% of patients with BRCA mutations and in 23.9% of those without mutations (58).

An open-label phase II trial randomly assigned patients with *BRCA*-mutated EOC, whose disease recurred within 12 months of prior platinum therapy, to receive olaparib 200 mg *bid* or olaparib 400 mg *bid* or pegylated liposomal doxorubicin (PLD) 50 mg/m^2 intravenously every 28 days (59). Median PFS times were 6.5 months, 8.8 months, and 7.1 months, respectively, with no significant difference between those treated with combined olaparib doses or PLD. The median PFS of 7.1 months in the PLD arm exceeded that seen in the previous phase III study by Gordon *et al*. (66) (4 months) including women with unknown *BRCA* status. Patients with HR-deficient tumors may derive more benefit from anthracycline-based treatments than unselected patients, as suggested by prior clinical studies on patients with recurrent EOC and primary breast cancer (67, 68).

A randomized, double-blind, placebo-controlled, phase II trial of olaparib maintenance enrolled patients with platinum-sensitive, recurrent, high-grade serous EOC who had received two or more platinum-based regimens and who had CR or PR to their most recent platinum-based chemotherapy (60). PFS was significantly longer for patients assigned to olaparib as maintenance within 8 weeks after completion of platinum-based chemotherapy than for those assigned to placebo maintenance [hazard ratio (HR)=0.35, 95% confidence interval (CI)=0.25-0.49; $p<0.001$). A preplanned analysis of this study by retrospective determination of *BRCA* status showed that PFS was better in the olaparib group than in the placebo group among the patients with germline or tumor *BRCA* mutation (HR=0.18, 95% CI=0.10-0.31; $p<0.0001$) (61). Tolerance to olaparib was similar in patients with mutated BRCA and the overall population.

Kaufman *et al*. administered olaparib monotherapy to 298 patients with germline $BRCA_{1-2}$ mutation and recurrent cancer of different types (63). The OR rates were 26.2% in overall group, 31.1% in EOC resistant to platinum, 12.9% in breast cancer with three or more prior chemotherapy regimens for metastatic disease, 21.7% in pancreatic cancer after gemcitabine, and 50% in hormone-refractory prostate cancer.

Domchek *et al*. confirmed that olaparib exerted antitumor activity in patients with germline $BRCA_{1-2}$ mutation with heavily pretreated EOC, including those with resistant/refractory disease after three or more prior chemotherapy lines (64, 65).

Olaparib in combination therapy. PARP inhibitors enhance the activity of DNA-damaging agents, such as cisplatin, carboplatin or cyclophosphamide, in preclinical tumor models (69, 70). For instance, the combination of the PARP inhibitor I AZD2281 with cisplatin or carboplatin increased the recurrence-free survival and OS in a genetically engineered mouse model of $BRCA_1$-deficient mammary tumor.

Phase I studies of cytotoxics and olaparib in humans have demonstrated dose-limiting myelosuppression, requiring intermittent dosing of olaparib (71-74) (Table II). Olaparib at 400 mg *bid* on days 1-7 plus carboplatin at an area under the curve (AUC) of 5 every 3 weeks was found to be safe and active in patients with germline $BRCA_{1-2}$ mutation with

Table I. *Phase II studies of olaparib in recurrent epithelial ovarian cancer.*

Audeh *et al*. (57)	57 EOC BRCA$_{1-2}$ mutated pts who received a median of 3 (range 1-16) previous CT regimens	Cohort 1=33 pts Olaparib 400 mg *bid* OR=11 (33.3%)	Cohort 2=24 pts Olaparib 100 mg *bid* OR=3 (12.5%)			
Gelmon *et al*. (58)	63 Pts with HG serous or undifferentiated EOC and target lesions	Olaparib 400 mg *bid*		pts	OR	
			All pts	63	18 (28.6%)	
			With *BRCA*$_{1-2}$ mut	17	7 (41.2%)	
			Without *BRCA*$_{1-2}$ mut	46	11 (23.9%)	
			pts	OR	PFS (months)	
Kaye *et al*. (59)	97 EOC BRCA1-2 mutated pts who recurred within 12 months of prior platinum	Olaparib 200 mg *bid*	32	8 (25%)	6.5	
		Olaparib 400 mg *bid*	32	10 (31%)	8.8	
		PLD 50 mg/m^2 every 28 days	33	6 (18%)	7.1	
			p-Value	ns	ns	
			pts	PFS (months)		
Lederman *et al*. (60)	265 Pts with platinum-sensitive, recurrent, HG serous EOC who received >2 platinum-based CT regimens and who responded to most recent platinum-based CT	Olaparib 400 mg *bid*	136	8.4		
		placebo	129	4.8		
				p<0.001		
Lederman *et al*. (61)	Preplanned analysis of prior study by BRCA status	Olaparib 400 mg *bid* Placebo	BRCA mutated: 136 pts PFS (months) 11.2 4.3 *p*-Value=0.002		BRCA wild-type: 118 pts PFS (months) 7.4 5.5 *p*-Value=0.005	
			pts	OR	PFS (months)	
Liu *et al*. (62)	90 EOC pts with measurable platinum-sensitive, recurrent HG serous or endometrioid disease or with germline BRCA1-2 mutations	Cediranib 30 mg daily + olaparib 200 mg *bid*	44	35 (79%)	17.7	
		Olaparib 400 mg *bid*	46	22 (48%)	9.0	
				p=0.002	*p*=0.05	
Kaufman *et al*. (63)	193 Pts with germline *BRCA*$_{1-2}$ mutations and recurrent EOC resistant to platinum	Olaparib 400 mg *bid*	OR 60 (31%)		SD 77 (40%)	

Domchek *et al*. (64)	167 Pts with germline *BRCA*$_{1-2}$ mutation and recurrent EOC	Olaparib 400 mg *bid*		Overall	Sensitive	Resistant	Refractory	Unknown
		<3 Prior CT regimens	pts	30	9	8	1	12
			OR	14 (47%)	6 (67%)	4 (50%)	0 (0%)	4 (33%)
		≥3 Prior CT regimens	pts	137	38	77	14	8
			OR	46 (34%)	17 (45%)	22 (29%)	2 (14%)	5 (62%)

EOC, Epithelial ovarian cancer; pts, patients; *BRCA*, breast-related cancer antigen; HG, high grade; mut, mutated; CT, chemotherapy; *bid*, twice daily; OR, objective response; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; ns, not significant; SD, stable disease.

recurrent EOC, with a OR rate of 71.4% among the 14 patients with platinum-sensitive disease and 25.0% among the 20 patients with platinum-resistant/refractory disease, respectively (73). In another study, olaparib at 400 mg *bid* on days 1-7 plus carboplatin AUC 3 to 5 on day 1 or 2 every 3 weeks achieved an OR in 17.9% and SD in 35.7% of 28 women with heavily pretreated high-grade serous EOC and negative germline *BRCA* testing (74). Grade 3 or 4 neutropenia, thrombocytopenia and anemia occurred in 23%, 20% and 13%, of the cases, respectively. Based on these data, the dose of carboplatin at an AUC of 4 was recommended in addition to olaparib for a phase II study in this clinical setting.

The combination of weekly paclitaxel at 60 mg/m^2 plus carboplatin at an AUC of 2 (3 weeks out of 4) with olaparib at 150 mg *bid* (for three consecutive days every week for each cycle) obtained an OR and SD in 52.5% and 25%, respectively, of 54 patients with recurrent EOC, with acceptable myelosuppression (75). The median OS was 24 months for germline those with BRCA mutation *versus* 16 months for those without mutation.

Olaparib has been also investigated in combination with the oral antiangiogenic agent cediranib [a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3] in recurrent EOC (62). Single-agent cediranib obtained an OR rate of 17% in this clinical setting (76).

In a randomized phase II study including 90 EOC women with measurable platinum-sensitive, recurrent, high-grade serous or endometrioid disease, or with germline *BRCA$_{1-2}$* mutations, median PFS was significantly longer for the cediranib plus olaparib arm than for the single-agent olaparib arm (HR=0.42, 95% CI=0.23-0.76; p=0.005) (62). Subset analysis demonstrated activity of cediranib plus olaparib in both women with germline *BRCA* mutations and in those with wild-type or unknown *BRCA* status. Grade 3 or 4 adverse events were more common with combination therapy, including fatigue (27.3% *versus* 10.9%), diarrhea (22.7% *versus* none), and hypertension (40.9% *versus* none). Randomised phase III clinical trials have shown that platinum-based doublets, such as carboplatin and paclitaxel, carboplatin and gemcitabine, and carboplatin and PLD, are effective in recurrent platinum-sensitive disease, with median PFS of 8-13 months (78-80). Because the median PFS in this study (17.7 months) compared favorably to that seen with platinum-based therapy, a phase III trial comparing the oral regimen with olaparib plus cediranid *versus* standard intravenous combination chemotherapy would be of great clinical relevance.

Other PARP inhibitors. Niraparib is a potent, selective inhibitor of PARP that induces synthetic lethality in pre-clinical tumor models with loss of BRCA and PTEN function (80). In a phase I trial, cohorts of three to six patients enriched for *BRCA$_1$* and *BRCA$_2$* mutation carriers received oral niraparib daily at doses escalating from 30 mg to 400 mg in a 21-day cycle to establish the MTD, that was found to be 300 mg (81). Eight (40%) out of the 20 *BRCA$_{1-2}$* mutation carriers with EOC had an OR, as did two out of the four mutation carriers with breast cancer. Antitumor activity was also detected in patients with sporadic high-grade serous EOC. Common toxic effects were grade 1 or 2 anemia, nausea, fatigue, thrombocytopenia, anorexia, neutropenia, constipation, and vomiting.

Veliparib inhibits both PARP1 and PARP2 and enhances the activity of temozolomide, cisplatin, carboplatin, cyclophosphamide, and radiation in syngenic and xenograft tumor models (69). In a phase II study enrolling 50 *BRCA* mutation carriers with recurrent EOC who had received three or more chemotherapy regimens,oral veliparib at 400 mg *bid* in a 28-day cycle obtained an OR in 20% of patients with platinum- resistant disease and in 35% of those with platinum-sensitive disease (82). The most common adverse events were similar to those reported for other PARP inhibitors.

Table II. *Phase I studies of cytotoxics and olaparib: maximum tolerated dose*.

Rajan *et al*. (71)	Olaparib 100 mg *bid* on days 1 to 4 Gemcitabine 500 mg/m^2 on days 3 and 10 Cisplatin 60 mg/m^2 on day 3
Samol *et al*. (72)	Olaparib100 mg *bid* Topotecan 1.0 mg/m^2/day × 3 days
Lee *et al*. (73)	Olaparib 400 mg *bid* on days 1-7* Carboplatin AUC 5
Rivkin *et al*. (75)	Olaparib 150 mg *bid* for 3 days every week Weekly paclitaxel 60 mg/m^2 (3 weeks out of 4) Weekly carboplatin AUC 2 (3 weeks out of 4)

bid, Twice daily; AUC, area under curve; MTD, maximum tolerated dose. *Highest tested dose; MTD was not reached.

The highly selective PARP inhibitor rucaparib exerts antiproliferative activity in human cancer cells out xenograft tumors with mutated or epigenetically silenced *BRCA$_{1-2}$*, and it enhanced the cytotoxicity of several DNA-damaging agents in EOC cell lines (83, 84).

The ARIEL2 phase II study tested a novel next-generation sequencing-based HR-deficient assay and algorithm to predict rucaparib sensitivity by assessing tumor *BRCA* status and genome-wide loss of heterozygosity (LOH) in a series of 206 patients with platinum-sensitive, recurrent, high-grade serous or endometrioid EOC (85). Rates of OR to oral rucaparib at 600 mg *bid* were 69% for *BRCA*-mutated tumors, 39% for wild-type BRCA and high LOH tumors, and 11% for wild-type *BRCA* and low LOH tumors, respectively (p<0.0001). Therefore the combination of *BRCA* analysis and genomic LOH seems to be useful for identifying those patients likely to respond to rucaparib.

Conclusion

The goal of maintenance therapy in clinical oncology is to prolong a meaningful survival endpoint, such as PFS, symptom-free survival and OS, without substantially interfering with the quality of life (86). Whereas maintenance chemotherapy does not seem to have an effective role (9, 87-91), promising results have emerged from trials with biological agents (11-13, 17, 18, 60, 61). In particular, PARP inhibitors represent very interesting novel therapeutic tools for the

Table III. *Phase III sturdily of and poly(adenosine diphosphate-ribose) polymerase inhibitors in epithelial ovarian cancer.*

NCT01844986. Phase III randomised, double blind, placebo-controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) EOC following first- line platinum- based chemotherapy.
NCT01874353. Phase III randomised, double blind, placebo-controlled study of olaparib maintenance monotherapy in patients with platinum-sensitive, relapsed, *BRCA*-mutated EOC with a complete or partial response following platinum-based chemotherapy.
NCT01847274. Phase III randomized, double blind trial of maintenance with niraparib *versus* placebo in patients with platinum-sensitive EOC who have either germline *BRCA* mutation or a tumor with high-grade serous histology and who have responded to their most recent chemotherapy containing a platinum agent.
NCT 01968213. Phase III trial designed to evaluate the effect of rucaparib *versus* placebo as maintenance treatment following platinum-based therapy in women with platinum-sensitive, relapsed, high- grade serous or endometrioid EOC.
GINECO PAOLA (Platin, Avastin and Olaparib in first-line advanced high-grade ovarian carcinoma patients) trial. Randomized, double-blind, phase III trial of olaparib versus placebo in combination with bevacizumab in women who have not progressed after first-line chemotherapy plus bevacizumab for advanced high-grade EOC.

management of HR-deficient EOC, able to significantly improve the PFS of women with recurrent, platinum-sensitive disease in CR or PR to their most recent platinum-based chemotherapy (60, 61, 92-94). More research is needed to assess whether PARP inhibitors have any role as maintenance treatment after first-line platinum-based chemotherapy and as palliative treatment of platinum-resistant disease.

Phase III trials are currently ongoing to further evaluate the role of PARP inhibitors in patients with EOC with mutated $BRCA_{1\text{-}2}$ or high-grade serous or endometrioid histological type after platinum-based chemotherapy (Table III).

Germline $BRCA_{1\text{-}2}$ testing should be offered to all women with non-mucinous EOC, regardless of age and family history (44, 95). However, HR deficiency has been observed not only in germline $BRCA_{1\text{-}2}$ mutation carriers, but also in patients with EOC with somatic mutations of $BRCA_1$ or $BRCA_2$, epigenetic silencing of $BRCA_1$, and loss of function of other genes (40, 41). Approximately half of all high-grade EOCs are HR-deficient, and therefore additional biological and clinical investigations are strongly warranted to identify this subset of tumors (46, 47, 96). Once HR deficiency becomes amenable to routine testing, a larger group of patients with EOC than those with mutated $BRCA_{1\text{-}2}$ will benefit from the use of PARP inhibitors (97).

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