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Development of new poly(ADP-ribose) polymerase (PARP) inhibitors in ovarian cancer: Quo Vadis?

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Abstract: Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer mortality among women, potentially due to ineffectiveness of screening tests for early detection. Patients typically present with advanced disease at diagnosis, whereas, up to 80% relapse and the estimated median progression-free survival (PFS) is approximately 12–18 months. Increased knowledge on the molecular biology of EOC resulted in the development of several targeted therapies, including poly(ADP-ribose) polymerase (PARP) inhibitors. These agents have changed the therapeutic approach of the EOC and exploit homologous recombination (HR) deficiency through synthetic lethality, especially in breast cancer genes 1 and 2 (*BRCA1/2*) mutation carriers. Furthermore, *BRCA* wild-type patients with other defects in the HR repair pathway, or those with platinum-resistant tumors may obtain benefit from this treatment. While PARP inhibitors as a class display many similarities, several differences in structure can translate into differences in tolerability and antitumor activity. Currently, olaparib, rucaparib, and niraparib have been approved by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) for the treatment of EOC, while veliparib is in the late stage of clinical development. Finally, since October 2018 talazoparib is FDA and EMA approved for *BRCA* carriers with metastatic breast cancers. In this article, we explore the mechanisms of DNA repair, synthetic lethality, efficiency of PARP inhibition, and provide an overview of early and ongoing clinical investigations of the novel PARP inhibitors veliparib and talazoparib.

Keywords: Ovarian cancer; breast cancer gene (BRCA); poly(ADP-ribose) polymerase inhibitors (PARP inhibitors); homologous recombination (HR); veliparib; talazoparib

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Introduction

Approximately 22,440 newly diagnosed cases of ovarian cancer and 14,080 deaths occurred in the United States in 2017 (1). Two thirds of patients present at advanced stages, whilst the estimated 5-year survival rate is 20–40%. The vast majority of ovarian cancers are epithelial in origin (90%), whereas 10% are non-epithelial; germ cell and sex cord stromal cell (5% each). They differ in epidemiology, etiology, and treatment. Epithelial ovarian cancer (EOC) is the most frequent cause of death from gynecologic cancer among women due to lack of an effective screening test. Histologically, it is predominantly divided into five main subtypes; high- and low-grade serous (75–80%), endometrioid and clear cell (10% each), and mucinous (3%) (2). Patients with EOC response usually well to the initial standard treatment, which includes cytoreductive surgery with either preoperative or adjuvant platinum-based chemotherapy; nevertheless, the estimated median progression-free survival (PFS) ranges from 12 to 18 months (3). Therefore, development and validation of functional biomarkers and novel therapeutic agents are of major importance for the improvement of patients' outcome.

Breast cancer genes 1 and 2 (*BRCA1/2*) mutations are the most significant molecular aberrations in ovarian cancer with established prognostic and predictive value following chemotherapy. Based on that, increased research focused on germline variant testing, risk stratification, early detection, and cancer prevention for *BRCA1/2* mutation carriers has been conducted (4). Cells with mutations in *BRCA1/2* genes have an impaired double-strand DNA breaks (DSBs). In any case of impairment of homologous recombination (HR), synthetic lethality induced by poly (ADP-ribose) polymerase (PARP) inhibition occurs and may target tumor tissue selectively (5,6). Furthermore, several somatic mutations beyond *BRCA1/2* genes have been recognized, including *RAD51*, and ataxia telangiectasia-mutated (*ATM*), which are also involved in HR repair (7). Tumors with these abnormalities are often sensitive to similar therapies (8).

Over the last decade, clinical trials led to the approval of several PARP inhibitors in ovarian cancer. Olaparib, rucaparib, and niraparib have all obtained US Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) approval in EOC in different settings. Veliparib and talazoparib are in earlier clinical development. Veliparib was evaluated mainly combined with chemotherapy or targeted agents (9), whilst at least *in vitro* talazoparib demonstrates

more potent antitumor activity, based on its enhanced PARP-DNA trapping ability (10).

The purpose of this article is to review the mechanisms of HR, and provide current evidence and future challenges in the development of the investigational PARP inhibitors veliparib and talazoparib.

Mechanisms of DNA repair

DNA damage often arises within the context of normal cellular processes. It can be spontaneous or caused by cell metabolism or by environmental agents (11). Base excision repair (BER) is the major DNA repair pathway responsible for the removal of DNA base damage and formation of single-strand DNA breaks (SSBs) and DSBs. The primary activity of PARP1/2 proteins, is post-translational poly-ADP ribosylation (PARylation) of substrate proteins involved in biological processes such as transcription and DNA damage repair. The idea of PARylation asserts that during DNA damage PARP1 is activated, on both SSB and DSB. In addition, several post-translational modifications also alter activity of PARP1, which is implicated in multiple signaling pathways (12). Once PARP is activated, downstream events of PARP signaling take place, involving either covalent PARylation of substrates, non-covalent binding of PAR polymer to proteins bearing a PAR-binding motif, liberation of free PAR to the cell or lowering cellular NAD⁺/ATP levels. This could lead to loss of genomic instability, cell death, and even carcinogenesis if not correctly repaired (13). HR and non-homologous end-joining (NHEJ) likely playing the largest role in DSB repair. How the cell determines whether HR or NHEJ will be used to repair a break depends on the phase of the cell cycle. HR predominates as a mechanism of repair during mid S and G2 phases (14). If an undamaged template DNA is unavailable, then the faster but error-prone NHEJ repair pathway is the primary method of DNA DSB repair in the cell (15). Additional DNA damage repair operational mechanisms include nucleotide excision repair (NER), mismatch repair (MMR), and translesional synthesis (16). In the presence of functional defects of both HR and classical NHEJ, inhibition of PARP1 inhibits alternative NHEJ, resulting in cell apoptosis (17).

Seventeen members of the PARP proteins have been described so far. PARP1 is responsible for approximately 90% of the PARylation activity, whereas PARP2 and to a lesser extent PARP3 function in fewer, but overlapping DNA repair processes (18). Binding of PARP to damaged

sites, its catalytic activity, and its eventual release from DNA are key elements for potential response of a cancer cell to DNA breaks introduced by certain chemotherapeutic agents, and radiation (19). When activated PARP, it recruits other DNA repair proteins (20).

PARP inhibition and synthetic lethality

Two preclinical studies published in 2005 promoted knowledge and clinical development of PARP inhibitors (5,6). In view of assessing the effects of PARP1 depletion, a plasmid expressing a short interfering RNA targeting mouse PARP1 was transfected into embryonic stem cells lacking wild-type *BRCA1/2*. These cells bore specific genomic mutations of *BRCA1/2*, lacked wild-type single allele and were directly compared to their isogenic wild-type counterparts. Investigators concluded that these cell lines with a *BRCA1/2* mutation were more sensitive to PARP inhibition than heterozygous mutants. This was based on the synthetic lethality, characterized by a bimodal dependency through which the loss of function of one gene in a cell does not have impact on viability, whilst the combined loss of both components results in cell death (21). The synthetic lethality between PARP inhibition and HR deficiency is overall produced due to SSBs repair failure. If the inhibitor stays bound within the PARP active site and the PARP protein is trapped on the DNA long enough to be encountered by the replication machinery, this can lead in a stalling of the replication fork, its collapse and the generation of a DNA DSB (21). Among evaluated PARP inhibitors, olaparib, niraparib, and rucaparib are approximately 100-fold more potent than veliparib, while talazoparib has the most enhanced trapping potency (10). It has been suggested a correlation between increased PARP trapping and high myelosuppression, which results on variation in dosing among PARP inhibitors.

Apart from mutations in *BRCA1/2*, genomic alterations involving other genes in HR deficiency pattern have been recognized (22). The term “BRCAness” describes the phenotype shared between *BRCA1/2*-mutated and non-*BRCA1/2*-mutated ovarian cancers, resulted in severe chromosomal instability due to deregulated HR (23). Indeed, BRCAness phenotype may be attributed in part to defective HR secondary to several mechanisms, including hypermethylation of the *BRCA1* promoter, somatic mutations of *BRCA1/2*, or *EMSY* amplification. Furthermore, several somatic mutations in genes beyond *BRCA* have been recognized in a wide variety of tumors.

For example, aberration of *ATM*, *BRIP1*, *RAD50*, *RAD51C*, *RAD51D*, *RAD52*, and DNA-dependent protein kinase (DNA-PK) is therapeutically important as expands the sensitivity to PARP inhibition beyond germline *BRCA1/2* mutations (24). Ongoing efforts are directed towards clinical application of synthetic lethality and interaction between PARP inhibition and HR deficiency. To this end, a precise comprehension of the implications of the different PARP inhibitors is challenging.

Clinical applications of PARP inhibitors in ovarian cancer

PARP inhibitors were originally developed as radio- and chemo-sensitising drugs, and are being investigated to a different extent and settings in EOC and other solid tumors (25). *Table 1* depicts the PARP inhibitors, which have obtained approval by FDA, and/or EMA for the treatment of EOC. Currently, novel agents are in clinical development. Veliparib was initially demonstrated in 2007 to potentiate the preclinical activity of temozolomide, platinum agents, and radiotherapy in a variety of tumors (9). Talazoparib specifically in the treatment of EOC is still at an early stage of clinical development. However, there are studies actively recruiting patients for the evaluation of talazoparib in several solid tumors. Talazoparib has currently EMA (and FDA) approval for metastatic breast cancer.

Historically, EMA approved in 2014 a capsule formulation of olaparib in maintenance setting for *BRCA* carriers with recurrent high grade serous EOC, or primary peritoneal cancer (study 19) (24). At the same year, FDA approved olaparib as the first-in-class PARP inhibitor for germline *BRCA*-mutated patients, previously treated with at least three lines of chemotherapy (study 42) (26). The tablet formulation of olaparib has been approved by both agencies as maintenance therapy for patients with platinum-sensitive relapsed EOC regardless of BRCA status (SOLO 2) (24,27). FDA approved olaparib maintenance treatment on December 19, 2018, based on the results of SOLO 1 trial (NCT01844986), examined the efficacy of olaparib versus placebo in subjects with *BRCA*-mutated advanced EOC, who were in complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy (28).

Rucaparib has been approved by FDA and EMA in December 2016 and May 2018 respectively, for patients who have been treated with two or more prior lines of platinum-based chemotherapy, and cannot tolerate further platinum-

Table 1 FDA-EMA approved indications for PARP inhibitors in advanced ovarian cancer based on the results of phase II/III studies

Doses/agency	Olaparib	Niraparib	Rucaparib
Recommended dose	Capsules: 400 mg BID Tablets: 300 mg BID	Capsules: 300 mg BID	Tablets: 600 mg BID
FDA approved indications	2014: recurrent gBRCA EOC with >3 previous lines of chemotherapy (capsules formulations) (study 42) 2017: maintenance treatment of patients with recurrent EOC, following CR or PR to platinum-based chemotherapy (tablets formulations) (SOLO 2)	2017: Maintenance treatment of patients with recurrent EOC, following CR or PR to platinum-based chemotherapy (NOVA TRIAL)	2016: monotherapy treatment in the setting of platinum sensitive, relapsed or progressive, g/sBRCA mutated EOC, treated with ≥2 previous lines of platinum-based chemotherapy, unable to tolerate further platinum-based treatment (Study 10, ARIEL 2) 2018: maintenance treatment in the setting of recurrent EOC, following CR or PR to platinum-based chemotherapy (ARIEL 3)
EMA approved indications	2014: maintenance treatment of BRCA mutants with platinum-sensitive relapsed EOC, following CR or PR to platinum-based chemotherapy (study 19) 2018: maintenance treatment of patients with platinum-sensitive relapsed EOC, following CR or PR to platinum-based chemotherapy, regardless of BRCA status (tablets formulations) (SOLO 2)		2018: monotherapy treatment in the setting of platinum sensitive, relapsed or progressive, g/sBRCA mutated EOC, treated with ≥2 previous lines of platinum-based chemotherapy, unable to tolerate further platinum-based treatment (ARIEL 3)

FDA, Food and Drug Administration; EMA, European Medicines Agency; BID, twice a day (bis in die); gBRCA, germline *BRCA* mutation; BRCA, breast cancer gene; EOC, epithelial ovarian cancer; CR, complete response; PR, partial response; g/sBRCA, germline/somatic *BRCA* mutation.

based chemotherapy. The efficacy was based on integrated analyses of data from study 10 and ARIEL2 (29-31).

FDA and EMA approved niraparib (March and November 2017, respectively) for the maintenance treatment of the responders to platinum-based chemotherapy (NOVA trial) (32). In June 2018 were presented the results of a phase II study of niraparib in heavily pre-treated patients with recurrent ovarian cancer (Quadra Trial) (33). Registration studies that led to approvals of PARP inhibitors for treatment of EOC are resumed in *Table 2*.

Based on the distinct chemical structures of PARP inhibitors and various off-target effects, the therapeutic strategy of re-challenge with a PARP inhibitor following disease progression needs to be further developed. In June 2019 was presented at the American Society of Clinical Oncology (ASCO) the largest clinical trial of prospective evaluation of PARP inhibitors failure, correlating tissue genomic mechanisms of resistance (36).

Preclinical pharmacokinetics and pharmacodynamics of veliparib

The pharmacokinetic profile of veliparib is characterized by high oral bioavailability and rapid absorption. The administration of the immediate-release formulation BID (bis in die) resulted in a peak-to-trough concentration ratio of 0.45 μM . Veliparib passes through the blood-brain barrier; its combination with temozolomide is highly effective in the treatment of intracranial tumors (9). The activity of veliparib combined with temozolomide has been demonstrated across a broad histologic spectrum of models in B-cell lymphoma, lung, pancreatic, ovarian, breast, and prostate cancer xenografts (37). Veliparib is primarily excreted from tubular cells into urine via OCT2. With this regard, drug dosage adjustment should be based on the creatinine clearance, whereas concurrent treatment with OCT2-inhibitors such as cimetidine, results in higher therapeutic dose of veliparib (9).

Table 2 Approval clinical trials of PARP inhibitors in ovarian cancer

Study (reference)	Phase	Enrolled patients	Treatment arms	Setting	Survival	P
STUDY 42 (26)	II	193	Olaparib 400 mg BID	1. Platinum-resistant, advanced HGSOc; 2. <i>BRCA</i> mutations	1. ORR: 34%; 2. MDR: 7.9 m; 3. PFS: 7 m; 4. OS: 16.6 m	–
SOLO 2 (27)	III	295	Arm A: olaparib 300 mg BID Arm B: placebo	1. Platinum-sensitive, advanced HGSOc or HGEoc; 2. At least two prior lines of platinum-based CTH; 3. <i>BRCA</i> mutations	Median PFS: 19.1 vs. 5.5 m	<0.0001
STUDY 10 (29)	I/II	42	Rucaparib 600 mg BID	1. Platinum-sensitive, advanced HGSOc or HGEoc; 2. gBRCAmut (phase II PART 2A)	ORR: 59.5%; MDR: 7.8 m	–
ARIEL 2 PART 1 (30)	II	192	Rucaparib 600 mg BID	Platinum-sensitive, advanced HGSOc or HGEoc	[A]: Median PFS: 1. <i>BRCA</i> mutants: 12.8 m; 2. <i>BRCA</i> wild type LOH high: 5.7 m; 3. <i>BRCA</i> wild type LOH low: 5.2 m [B]: ORR: 1. <i>BRCA</i> mutants: 80%; 2. <i>BRCA</i> wild type LOH high: 39%; 3. <i>BRCA</i> wild type LOH low: 13%	<0.0001; 0.011; 0.011
NOVA (32)	III	555	Arm A: niraparib 300 mg BID Arm B: placebo	1. Platinum-sensitive, advanced HGSOc; 2. At least two prior lines of platinum-based CTH; 3. Stratification by gBRCAmut	Median PFS: 1. gBRCA mutants: 21 vs. 5.5 m; 2. <i>BRCA</i> wild type HRD (+): 12.9 vs. 3.8 m; 3. overall non-gBRCA mutants: 9.3 vs. 3.9 m	<0.0001; <0.00001; <0.0001
QUADRA (33)	II	45	Niraparib 300 mg BID	1. Platinum-sensitive, advanced HGSOc; 2. HRD positive	ORR 27.5%; DCR 68.6%	–
STUDY 19 (34)	II	265	Arm A: olaparib 400 mg BID Arm B: placebo	1. Platinum-sensitive, advanced HGSOc; 2. At least two prior lines of platinum-based CTH; 3. Unselected for <i>BRCA</i> status	[A]: Median PFS: 1. overall population: 8.4 vs. 4.8 m; 2. <i>BRCA</i> mutants: 11.2 vs. 4.3 m; 3. <i>BRCA</i> wild type: 7.4 vs. 5.5 m [B]: OS: 1. overall population: 29.8 vs. 27.8m; 2. <i>BRCA</i> mutants: 34.9 vs. 31.9 m; 3. <i>BRCA</i> wild type: 24.5 vs. 26.2 m [C]: ORR: 12% vs. 4%	<0.001; <0.0001; 0.0075 0.44; 0.19; 0.96 0.12
SOLO 1 (35)	III	451	Arm A: olaparib 300 mg BID Arm B: placebo	1. Platinum-sensitive, advanced HGSOc; 2. <i>BRCA</i> mutations	Median PFS: NR vs. 13.8 m	<0.001

BID, twice a day (bis in die); HGSOc, high-grade serous ovarian cancer; CTH, chemotherapy; *BRCA*, breast cancer gene; PFS, progression-free survival; m, months; OS, overall survival; ORR, overall response rate; MDR, median duration of response; HGEoc, high-grade endometrioid cancer; NR, not reached; gBRCAmut, germline mutation; LOH, loss of heterozygosity; DCR, disease control rate.

In terms of mechanisms of action, apart from “PARP-trapping”, it is fundamental the sensitizing effect of veliparib to DNA-damaging drugs, including oxaliplatin, irinotecan, cisplatin, carboplatin and cyclophosphamide, and equally the radiotherapy (38).

Veliparib in clinical practice

The analysis of ongoing studies, assessing veliparib as single

agent or, in combination with cytotoxics, revealed an overall objective response rate (ORR) ranging from 14.3% to 79%.

Phase I/II studies of veliparib monotherapy

A phase I trial, presented in 2014, assessed pharmacokinetics, pharmacodynamics and clinical efficacy of veliparib (39). Among 88 enrolled patients with platinum-refractory EOC or basal-like breast cancer, 60 were *BRCA*

Table 3 Studies of single agent veliparib in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Phase	Enrolled patients	Treatment arms	Setting	Survival	Trial
Puhalla S, et al., 2014 (39)	I	88	3+3 dose-escalation trial Nine dose levels (50 mg BID to 500 mg BID)	Platinum-refractory OC60/88 BRCA mutants	ORR: 40% ORR among BRCA mutated: 23 ORR among BRCA wild-type: 4%	NCT00892736, completed
Steffensen KD, et al., 2017 (40)	I/II	48	Phase I: 16 patients (MTD 300 mg BID) Phase II: 32 patients	Platinum-sensitive or resistant OC BRCA mutants	ORR: 65% PFS: 5.6 m OS: 13.7 m	NCT01472783, completed
Nishikawa T, et al., 2017 (41)	I	16	3+3 dose-escalation trial 4-week cycle treatment Two dose levels (200 mg BID and 400 mg BID)	14/16 high grade serous OC Median of three or more prior chemotherapies (range, 1–7)	Veliparib MTD: 400 mg BID ORR: 14.3% PFS: 7.26 m	Completed
Coleman RL, et al., 2015 (42)	II	50	Veliparib 400 mg BID 4-week cycle treatment Allowed dose modifications	Platinum-resistant OCBRCA mutants	ORR: 26% ORR in platinum-sensitive setting: 35% ORR in platinum-resistant setting: 20% PFS: 8.1 m OS: 19.7 m	NCT01540565, completed

BID, twice a day (bis in die); OC, ovarian cancer; BRCA, breast cancer gene; ORR, overall response rate; MTD, maximum tolerated dose; PFS, progression-free survival; m, months; OS, overall survival.

mutants. The recommended phase II dose (RP2D) was 400 mg BID, and the half-life 5.2 hours. ORR was higher in BRCA mutated, as compared to BRCA wild-type patients (23% and 4%, respectively). The most common toxicities included nausea, fatigue, and lymphopenia.

More recently, a phase I/II trial evaluated veliparib monotherapy in 48 subjects with germline BRCA mutated EOC (40). Veliparib was given BID in a 4-weekly treatment cycle, and the maximum tolerated dose (MTD) was 300 mg BID. Platinum-sensitive subset of patients attained longer PFS (P=0.037) and OS (P=0.02) than platinum-resistant. The high ORR of 65% (6% CR, 59% PR), in patients with relapsed, platinum-resistant ovarian cancer, should be highlighted. Overall, the tolerance was acceptable, and most common treatment related adverse events included grade 2 fatigue and nausea (22% each), followed by vomiting (9%).

In a small phase I dose-escalation study, 14 out of 16 enrolled Japanese patients had high-grade serous EOC and were treated with veliparib BID (41). The RP2D was 400 mg BID, whilst two patients experienced PR as

best achieved response. The most prevalent grade 3 or 4 toxicities included fatigue and manifestations of the gastrointestinal system.

Based on the promising results of early phase studies, the single-arm, phase II, Gynecologic Oncology Group (GOG) 280 trial (NCT01540565) was published in 2015 (42). Veliparib was administered at a dose of 400 mg BID to a cohort of 50 BRCA mutated EOC patients, pretreated with a maximum of three lines of chemotherapy. The ORR of veliparib was 26% [90% confidence interval (CI), 16–38%], and the study met its primary endpoint. Furthermore, subgroup analysis revealed responses of 35% and 20%, in platinum-sensitive and resistant setting respectively, which was not significantly different (P=0.33). However, 31 patients (62%) experienced progressive disease while on treatment. Treatment-associated adverse events were not prominently featured; anemia and leukopenia were of grade 1/2, whilst nausea and vomiting occur mostly during first cycle treatment.

Table 3 lists the available phase I and II studies of single

agent veliparib.

Phase I studies of veliparib combined with chemotherapy

In 2012, Kummar *et al.* published the report of a single-arm, phase I study (NCT00810966), evaluated veliparib combined with metronomic oral cyclophosphamide (43). Thirty-five patients diagnosed with both lymphomas and refractory solid tumors, including 11 EOC, were enrolled. A standard 3+3 escalation design was employed, and starting dose of veliparib was 20 mg daily, combined with cyclophosphamide for the first 7, 14, or 21 days of the cycle. Cyclophosphamide was given 50 mg daily throughout a 3-weekly schedule. The MTD was obtained at veliparib 60 mg with cyclophosphamide 50 mg daily. As far as treatment efficacy is concerned, 7 participants (20%) experienced PRs.

In 2015 was presented the report of a phase I study of veliparib in combination with bevacizumab, paclitaxel and carboplatin in newly diagnosed patients with stage II–IV EOC or carcinosarcoma (GOG 9923; NCT00989651) (44). Veliparib starting dose was 30 mg BID given on 3-weekly cycles for the initial 6 treatment cycles. Bevacizumab was administered at 15 mg/kg intravenously, each first day 1 from cycle 2 to 22. The RP2D for veliparib was 150 mg BID in combination with the remaining regimens. Based on the NCT00989651, it is currently active the 3-arm phase III trial GOG 3005 (NCT02470585) (45).

At the same setting of the combination of veliparib with chemotherapy and bevacizumab, the phase I, GOG 9927 trial, enrolled 39 patients with relapsed platinum-sensitive EOC (NCT01459380) (46). The recommended MTD of veliparib was 80 mg BID, when was combined with pegylated liposomal doxorubicin 30 mg/m² and carboplatin area under the curve (AUC) 5 on 4-weekly cycle. At MTD, 12 additional patients were enrolled and treated with bevacizumab. Among them, 9 exhibited dose-limiting toxicities, such as thrombocytopenia, neutropenia, hypertension, and sepsis.

It has been suggested that mitomycin C (MMC) is involved in generating DNA DSBs, activation of the Fanconi anemia (FA) pathway and veliparib-induced sensitization (47). Based on this concept was conducted a 3+3 dose escalation trial of veliparib as monotherapy, or combined with MMC. Sixty-one patients with HR deficient solid tumors were enrolled and randomized to each arm, through 14 dose levels (NCT01017640) (48). The MTD for single agent veliparib was 300 mg BID to FA-

deficient patients. In the combination strategy, MMC was recommended at dose of 10 mg/m², followed by veliparib 200 mg BID in a 4-weekly cycle with 21 days on and 7 days off. Veliparib as monotherapy did not produce a substantial number of tumor regressions. This modest clinical benefit is associated with veliparib's spectrum of doses below MTD, and the additional antiapoptotic stimulus to which the repair deficient cell has become addicted.

In 2017 was published a small Japanese phase I dose-escalation trial (NCT02483104), evaluated in newly diagnosed advanced EOC, veliparib in combination with 3-weekly cycles of carboplatin AUC 6 and paclitaxel 80 mg/m² (days 1, 8, 15) (49). Patients were treated with the platinum-doublet chemotherapy for six cycles in total; veliparib was incorporated throughout the course of treatment, and the RP2D was 150 mg BID. Among 5 assessed for response patients, 4 experienced PR, and 1 CR, respectively. However, these findings should be interpreted cautiously, taking into account the small sample size, and lack of random assignment and control group.

Another small phase I study (NCT01154426) evaluated veliparib combined with single agent gemcitabine in advanced solid tumors (50). Gemcitabine was given at dose of 500–750 mg/m², administered either thrice on 4-weekly, or twice on 3-weekly schedule. Veliparib was escalated from 10 to 40 mg BID during gemcitabine's weeks. Among 31 enrolled patients, 23 developed grade 3/4 side effects, primarily myelosuppression. The recommended MTD were 750 mg/m² for gemcitabine and 20 mg for veliparib BID on the 3-weekly regime. Among 27 patients, 3 achieved PR and 15 stable disease (SD), respectively. However, correlation between response and *BRCA* status is difficult to be justified, and the combination should be further explored.

Veliparib combined with the doublet of carboplatin/gemcitabine has been investigated in a phase I dose-escalation study of 75 patients with advanced EOC and breast cancers (NCT01063816) (51). The most prevalent adverse event was the myelosuppression resulting in discontinuation in 11% of patients, and dose reduction for veliparib and gemcitabine were required in 20 (27%) and 27 patients (36%), respectively. Median PFS for the entire study population was 7.0 months (95% CI, 5.3–8.4 months). This PFS benefit was more prominent in *BRCA* carriers [8.6 months (95% CI, 7.1–11.7 months)] than in *BRCA* wild-type/unknown subgroup [5.9 months (95% CI, 4.1–9.9 months)]. Equally, *BRCA*-mutants achieved higher ORR of 68.9% as compared to the 42.8% of the wild-type/unknown *BRCA* patients.

Finally, a phase I study (NCT01012817) evaluated the combination of veliparib and weekly topotecan in several solid tumors, including EOC (52). The treatment was well tolerated, and in line with the previous studies, resulted in prolonged ORR in *BRCA1/2*, or *RAD51D* mutants.

Table 4 details phase I studies of veliparib combined with chemotherapy.

Phase II/III studies of veliparib combined with chemotherapy

A randomized phase II trial (NCT01306032) randomized 72 pretreated, *BRCA*-mutant, EOC patients to the combination of veliparib with low dose cyclophosphamide, versus cyclophosphamide monotherapy (55). DNA repair defects were not predictive biomarkers for either cyclophosphamide single agent or the veliparib combination. Finally, neither ORR (11.8% versus 19.4%, respectively), nor median PFS (2.1 versus 2.3 months, respectively; $P=0.68$) were improved with the combination. Based on that, the trial was early terminated.

Taken the *in vitro* synergy of topotecan with veliparib, a phase I/II dose escalation clinical trial was conducted to investigate the combination in the setting of recurrent, *BRCA1/2* wild-type or unknown EOC (NCT01690598) (56). Twenty-seven enrolled patients were treated with an initial dose of veliparib, 30 mg BID, and topotecan, 3 mg/m² in 4-week treatment cycles. The reported efficacy was modest with median PFS of 2.8 months (95% CI, 2.6–3.6 months), and OS of 7.1 months (95% CI, 4.8–10.8 months). However, these findings should be interpreted in light of the negative prognostic factors of the study population. Haematological toxicities of grade 1 and 2 included mostly anemia (81.5%), followed by thrombocytopenia (29.6%) and neutropenia (22.2%).

Furthermore, the results of a randomized phase II study in recurrent high-grade serous EOC, evaluating veliparib combined with temozolomide versus pegylated liposomal doxorubicin are pending (NCT01113957) (57). Finally, the phase III GOG 3005 is an ongoing, randomized, double-blind trial, with aim to investigate the efficacy of veliparib in combination with carboplatin and paclitaxel in high-grade serous EOC, or primary peritoneal cancer patients (NCT02470585) (45). The recruitment target size is 1,140 patients, and this is the only phase III trial of veliparib in first-line treatment.

Phase II/III clinical trials of veliparib in combination with chemotherapy for the treatment of EOC are resumed in *Table 5*.

Veliparib in combination with radiotherapy

Preclinical evidence suggests that low-dose fractionated whole abdominal radiation (LDFWAR) combined with veliparib is an effective therapeutic option. A phase I dose escalation trial enrolled 22 patients with advanced solid tumors and peritoneal carcinomatosis, including 8 subjects with EOC (58). SD was maintained for 24 weeks or longer in 33% of participants. PFS was 7.92 months in the platinum-sensitive setting versus 3.58 months in the platinum-resistant subset.

In the final publication, 32 patients were finally enrolled, including 18 with EOC (56%) (59). The established MTD and RP2D for veliparib was 250 mg BID. Patients with platinum-resistant and those with platinum-sensitive recurrence, achieved a median OS of 5.8 and 10.9 months, respectively. The most common haematological adverse event of grade 3/4 was lymphopenia (59%), followed by thrombocytopenia (12%), anemia (9%), and neutropenia (6%). However, due to lack of specific biomarkers, incorporation of somatic genomic testing and HR deficiency score should be planned, in view of optimization of the efficacy of this therapeutic strategy.

Early randomized studies of veliparib in combination with radiotherapy are depicted in *Table 6*.

Talazoparib

Talazoparib in the treatment of EOC is still at an early stage of clinical development. However, preclinical studies have demonstrated activity in several solid tumors (60–63). Following olaparib, talazoparib was the second FDA and EMA approved drug for *BRCA*-mutated, *HER2*-negative breast cancer. Superior radiosensitizing capacity of talazoparib as compared to veliparib is probably based to its enhanced PARP trapping ability (64). Talazoparib has been shown to be the more potent PARP inhibitor (10), but equally has the highest rates of myelosuppression, particularly anemia and neutropenia in clinical trials (65).

Phase I studies of talazoparib monotherapy

Talazoparib was initially evaluated in 2017, with the first-in-human, 2-stage, dose-escalation, phase I study in over 100 patients with germline *BRCA1/2* mutated advanced or recurrent solid tumors, previously treated with platinum-based chemotherapy (NCT01286987) (66). Thirty-four

Table 4 Phase I studies of veliparib in combination with chemotherapy in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Enrolled patients	Treatment arms	Setting	Results	Trial
Kummar S, <i>et al.</i> , 2012 (43)	35	3+3 dose-escalation trial 3-week cycle treatment Single-arm study: Veliparib (20 mg up to 70 mg OD) + cyclophosphamide (50 mg or 100 OD)	Metastatic solid tumors; low-grade lymphomas; any <i>BRCA</i> status	Veliparib MTD: 60 mg OD Cyclophosphamide MTD: 50 mg OD ORR: 37% ORR among <i>BRCA</i> mutants: 69%	NCT00810966, completed
Bell-McGuinn KM, <i>et al.</i> , 2015 (44)	189	3+3 dose-escalation trial 3-week cycle treatment 3 treatment arms: Arm (A): carboplatin and paclitaxel, q3week + veliparib; Arm (B): carboplatin q3week and paclitaxel q1 week + veliparib; Arm (C): paclitaxel (IV), cisplatin (IP), and paclitaxel (IP) q3week, followed by bev + veliparib	Newly diagnosed, stage II–IV OC	Veliparib RP2D: 150 mg BID	NCT00989651, completed
Landrum LM, <i>et al.</i> , 2016 (46)	39	3+3 dose-escalation trial 4-week cycle treatment Treatment arms: Arm (A): PLD and carboplatin + veliparib (BID, days 1–7) + bev; Arm (B): PLD and carboplatin + veliparib (BID, days 1–28) + bev	Platinum-sensitive OC	Veliparib MTD 80 mg BID DLT in 75% of patients with bev ORR: 68%	NCT01459380, completed
Villalona-Calero MA, <i>et al.</i> , 2016 (48)	61	3+3 dose-escalation trial 4-week cycle treatment 2 treatment arms: Arm (A): veliparib; Arm (B): veliparib (BID, days 1–7, 1–14, or 1–21) + MMC	Solid tumors; any <i>BRCA</i> status	MMC MTD: 10 mg/m ² Veliparib MTD: 200mg BID, days 1–21 ORR: 39%	NCT01017640, completed
Nishio S, <i>et al.</i> , 2017 (49)	9	3+3 dose-escalation trial 3-week cycle treatment Veliparib + carboplatin + paclitaxel, q3week	Newly diagnosed, stage Ic–IV OC	RP2D of Veliparib: 150 mg BID ORR: 100% (5/9 evaluated patients)	NCT02483104, completed
Stoller R, <i>et al.</i> , 2017 (50)	31	Arm (A): veliparib (BID, days 1–21) + gemcitabine (days 1, 8, and 15, 28-day cycle) Arm (B): veliparib (BID, days 1–14) + gemcitabine (days 1, and 8, 21-day cycle)	Solid tumors	Gemcitabine MTD: 750 mg/m ² on days 1 and 8 on a 21-day cycle Veliparib MTD: 20 mg BID days 1–14 on a 21-day cycle ORR: 66.6% (27/31 evaluated patients)	NCT01154426, completed

Table 4 (continued)

Table 4 (continued)

Author, year of publication (reference)	Enrolled patients	Treatment arms	Setting	Results	Trial
Gray HJ, et al., 2018 (51)	75	3-week cycle treatment Gemcitabine starting dose 1,000 mg/m ² (days 1 and 8) Carboplatin + gemcitabine, followed by optional maintenance veliparib	Solid tumors (54/75 OC)	Veliparib MTD and RP2D: 250 mg BID Carboplatin MTD and RP2D: AUC4 Gemcitabine MTD and RP2D: 800 mg/m ² ORR: 79% PFS: 7 m PFS among BRCA mutant OC: 8.6 m	NCT01063816, completed
Wahner Hendrickson AE, et al., 2018 (52)	51	3+3 dose-escalation trial 4-week cycle treatment Experimental treatment arm: veliparib (BID, days 1–3, 8–10 and 15–17) + topotecan (days 2, 9 and 16)	Metastatic solid tumors (45/51 OC); 14/45 mutant OC	Veliparib MTD and RP2D: 300 mg BID Topotecan MTD and RP2D: 3 mg/m ² ORR 71% ORR among 14 BRCA mutant OC: 71% ORR among 31 BRCA wild-type OC: 52%	NCT01012817, active, not recruiting
Kummar S, et al., 2011 (53)	24	3+3 dose-escalation trial 3-week cycle treatment Single-arm of veliparib BID + topotecan	Solid tumors (5/24 OC); lymphomas	Topotecan MTD: 0.6 mg/m ² , days 1–5 Veliparib MTD: 10 mg BID, days 1–5	NCT00553189, completed
LoRusso PM, et al., 2016 (54)	35	3+3 dose-escalation trial 3-week cycle treatment Single-arm of veliparib BID + topotecan	Solid tumors (9/35 OC); OC were BRCA1/2 mutants	Veliparib MTD: 40 mg BID ORR in OC: 78%	NCT00576654, active, not recruiting

OD, once a day (omne in die); MTD, maximum tolerated dose; BRCA, breast cancer gene; ORR, overall response rate; BID, twice a day (bis in die); IV, intravenously; IP, intraperitoneal; OC, ovarian cancer; RP2D, recommended phase 2 dose; PLD, pegylated liposomal doxorubicin; Bev, bevacizumab; DLT, dose-limiting toxicity; MMC, mitomycin C; AUC, area under the curve; PFS, progression-free survival; m, months.

Table 5 Phase II/III studies of veliparib in combination with chemotherapy in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Phase	Enrolled patients	Treatment arms	Setting	Results	Trial
(45)	III	1,140	Arm [1]: carboplatin + paclitaxel followed by maintenance placebo Arm [2]: carboplatin + paclitaxel + veliparib followed by maintenance placebo Arm [3]: carboplatin + paclitaxel + veliparib followed by maintenance veliparib	Advanced HGSOC Any <i>BRCA</i> mutation	Waiting results	NCT02470585 (GOG 3005), active, not recruiting
Kummar S, <i>et al.</i> , 2015 (55)	II	72	Arm (A): cyclophosphamide (50 mg OD) Arm (B): cyclophosphamide (50 mg OD) + veliparib (60 mg OD)	Primary peritoneal, fallopian tube, or HGSOC Any <i>BRCA</i> mutation	ORR on arm (A): 36% ORR on arm (B): 26% PFS on arm (A): 2.3 m PFS on arm (B): 2.1 m	NCT01306032, completed
Hjortkjær M, <i>et al.</i> , 2018 (56)	I/II	27	3+3 dose-escalation trial 4-week cycle treatment Phase I: 12 patients Phase II: 15 patients Experimental treatment arm: veliparib (BID, days 1–3, 8–10 and 15–17) + topotecan (days 2, 9 and 16)	Primary peritoneal, fallopian tube Platinum-resistant or partially sensitive OC <i>BRCA1/2</i> unknown/wild-type	Phase I study veliparib MTD: 30mg BID Phase II study topotecan MTD: 2 mg/m ² ORR: 37% PFS: 2.8 m OS: 7.1 m	NCT01690598, completed
(57)	II	168	Arm [1]: veliparib + temozolomide Arm [2]: PLD	Recurrent HGSOC Germline <i>BRCA</i> Sporadic OC	Waiting results	NCT01113957, completed

HGSOC, high-grade serous ovarian cancer; *BRCA*, breast cancer gene; OD, once a day (omne in die); ORR, overall response rate; PFS, progression-free survival; m, months; OC, ovarian cancer; MTD, maximum tolerated dose; BID, twice a day (bis in die); OS, overall survival; PLD, pegylated liposomal doxorubicin.

ovarian cancer patients were enrolled in 9 cohorts, and the established MTD in the expansion cohort was 1 mg per day. A subset of 17 patients with *BRCA1/2*-mutant high-grade serous EOC was treated with doses of at least 0.1 mg/day. Radiological, biochemical and clinical benefit responses were achieved by 44%, 70% and 82%, respectively; nevertheless, response rates were much lower in patients with platinum-resistant disease (20%). The estimated median PFS was 36.4 weeks, whilst the achieved ORR to talazoparib was 50% (7/14) in *BRCA1/2* patients. Treatment related adverse events included mostly fatigue (37%), anemia (35%), and nausea (32%), whilst grade 3 to 4 side effects were anemia (24%) and

thrombocytopenia (18%).

At the same period was published a phase I/II trial evaluated talazoparib combined with carboplatin in several solid tumors, including EOC (8%) (67). Twenty-four patients were enrolled in four cohorts. Frequent grade 3/4 side effects were neutropenia (63%), which was more prominent in germline *BRCA* mutants, followed by anemia (38%), thrombocytopenia (29%), and fatigue (13%). One complete and two PRs (14%) were achieved by patients with germline *BRCA1/2* mutations. Finally, POSITION is an ongoing phase I study assessing the influence of talazoparib on DNA copy number and RNA expression in patients with

Table 6 Phase I studies of veliparib in combination with radiotherapy in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Enrolled patients	Treatment arms	Setting	Results
Reiss KA, <i>et al.</i> , 2015 (58)	22	Veliparib (80–320 mg OD) for 3 cycles + LDFWAR (21.6 Gy in 36 fractions, days 1 and 5 for weeks 1–3 of 3 cycles)	Solid tumors with peritoneal carcinomatosis (8/22 OC)	ORR: 57% PFS: 4.4 m OS: 13 m
Reiss KA, <i>et al.</i> , 2017 (59)	32	Veliparib (40–400 mg BID, days 1–21, q4 weeks) for 3 cycles + LDFWAR (21.6 Gy in 36 fractions, days 1 and 5 for weeks 1–3 of 3 cycles)	Solid tumors with peritoneal carcinomatosis (18/32 OC)	Veliparib MTD: 250 mg BID Overall PFS: 3.6 m Overall OS: 9.2 m PFS in OC: 4.6 m OS in OC: 9.3 m PFS in BRCA1/2 mutants: 4.5 m OS in BRCA1/2 mutants: 10.2 m PFS in non-BRCA1/2 mutants: 3.6 m OS in non-BRCA1/2 mutants: 7.9 m

OD, once a day (omne in die); LDFWAR, low-dose fractionated whole abdominal radiation; OC, ovarian cancer; BRCA, breast cancer gene; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; m, months; OS, overall survival; BID, twice a day (bis in die).

advanced stage EOC (NCT02316834) (68).

Table 7 provides summary results of phase I studies of talazoparib for treatment of ovarian cancer.

Phase II/III studies of talazoparib monotherapy beyond ovarian cancer

Currently, there are not available phase II or III clinical trials of talazoparib monotherapy in EOC. However, such data could be extrapolated from ongoing studies in metastatic breast cancer (65,69). Indeed, the benefit of talazoparib, specifically in BRCA mutants, has been reported in the phase II ABRAZO study (NCT02034916) (69). Eighty-four patients, pre-treated with platinum or other cytotoxic regimens, were enrolled in the study. The reported ORR for those with *BRCA1/2* mutations was 23% and 33%, respectively. Similarly, triple-negative breast cancer patients, and those with expressed estrogen and progesterone receptors, achieved an ORR of 26% and 29%, respectively.

FDA and EMA granted standard approval of talazoparib in advanced, *HER2*-negative advanced or metastatic breast cancer with germline *BRCA1/2* mutations, based on data gathered from EMBRACA study (NCT01945775) (65). This is a phase III, open-label study, which compared

talazoparib with standard single agent treatment. The primary endpoint of median PFS was 8.6 months in talazoparib arm, significantly higher than 5.6 months in the chemotherapy arm [HR: 0.54 (95% CI, 0.41–0.71), $P < 0.0001$]. Furthermore, response rates in talazoparib and chemotherapy group, were 63% and 27%, respectively. Similarly, quality of life was importantly improved in favour of talazoparib. Efficacy of the agent in triple-negative, BRCA wild-type breast cancer, will be evaluated by the ongoing phase II trial NCT02401347.

Several studies are in progress in prostate cancer. NCT03148795 is a phase II study aiming to assess talazoparib in patients with metastatic, castration resistant disease with defects in DNA repair mechanisms (70), whilst phase III study TALAPRO-2 (NCT03395197), is evaluating the addition of talazoparib to enzalutamide at the same setting (71).

Additionally, the single-arm phase 2 study NCT01989546 is still recruiting patients with several solid tumors and *BRCA1/2*-mutations, for the evaluation of talazoparib in platinum-sensitive setting (72).

As far as concerned ovarian cancer, two phase II trials have already been withdrawn (Table 8). NCT02326844 enrolled patients with *BRCA1/2* mutations, following

Table 7 Phase I studies of talazoparib in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Enrolled patients	Treatment arms	Setting	Results	Trial
de Bono J, <i>et al.</i> , 2017 (66)	113	Talazoparib 1 mg daily	1. Solid tumors (34/113 platinum-treated EOC) 2. gBRCAm (25/34 EOC)	1. ORR: 41.7% 2. gBRCAm: ORR: 55% in platinum-sensitive; ORR: 20% in platinum-resistant 3. PFS: 36.4 months	NCT01286987 Completed
Dhawan MS, <i>et al.</i> , 2017 (67)	24	Talazoparib + carboplatin Talazoparib starting dose of 0.75 mg daily One cycle equaled 21 days	1. Solid tumors (2/24 EOC) 2. 14/24 (58%) of patients received prior platinum CTH 3. gBRCAm (7/24, 29%) 4. sBRCAm (3/24, 12.5%)	1. 14% ORR 2. 52% SD 3. Dose reduction: 50% 4. Dose interruptions: 75% 5. Pharmacokinetics	Completed
(68)	30	Talazoparib 1 mg daily	1. EOC 2. Neoadjuvant setting	Pending	NCT02316834 Ongoing

EOC, epithelial ovarian cancer; BRCA, breast cancer gene; gBRCAm, germline *BRCA* mutation; ORR, objective response rate; PFS, progression-free survival; CTH, chemotherapy; sBRCA, somatic *BRCA* mutation; SD, stable disease; LOH, loss of heterozygosity; HRD, homologous recombination deficiency.

Table 8 Phase II studies of talazoparib in ovarian cancer (www.clinicaltrials.gov)

Author, year of publication (reference)	Phase	Patients number	Description	Population	Outcome	Trial, status
(73)	II	3	Talazoparib 1 mg daily	1. Recurrent and/or metastatic EOC 2. Progression on PARP inhibitors monotherapy 3. gBRCAm	1. Objective response (CR + PR) 2. Safety 3. Duration of response 4. PFS	NCT02326844 Terminated (closed by the Cancer Therapy Evaluation Program)
(74)	II	N/A	Arm 1: talazoparib 1 mg daily Arm 2: talazoparib 1 mg daily + temozolomide 37.5 mg/m ² on days 1–5	1. Recurrent EOC, primary peritoneal or fallopian tube cancer 2. <3 prior lines of CTH 3. gBRCAm, or sBRCAm, or HRD(+)	ORR	NCT02836028 Withdrawn

EOC, epithelial ovarian cancer; PARP, poly(ADP-ribose) polymerase; BRCA, breast cancer gene; gBRCAm, germline *BRCA* mutation; CR, complete response; PR, partial response; PFS, progression-free survival; N/A, not available; CTH, chemotherapy; sBRCA, somatic *BRCA* mutation; HRD, homologous recombination deficiency; ORR, objective response rate.

primary progression on prior PARP inhibitor therapy (73). This study addresses the important issue of whether re-challenging with an alternative PARP inhibitor may be associated with therapeutic benefit. Similarly, the withdrawn phase II randomized study NCT02836028 had been planned to assess talazoparib combined or not with temozolomide in patients with relapsed ovarian cancer and defects in DNA repair pathway (74).

Conclusions and future directions

PARP inhibitors have attracted great attention and illustrate a paradigm of bench-to-bedside medicine. HR deficiency remains a strong predictor of clinical benefit from these agents. Besides ovarian cancer, PARP inhibitors may be effective in subsets of patients with breast, prostate, and even pancreatic tumors. On December 27, 2019 FDA approved olaparib for the maintenance treatment of patients with metastatic pancreatic cancer, who were carriers of germline *BRCA1/2* mutations, based on the results of POLO trial (NCT02184195). The ORR was 23.1% in the olaparib versus 11.5% in the placebo arm, whereas median duration of response was 24.9 months as compared to 3.7 months, respectively. Mutations in DNA repair related genes are frequent in those tumors, which highlights further that evaluation of molecular alterations should be incorporated in clinical practice. Apparently, combination treatment strategies can induce HR pathway deficiency in cancers with *de novo* or acquired HR proficiency to PARP inhibitors. Moreover, PARP inhibitors may be effective in patients with somatic *BRCA1/2* mutations to the same extent as in those with germline *BRCA1/2* mutations. As such, somatic genomic analysis and clinical qualification of biomarkers, enabling patient stratification, promote delivery of precision medicine. Adverse events associated with PARP inhibitors should be carefully evaluated. Myelosuppression may require dose reduction. Optimization of toxicities could be achieved by modifying treatment modalities (continuous versus intermittent, concurrent to chemotherapy versus maintenance). Several clinical trials are ongoing, in different settings. Even though newer PARP inhibitors, demonstrate increased potency, it has not yet been fully clarified whether this translates into greater efficacy.

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Footnote

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