Veliparib Monotherapy to Patients With *BRCA* Germ Line Mutation and Platinum-Resistant or Partially Platinum-Sensitive Relapse of Epithelial Ovarian Cancer

A Phase I/II Study

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Objective: A new treatment principle, which seems to radically change the treatment approach in ovarian cancer (OC), has developed over the past few years. Poly(ADP-ribose) polymerase inhibitors work by interfering with mechanisms important to DNA damage repair. Cancer cells that already have defects in the *BRCA* genes are particularly sensitive to treatment with poly(ADP-ribose) polymerase inhibitors. The main purpose of this study was to investigate the effect of veliparib in patients with known *BRCA1/2* mutations and with a platinum-resistant or intermediate sensitive relapse of OC.

Methods: Major eligibility criteria were primary epithelial ovarian/fallopian/peritoneal cancer patients with a platinum-resistant or intermediate sensitive relapse of OC and with evaluable disease by either Response Evaluation Criteria In Solid Tumors or Gynecological Cancer Intergroup CA-125 criteria. Patients were treated with oral veliparib twice daily on days 1 to 28.

Results: Sixteen patients were enrolled in the phase I part, and a maximum tolerable dose of 300 mg twice daily was established. The phase II part enrolled 32 patients with a median of 4 previous treatment regimens. The overall response rate combining Response Evaluation Criteria In Solid Tumors and CA-125 response was 65% (6% complete response and 59% partial response). Progression-free and overall survival rates of the intention-to-treat population were 5.6 months (95% confidence interval, 5.2–7.3 months) and 13.7 months (95% confidence interval, 10.2–17.3 months), respectively. The most common phase II treatment-related grade 2 toxicities included fatigue (22%), nausea (22%), and vomiting (9%).

Conclusions: Treatment with veliparib in heavily pretreated patients with relapse of OC demonstrates a considerable efficacy with an acceptable toxicity profile.

Key Words: BRCA, Ovarian cancer, PARPi, Platinum resistance, Synthetic lethality

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The treatment options for recurrent ovarian cancer (OC) depend on the interval between primary/previous treatment and recurrence. Patients relapsing within 6 months after end of primary or later platinum-based regimens are considered platinum resistant and are offered treatment with pegylated liposomal doxorubicin or topotecan. Patients relapsing 6 to 12 months after previous platinum-based chemotherapy are regarded partially platinum sensitive and can be offered combination chemotherapy or retreatment with a taxane and platinum regimen, which is generally used for patients relapsing for more than 12 months after primary treatment. However, the concept of prolongation of treatment-free interval (TFI) especially in partially platinum-sensitive patients by intercalation of a platinum-free regimen has been widely discussed over the past year, although it has not yet been adapted into clinical practice.

Currently, randomized trials support the use of either pegylated liposomal doxorubicin or topotecan as second-line therapy in women with recurrent platinum-resistant OC.[1–5] Generally speaking, the effect of chemotherapy in recurrent OC is poor, which has prompted the development of biological targeted treatment. However, the results have shown only modest improvement, and there is an obvious need for new treatment modalities.

Germline mutations in *BRCA1* and *BRCA2* genes confer a high lifetime risk of OC. *BRCA1* and *BRCA2* belong to a class of genes known as tumor suppressors, which maintain genomic integrity to prevent genetic changes that can lead to development of several cancer types such as breast cancer or OC.[6] The BRCA1 and BRCA2 protein products are essential for repair of damaged DNA especially by recognizing and repairing DNA double-strand breaks by homologous repair.[7]

DNA repair enzymes, poly(ADP-ribose) polymerase 1 and 2 (PARP1/PARP2), also have a well-established role in DNA repair processes. Poly(ADP-ribose) polymerase 1 is crucial for the recognition and repair of single-strand DNA breaks and in particular base excision repair. Inhibition of PARP1 leads to failure of single-strand DNA repair, which when encountered by a DNA replication fork will result in a DNA double-strand break, resulting in the necessity of BRCA-mediated repair. Inhibition of base excision repair by PARP inhibitors may therefore be selectively lethal to *BRCA*-mutated cancer cells by exploiting these mechanisms.

This new, potential therapeutic approach to the treatment of cancer has been called synthetic lethality and occurs between 2 genes, when loss of 1 gene function (either PARP *or* BRCA) is compatible with cellular viability, but loss of both (PARP *and* BRCA) is lethal.

Veliparib (ABT-888)[8] is one of several recently developed oral inhibitors of PARP1 and PARP2 currently in clinical trials. The main purpose of this protocol was to investigate the clinical effect of veliparib in ovarian patients with known *BRCA1/2* mutations and with a partially platinum-sensitive relapse or platinum-resistant relapse of their disease.

MATERIALS AND METHODS

Study Design

This study was a phase I/II single-arm, open-label, single-center study. The primary objectives of the phase I part were to determine maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), and the recommended phase II dose. The phase I dose escalation part of the study was a typical 3-to-3 study design with 6 patients per cohort. No intrasubject dose escalation was allowed.

When continuing to the phase II part, the main objective was to investigate the response rate in platinum-resistant and partially platinum-sensitive OC patients with known germline *BRCA* mutations treated with veliparib monotherapy. Secondary objectives were to investigate the clinical safety and toxicity as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0, progression-free survival (PFS), and overall survival (OS). A biobank with tumor tissue and blood was established for later analysis.

Patients

Patients with histologically confirmed epithelial primary ovarian, fallopian, or peritoneal cancer stage I to IV with a germline *BRCA1/2* mutation and with verified progression by either Response Evaluation Criteria In Solid Tumors (RECIST) criteria and/or Gynecological Cancer Intergroup (GCIG) CA-125 criteria after previous first-line chemotherapy or progression after later lines of cytotoxic treatment were eligible for inclusion in the protocol. Moreover, patients were required to have platinum-resistant or partially platinum-sensitive disease defined as relapse within 6 months of previous first line/later lines of platinum-based therapy or disease relapse within 6 to 12 months of previous first line/later lines of platinum-based therapy.

Other eligibility criteria included the following: age 18 years or older; performance status 0 to 2; measurable disease by RECIST version 1.1 or evaluable by CA-125 GCIG criteria; adequate bone marrow, liver, and renal function and coagulation parameters; written informed consent; and tissue available for biobank storage.

Key exclusion criteria included previous treatment with a PARP inhibitor, platinum-refractory disease, and central nervous system metastasis.

Study Treatment

Patients received oral veliparib twice daily on days 1 to 28 (4-weekly treatment cycle). The starting dose in the phase I dose escalating study was 300 mg twice a day (BID), which was the dosing level reached at the NCI STEP 8282 study without DLT.

Treatment cohorts were dosed in escalating order only after the safety of the previous dose level had been established, or until an MTD has been determined. Dose escalation occurred in stepwise 100-mg increments of the immediate previous dose group, in the absence of grade 3 or more drug-related toxicity of the previous level. At least 3 subjects were dosed at each level. A cohort was planned expanded to 6 subjects if 1 of 3 subjects experienced DLT. If fewer than 30% (0/3 or $\leq$1/6) of subjects within a cohort experienced a DLT, dose escalation continued to the next dose level.

The MTD was defined as the dose level 1 step below the DLT. The dose of veliparib for the phase II part was the MTD determined in the phase I part of the study.

Courses were repeated every 28 days in the absence of disease progression or unacceptable toxicity. Patients were treated until clinical, radiological, or CA-125–defined progression; unacceptable toxicity; or patient refusal.

Efficacy and Toxicity Assessment

Tumor assessment was performed at baseline and after every third cycle by computed tomography scans of chest, abdomen, and pelvis according to RECIST[9] version 1.1 and by CA-125 GCIG-modified criteria[10–13] every third cycle. Response and progression were determined by using the definitions[13] incorporating RECIST 1.1 and CA-125 as agreed by the GCIG. Patients were not evaluable (NE) by RECIST if they had no measurable target lesions according to RECIST version 1.1 (then patients could be included only if they had CA-125–measurable disease), and patients were NE by CA-125 RECIST criteria if their baseline CA-125 value was less than 70 kU/L and could vice versa be enrolled in the protocol only if they had RECIST-measurable disease.

No independent review was performed, but the regional Good Clinical Practice (GCP) unit according to the International Conference on Harmonisation GCP guidelines with regular inspections monitored the protocol.

Evaluation of safety of the treatment was based on the history, clinical examination, and analysis of a number of hematological and biochemical parameters. Toxicities were recorded at baseline and on day 1 of each cycle as adverse events on the adverse event case report form and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0. Progressive patients were observed for OS every 3 months.

Progression-free survival was measured from date of first dose of study treatment to progression or death, whichever came first.

Overall survival was calculated from date of first dose of study treatment to date of death of any cause.

Statistical Considerations

Simon's[14] 2-stage minimax design was used for assessment of the phase II part of the trial, which was divided into 2 steps. The target level for response was set at 40% and 20% as the lower level of clinical interest. With a significance level of 5% and a power of 80%, the trial was planned to include 18 patients in the first step (stage I). If less than 4 responses were seen in stage 1, the trial was to be terminated. Otherwise, accrual continued to stage II with inclusion of an additional 15 patients for a total of 33 patients.

If more than 10 patients among the 33 patients responded, the trial was defined as sufficiently promising to warrant a phase III trial. The 2-stage statistical design did not distinguish between RECIST-measurable response rates and CA-125 response rates as it was decided in the planning phase of the study to use the combined overall response rate as described in the reference by Rustin et al.[13]

Post hoc analysis showed the 2-stage design would also have been met with only RECIST-measurable disease because there were 14 RECIST responders (complete response [CR] + partial response [PR]) in the phase II part of the study with 8 RECIST responders in stage I and 6 responders in stage II.

Only patients who have received 3 cycles of treatment were considered evaluable for response unless progressive disease (PD) has occurred. All patients who had received at least 1 dose were considered evaluable for toxicity.

Univariate PFS and OS analysis was performed using the Kaplan-Meier plots and compared by the log-rank test. All tests were 2-sided.

Statistical analyses were performed with the NCSS software (version 2007; Kaysville, Utah, http://www.ncss.com). A $P < 0.05$ was considered statistically significant.

Ethical Considerations

The Helsinki II Declaration was complied with unconditionally, and the study was conducted in accordance with the protocol, the International Conference on Harmonisation GCP guidelines, and applicable official requirements/legislation. The Danish Medicines Agency (no. 2011051164), The Regional Committees on Health Research Ethics for Southern Denmark (no. S-20110097), and the Danish Data Protection Agency have approved the study (ClinicalTrials.gov NCT01472783).

RESULTS

Patients

The phase I part of the study accrued patients from November 2011 to August 2012 and continued in phase II from September 2012 to March 2015 with enrollment of a total of 48 patients, 16 patients in phase I and 32 patients in phase II. The phase II was intended to include 33 patients according to protocol, but 1 patient was withdrawn after inclusion because pathology and chart review revealed that her primary diagnosis was not OC but endometrial cancer, and she was withdrawn because of this protocol violation. Most of the included patients were heavily pretreated with a median of 4 previous lines for both phases I and II, and most of the patients were platinum resistant, and 12.5% of the patients were resistant already after first-line therapy; 50% of the patients became resistant during later lines of platinum therapy in phase I and 12.5% and 59.4%, respectively, in phase II (Table 1), whereas the remaining patients were intermediate platinum sensitive. None of the patients were sheer platinum sensitive with a platinum-sensitive relapse of more than 12 months after the last platinum-containing regimen. *BRCA* mutation analysis was performed from the referring hospital before treatment initiation. No central secondary confirmation of *BRCA* analysis was performed. *BRCA1* mutation was present in 71% of patients, whereas 29% had a *BRCA2* mutation. There was no significant difference in the distribution between phase I and phase II. Patient characteristics are outlined in Table 1.

Treatment Administration and Toxicity

Patients included in phase I received a total of 119 cycles with a median number of 3 cycles (range, 0–49 cycles). The first step in the phase I part included 3 patients at 300 mg BID (50-mg capsules). Two patients experienced grade 1 nausea, vomiting, stomach pain, and bloating, but no DLTs were observed, and 3 new patients were dose escalated to 400 mg BID. In this cohort, 1 patient experienced grade 3 nausea and vomiting. Another 3 patients were included at the same dose

TABLE 1. Baseline patient demographics and clinical characteristics

Baseline Characteristics	Phase I (n = 16) No. Patients	Phase II (n = 32) No. Patients
Age, y		
Mean	56.3	57.2
Median	54.8	57.5
Range	28–77	46–71
Performance status		
0	11 (68.8%)	19 (59.4%)
1	4 (25.0%)	12 (37.5%)
2	1 (6.3%)	1 (3.1%)
CA-125 baseline level, U/L		
Median	311	530
Range	20–13,514	17–32,621
Primary site		
Ovarian	14 (87.5%)	27 (84.4%)
Tubal	0 (0.0%)	2 (6.3%)
Peritoneal	2 (12.5%)	3 (9.4%)
FIGO stage		
I	0 (0.0%)	4 (12.9%)
II	0 (0.0%)	1 (3.2%)
III	7 (43.8%)	14 (45.2%)
IV	9 (56.3%)	12 (38.7%) (Unknown: 1)
Grade		
Low grade	0 (0.0%)	0 (0.0%)
High grade	13 (100%) (Not graded—cytology or biopsy only: 3)	28 (100%) (Not graded—cytology or biopsy only: 4)
Histological type		
Serous	12 (75.0%)	27 (84.4%)
Endometrioid	1 (6.3%)	3 (9.4%)
Transitiocellular	1 (6.3%)	0 (0.0%)
Mixed	0 (0.0%)	2 (6.3%)
Other (adenocarcinoma not further classified due to cytology only or metastatic biopsy)	2 (12.5%)	0 (0.0%)
No. previous lines of chemotherapy		
Median	4	4
Range	1–11	1–7
Platinum resistance		
Primary platinum resistant after first-line therapy	4 (12.5%)	4 (12.5%)
Platinum resistant after later lines	8 (50.0%)	19 (59.4%)
Intermediate platinum sensitivity after later lines	4 (12.5%)	9 (28.1%)

level, and DLTs were seen in 2 patients (grade 3 vomiting and nausea). The MTD according to protocol required no more than 1:6 patients with DLT of a given dose level, and therefore, another 4 patients were treated with 300 mg BID, and no DLTs were experienced. This step included 4 patients instead of the planned 3 patients because it was decided to replace 1 patient who received only 6 days of cycle 1 treatment and was terminated because of psychological problems, general discomfort, and refusal to further treatment, but the data from this patient are reported regarding toxicity. In July 2012, the pharmaceutical

company supplied new 100-mg capsules instead of 50-mg capsules, and it was decided to retest the higher 400-mg BID dose in 3 patients, given that it would potentially be better tolerated with half the amount of oral capsules to ingest. However, DLT was seen in 2 patients (grade 3 nausea/vomiting/restlessness), and MDT was determined at 300 mg. Phase II patients (n = 32) received a total of 247 veliparib treatment cycles with a median treatment duration of 6 cycles (range, 1–34 cycles).

Reasons for treatment discontinuation in phase I were PD in 10 patients, toxicity in 2 patients, patient's wish in 1 patient, postponed treatment in 2 patients, and death in 1 patient. Regarding phase II treatment, discontinuation was caused by disease progression in 31 patients and toxicity in 1 patient.

The most common treatment-associated toxicities were fatigue and nausea and vomiting. Adverse events are listed in Table 2 for both phase I and phase II and are presented as the worst grade per patient. No patients had their dose reduced in phase II.

TABLE 2. Treatment-related toxicity (reported as possible, probably, or uncertain related to veliparib) for all intention-to-treat patients—phase II

	No. Adverse Events by Grade (n = 32)		
Adverse Event	**Grade 1, n (%)**	**Grade 2, n (%)**	**Grade 3, n (%)**
Anemia	8 (25)	2 (6)	1 (3)
Neutropenia	0 (0)	0 (0)	1 (3)
Thrombocytopenia	3 (9)	0 (0)	0 (0)
Fatigue	11 (34)	7 (22)	1 (3)
Alopecia	1 (3)	0 (0)	0 (0)
Constipation	5 (16)	1 (3)	0 (0)
Diarrhea	1 (3)	2 (6)	0 (0)
Nausea	15 (47)	7 (22)	1 (3)
Vomiting	6 (27)	3 (9)	1 (3)
Stomatitis (dry mouth)	3 (9)	0 (0)	0 (0)
Neuropathy—motor	0 (0)	0 (0)	0 (0)
Neuropathy—sensory*	1 (3)	0 (0)	0 (0)
Skin toxicity/rash	1 (3)	0 (0)	0 (0)
Edema	4 (13)	1 (3)	0 (0)
Pain†	1 (4)	0 (0)	0 (0)
Hypomagnesemia	7 (22)	1 (3)	0 (0)
Hypocalcemia	2 (6)	0 (0)	1 (3)
Hypercalcemia	1 (3)	0 (0)	0 (0)
Dizziness	6 (19)	1 (3)	0 (0)
Restlessness	3 (9)	0 (0)	0 (0)
Hot flushes	2 (6)	1 (3)	0 (0)
Headache	2 (6)	0 (0)	0 (0)
Seizure	2 (6)	0 (0)	0 (0)
Cough	1 (3)	0 (0)	0 (0)
Dysgeusia	2 (6)	0 (0)	0 (0)
Deep vein thrombosis	0 (0)	1 (3)	0 (0)
Pulmonary embolism	0 (0)	1 (3)	0 (0)
Acid reflux	1 (3)	0 (0)	0 (0)

There were no grade 4 treatment-related toxicities.

*46.9% of the patients had preexisting baseline neuropathy (sensory) grade 1/2.

†53.1% of the patients had preexisting baseline pain (mostly abdominal) grade 1/2.

Response and Survival

Of the first 18 patients included in step 1, phase II, 11 patients had either a CA-125 or a RECIST PR and 1 patient had a CR. Consequently, accrual continued for a total of 32 patients. Responses according to both CA-125 and RECIST are shown in detail in Table 3. All patients were eligible by either RECIST or CA-125 except for 1 patient who stopped treatment early after only a few weeks of treatment because of grade 3 toxicity (nausea and vomiting) and had no further imaging or CA-125 measurements performed and were therefore NE by both RECIST and CA-125. Response rates in platinum intermediate sensitive were almost similar to the response rates detected among patients with platinum-resistant disease. In total, 65% of the included patients had either CR or PR as their overall response when combining RECIST and CA-125 response. Median duration of response for the 21 overall responders (investigator assessed) was 7.6 months (95% confidence interval [CI], 5.5–9.2 months).

Median PFS was 5.6 months (95% CI, 5.2–7.3 months), and OS was 13.7 months (95% CI, 10.2–17.3 months). Patients with platinum-intermediate-sensitive disease had significantly longer PFS ($P = 0.037$) and OS ($P = 0.02$) compared with patients with platinum-resistant disease, as illustrated in Figure 1.

DISCUSSION

The present trial found an unprecedented high response rate of 65% in patients with recurrent OC no longer sensitive to platinum and with a favorable toxicity profile.

In this group of patients with multiple disease relapses and a relatively poor prognosis, there was 1 patient in phase I who received 49 cycles (4 years of treatment) and another patient in phase II who was treated with 34 cycles (almost 3 years of treatment). The only other option for many of these women would have been palliative chemotherapy or perhaps no treatment as most patients were heavily pretreated. Therefore, a daily oral treatment without the otherwise commonly encountered chemotherapy toxicity was extremely attractive, well tolerated, and patient friendly, with attendance at the outpatients department only once a month. A total of 10 patients (21%) received at least 10 cycles of treatment, but despite the fact that a large proportion of patients had benefit from treatment, resistance ultimately occurred at some point in all patients with disease progression. Patients with germline *BRCA* mutations appear to be positively correlated with increased survival and responsiveness to chemotherapy. Because of this characteristic "BRCA feature," it can be anticipated that patients with BRCA-associated OC will be exposed to multiple lines of various chemotherapeutic agents during their treatment. With this in

TABLE 3. Response rates

Response	Overall Response	CA-125 Response	RECIST Response
Single-Agent Veliparib (Phase II Data)			
CR	2 (6%)	4 (13%)	1 (3%)
PR	19 (59%)	14 (44%)	13 (41%)
SD	2 (6%)	5 (16%)	9 (28%)
PD	8 (25%)	2 (6%)	6 (19%)
NE	1 (3%)	7 (22%)	3 (9%)

Single-Agent Veliparib Divided Into Platinum Intermediate Sensitive and Platinum Resistant (Phase II Data)

	Overall Response		CA-125 Response		RECIST Response	
Response	Platinum Intermediate Sensitive	Platinum Resistant	Platinum Intermediate Sensitive	Platinum Resistant	Platinum Intermediate Sensitive	Platinum Resistant
CR	1 (10%)	1 (5%)	2 (20%)	2 (9%)	1 (10%)	0 (0%)
PR	6 (60%)	13 (59%)	4 (40%)	10 (46%)	4 (40%)	9 (41%)
SD	0 (0%)	2 (9%)	1 (10%)	4 (18%)	1 (10%)	8 (36%)
PD	3 (30%)	5 (23%)	0 (0%)	2 (9%)	3 (30%)	3 (14%)
NE	0 (0%)	1 (5%)	3 (30%)	4 (18%)	1 (10%)	2 (9%)

The 4 patients with primary platinum resistance are not shown separately. They showed an overall response of 1 CR, 1 PR, 1 SD, and 1 PD.

mind, chemotherapy TFIs or prolongation of TFI with a PARP inhibitor such as veliparib or others may be of particular importance to this patient population, as they allow adequate recovery from cumulative adverse reactions in preparation for additional treatment regimens with more cytotoxic chemotherapy. With a very high overall response rate of 70% in the subgroup of patients with partially platinum-sensitive disease, it is an obvious opportunity to consider treating these patients with a PARP inhibitor instead of reinducing platinum-based chemotherapy, also in order to extend the TFI.

One of the first communications on clinical activity of PARP inhibitors, published in the *New England Journal of Medicine*, indicated a high efficiency in breast, ovarian, and prostate cancers with *BRCA1* and *BRCA2* mutations treated with single-agent olaparib in a phase I trial.[15] This early phase I study was expanded to evaluate olaparib in an OC cohort of *BRCA1* and *BRCA2* mutation carriers to further evaluate tumor activity. Twenty patients had CR or PR by RECIST and/or GCIG CA-125 criteria, and 3 patients had stable disease (SD) for longer than 4 months, resulting in a clinical benefit rate of 46%.[16] Statistically significant differences in response among platinum-sensitive, platinum-resistant, and platinum-refractory populations (61%, 42%, and 15%, respectively) were shown in a post hoc analysis.

The results promoted a US Food and Drug Administration (FDA) accelerated approval in December 2014 to olaparib (Lynparza) for women with advanced OC and a germline *BRCA* mutation who have received 3 or more chemotherapy regimens.

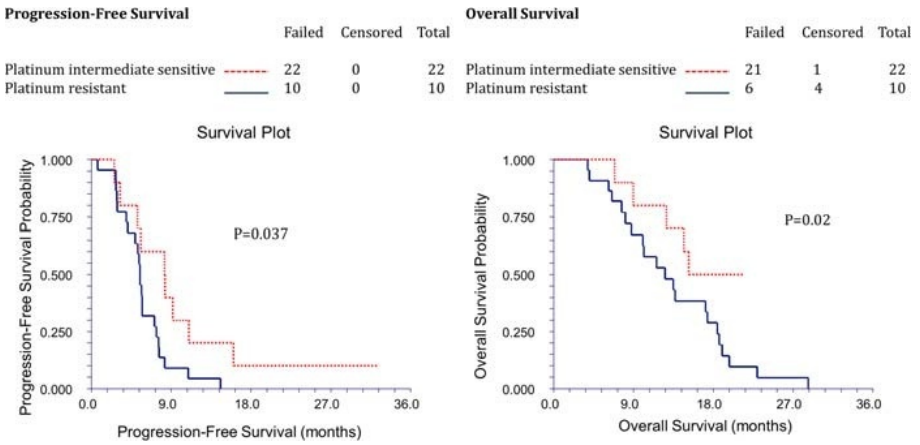

FIGURE 1. Progression-free survival and OS for all intention-to-treat patients' phase II data (n = 32).

The FDA approval of olaparib was based on a multicenter phase II study[17] including ovarian, breast, pancreatic, and prostate cancer patients. In the 193 participants with germline BRCA mutated OC, an objective response rate (CR or PR) of 31.1% was reported, and an additional 40% of the patients had SD for more than 8 weeks, supporting the clinical benefit of this new treatment principle.

The effect of PARP inhibitors in OC has been further underlined in another phase II study[18] with 33 OC patients, most of them platinum resistant. The response rate according to RECIST criteria was 33% (6% CR and 27% PR). A higher response rate of 61% was found according to RECIST and/or GCIG CA-125 criteria, which are in agreement with our results. The median duration of response was 9.6 months and with a comparable median PFS of 5.8 months. The treatment was also well tolerated.

The PARP inhibitor used in the present study, veliparib, has also been investigated in another phase II study[19] with 50 patients but treated with a higher dose of 400 mg BID in BRCA-positive patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. In this similar study, 30 patients (60%) were platinum resistant. The median number of cycles administered was 6, and the median PFS was 8.1 months. The response rate was lower with 2 patients (4%) with a CR and 11 patients (22%) with a PR compared with that of the present study, but it should be noted that the evaluation was based on RECIST alone compared with our study. Conversely, their response exclusively determined by RECIST is not much different for the strict RECIST response rates reported separately in our study (3% and 41%, respectively). The difference is small and probably of minor importance. Our study included patients with a worse prognosis because we did not include sheer platinum-sensitive patients who typically have a somewhat better prognosis.

Moreover, several randomized phase II or phase III studies[20–23] have been conducted in patients with platinum-sensitive relapse, but in these studies with either olaparib or niraparib, the explored PARP inhibitor has mainly been used as maintenance therapy after response to platinum-based treatment of recurrent disease. Based on phase III data, the FDA approved niraparib in March 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy.

A further PARP inhibitor rucaparib has also been investigated in several trials. In the ARIEL2 trial[24] including 204 patients with platinum-sensitive relapse, the median duration of treatment was 5.7 months with median PFS after rucaparib treatment of 12.8 months (95% CI, 9.0–14.7) in the *BRCA* mutant subgroup (n = 40). This study also led to FDA approval of rucaparib in December 2016 for treatment of patients with deleterious *BRCA* mutation (germline and/or somatic)–associated advanced OC who had been treated with 2 or more chemotherapies.

In these studies, the effect of PARP inhibitor treatment has also been striking and mainly in patients with a deleterious (germline and/or somatic) *BRCA* mutation, and one cannot avoid to reach the obvious conclusion that it is a class effect across different PARP inhibitors.

Multiple first-line studies across all PARP inhibitors are ongoing, pursuing the convincing results detected in the relapse setting. One of these, the M13-694/GOG3005 study, is a phase III placebo-controlled randomized trial that is evaluating veliparib in combination with frontline chemotherapy and as frontline maintenance is the only phase III trial to include a PARP inhibitor concomitant with frontline chemotherapy, although several phase III trials (SOLO-1, PRIMA, and PAOLA-1) evaluate the use of a PARP inhibitor frontline, but only as maintenance therapy.

This is a new era for patients with OC, and leaves a hope that successful treatment with PARP inhibitors will eventually become a general treatment for these patients internationally.

In conclusion, the present study demonstrated high efficacy of veliparib in heavily pretreated patients with recurrent epithelial OC no longer sensitive to platinum-based treatment.

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