Gynecologic Oncology 137 (2015) 386–391

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation — An NRG Oncology/Gynecologic Oncology Group study ☆

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HIGHLIGHTS

- Veliparib has single-agent activity among germline BRCA1/2 mutation carriers.
- Adverse events were observed but generally mild and managed conservatively.
- Responses were observed among platinum-sensitive and -resistant recurrent disease patients.

ARTICLE INFO

Article history:
Received 11 February 2015
Accepted 16 March 2015
Available online 24 March 2015

Keywords:
Veliparib
Ovarian cancer
PARP inhibitor
Toxicity
Phase II trial
BRCA1, BRCA2 mutation

ABSTRACT

Background. Veliparib is a potent small molecule inhibitor of PARP-1/2, which is cytotoxic in tumor cells with deficiencies in *BRCA1* or *BRCA2*. We studied the clinical activity and toxicity of veliparib in ovarian cancer patients carrying a germline *BRCA1* or *BRCA2* mutation (*gBRCA*).

Methods. Eligibility included three or fewer prior chemotherapy regimens, measurable disease and no prior use of a PARP inhibitor. Veliparib was administered at 400 mg orally BID with one cycle being 28 days. The two-stage Simon design was capable of detecting a 25% response probability with 90% power while controlling alpha = 10% (at a 10% assumed null response probability).

Results. The median age of the 50 eligible patients was 57 years (range 37–94) and 14, 18, and 18 patients had 1, 2, and 3 prior therapies respectively. Thirty patients (60%) were platinum-resistant. The median number of cycles administered was 6 (1–27). There was one grade 4 thrombocytopenia. Grade 3 adverse events were: fatigue (n = 3), nausea (2), leukopenia (1), neutropenia (1), dehydration (1), and ALT (1). Grade 2 events >10% were: nausea (46%), fatigue (26%), vomiting (18%), and anemia (14%). The proportion responding was 26% (90% CI: 16%–38%, CR: 2, PR: 11); for platinum-resistant and platinum-sensitive patients the proportion responding was 20% and 35%, respectively. The most common reason for treatment discontinuation was progression (62%). Twenty-nine patients are alive; two with SD remain on veliparib. The median PFS is 8.18 months.

☆ This trial was registered at clinicaltrials.gov (NCT01540565).

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http://dx.doi.org/10.1016/j.ygyno.2015.03.042

Conclusions. The single agent efficacy and tolerability of veliparib for BRCA mutation-associated recurrent ovarian cancer warrants further investigation.

1. Introduction

Synthetic lethality was first described by the American geneticist Calvin Bridges in 1922 who noted when crossing fruit flies that certain non-allelic genes were lethal only in combination [1]. His colleague Theodore Dobzhansky coined the term 20 years later [2], and in 1997 Hartwell et al. proposed exploiting this phenomenon as an anti-cancer strategy [3]. Clinically, one of the more developed synthetic lethality programs has been the administration of poly-(ADP-ribose) polymerase (PARP) inhibitors in patients carrying a mutation in the tumor suppressor genes, *BRCA1* or *BRCA2* [4]. The BRCA1 and BRCA2 proteins both function in the performance of error-free repair of double-strand DNA breaks through homologous recombination [5]. Loss of functional protein via germline or somatic mutation leads to increased reliance on more error prone DNA repair mechanisms, promoting carcinogenesis. The loss of homologous recombination DNA repair in ovarian carcinomas associated with *BRCA1* or *BRCA2* mutations leads to increased sensitivity to platinum-based agents and longer survival [6]. Preclinically, it was observed that cells lacking functional *BRCA1* or *BRCA2*, were up to 1000 fold more sensitive to PARP inhibition than wild type cells [7,8]. The exact mechanism by which this synthetic lethality is leveraged is not completely understood, but likely occurs due to the functionality of PARP in repairing single strand defects as well as, release of governance over error-prone non-homologous end joining (NHEJ) pathways leading to more frequent mitotic catastrophe and cellular death [9].

Clinically, evidence of tumor response has been documented in several clinical settings among germline BRCA mutation carriers, including treatment of measurable breast or ovarian metastases as well as, secondary maintenance in patients with ovarian carcinoma responding to platinum [10–15]. Veliparib (ABT-888) is a novel small molecule agent that inhibits PARP-1 and PARP-2 at nanomolar concentrations [16]. It has good oral bioavailability and crosses the blood–brain barrier. In syngeneic and xenograft tumor models, veliparib potentiates temozolomide, platinum compounds, cyclophosphamide, and radiation [16].

In the clinical arena veliparib has been predominantly studied in combination with cytotoxic chemotherapy. In the I-SPY2 breast cancer trial, the combination of veliparib and carboplatin graduated with the triple-negative signature [17]. As documented for other PARP inhibitors, objective responses were observed and indicated further clinical investigation. However, limited information exists regarding the efficacy of single agent veliparib. A single-agent phase I study demonstrated the maximum tolerated dose to be 400 mg BID [18–20]. In light of these findings and the strong preclinical and clinical rationale, we conducted an open label, phase II, multi-centered clinical trial to evaluate veliparib in a population of BRCA mutation-carrying women with recurrent ovarian cancer. Herein, we demonstrate that veliparib met prespecified efficacy parameters warranting further clinical investigation.

2. Methods

2.1. Patients

Eligible patients had histologic documentation of primary ovarian, fallopian tube, or primary peritoneal cancer by central pathology review [Gynecologic Oncology Group (GOG) Pathology Committee] and carried a deleterious mutation in *BRCA1* or *BRCA2* (confirmation was required via clinical report, BRCAnalysis, Myriad Genetics, Salt Lake City, UT). Up to 3 prior cytotoxic regimens were allowed. GOG performance status 0–2 was allowed for one previous regimen; 0–1, for 2–3 regimens. Prior biological therapy was allowed. All patients were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST 1.1), have discontinued prior chemotherapy (≥3 weeks) and hormonal therapy (≥1 week) before registration, and recovered from effects of recent surgery, radiotherapy, or chemotherapy [21]. Other eligibility and ineligibility are presented in the Supplemental Methods. All patients signed approved informed consent in accordance with federal, state, and local requirements and provided authorization, permitting release of personal health information.

2.2. Treatment

Enrolled patients received veliparib 400 mg orally BID until progression or intolerance. One cycle equaled 28 days. Dose modifications were allowed (300 mg BID and 200 mg BID) for toxicity. Patients were to take veliparib 12 h apart; dosing delays of ≥4 h were skipped. Veliparib could be taken with or without food but patients were cautioned about agents inhibiting CYP1A2 or CYP3A4. A pill calendar was kept by the patient and reviewed at each visit, as were concomitant medications. As nausea was an anticipated side effect, patients were instructed on the use of anti-emetics.

2.3. Toxicity

Toxicity was monitored before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version-4). Veliparib was held up to a maximum of 3 weeks for grade 3–4 hematological or non-hematological toxicity. Continuation with dose reduction was allowed if there was recovery to grade 0–1. Grade 2 or greater peripheral neuropathy required reduction of one dose level and delay of subsequent therapy until resolution to grade 0–1 for a maximum of 3 weeks. In addition, veliparib could be held and/or reduced for grade 2 toxicity not adequately controlled by concomitant medication and/or supportive care. It was anticipated patients could have nausea and diarrhea with veliparib limiting dose compliance. As such, investigators were allowed to reduce the dose of veliparib within a treatment cycle for persistent grade 1–2 toxicity. Dose reduction was preferred to dose delay. However, patients experiencing a treatment-related dose delay of ≥3 weeks or intolerable toxicity at the lowest dose (200 mg PO BID) were removed from study. No dose escalations were allowed. Treatment was planned until disease progression or adverse events prohibited further therapy.

2.4. Evaluation criteria

All patients had measurable disease and were evaluated for clinical efficacy using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [21]. Target lesions were to be ≥1 cm in longest diameter by computed tomography or magnetic resonance imaging, ≥2 cm by chest X-Ray, or ≥1 cm by physical exam using calipers, except lymph nodes, which were to be ≥1.5 cm on the short axis [22]. CA-125 information was collected, but was not used as a criterion for progression. However, patients achieving a complete clinical response of measurable disease had to additionally have a normalized CA-125, if it was elevated upon study entry. Assessment was performed at baseline, every other cycle for the first six months, and every three months thereafter until documentation of disease progression was obtained or as clinically indicated.

2.5. Statistical methods

The primary endpoint of this trial was objective tumor response as assessed by the investigator. The null hypothesis relating to uninteresting levels of activity was determined from results of a study evaluating a PARP agent, previously reported in the literature and an analysis of a historical control of recurrent ovarian cancer patients with high grade serous cell type [23]. The null hypothesis specified the probability of a patient experiencing a tumor response to be ≤10%. Interesting levels of the proportion responding under the alternative hypothesis was ≥25%. To evaluate these hypotheses in a two-stage design, a method provided by Chen and Ng was used to determine if there were sufficient objective responses to continue study into the second stage and deem the drug worthy of further investigation [22]. The targeted accrual for stage 1 was 23 (allowed to deviate from 19–26 patients [24]) and at least three responses were required before the study would open to the second stage. If met, then 48 patients was the targeted accrual (allowed to deviate 44–51 patients) requiring at least 8 responses before declaring the regimen worthy of further investigation. This study had a 45.9% probability of early termination under the null hypothesis. The study had a level of significance of 10.2% with 92.1% power under the alternative with true probability of response equal to 25%.

Secondary objectives were progression-free survival (PFS), event-free survival (EFS) and overall survival (OS), the proportion of patients who survived progression-free/event-free for at least six months (PFS6/EFS6), and the frequency and severity of treatment-related adverse events. PFS was defined as the time from study enrollment until progression or death; EFS was defined as the time until progression, death, or subsequent therapy, and OS was defined as the time from registration until death or last visit. Kaplan–Meier estimates of the survival function were provided for both PFS and OS [25]. Estimated proportions between groups were compared by Fisher's exact test.

Exploration of response modifiers, such as single nucleotide polymorphisms (SNPs) in DNA repair genes, PARP1 expression levels, and P-glycoprotein transporter regulation will be reported subsequently.

3. Results

3.1. Patient's characteristics

Fifty-two patients were enrolled from April 2012 through November 2012; two were excluded, one for inadequate pathology and one for a clerical error. This left 50 evaluable patients for toxicity and response. Table 1 presents patient characteristics. Of note, 72% of patients received two or three prior regimens of therapy and 60% were platinum-resistant. As expected, the majority of patients had serous epithelial cancer and aged younger (median 57 years, range: 37–94) than typical recurrent ovarian cancer patients without BRCA mutations.

3.2. Adverse events

The median dose intensity over all patients across all cycles was 17,525 mg/cycle (first and second quartiles were 12,000 and 22,239 mg/cycle, respectively). This translates into a median of 78.2% of the targeted dose (Q1 and Q3 are 54 and 99%, respectively). A plot of the empirical cumulative distribution function is provided in Supplemental Figs. 1 and 2. Table 2 lists hematological and non-hematological toxicities. There were no fatal events observed related to the study agent. The most common hematological toxicity was anemia and leukopenia, but was predominantly grades 1–2. There was one grade 3

Table 1
Patient demographics (N = 50).

Characteristic	Category	No. of cases	% of cases
Age	30–39	2	4.0
	40–49	15	30.0
	50–59	14	28.0
	60–69	15	30.0
	70–79	2	4.0
	80–89	1	2.0
	90–99	1	2.0
Race	Unspecified	2	4.0
	Asian	1	2.0
	African American	2	4.0
	Hispanic	2	4.0
	White	43	86.0
Performance status	0	33	66.0
	1	17	34.0
Site of disease	Ovary	44	88.0
	Fallopian tube	1	2.0
	Peritoneum	5	10.0
Cell type	Serous	41	82.0
	Mixed epithelial	2	4.0
	Undifferentiated	2	4.0
	Adenocarcinoma, NOS	4	8.0
	Other	1	2.0
Prior chemotherapy	1 prior regimen	14	28.0
	2 prior regimens	18	36.0
	3 prior regimens	18	36.0
Prior radiation	No	46	92.0
	Yes	4	8.0
Prior immunotherapy	No	47	94.0
	Yes	3	6.0
Prior surgery	No	1	2.0
	Yes	49	98.0
Platinum sensitivity*	Platinum resistant	30	60.0
	Overall platinum sensitive	20	40.0
	GOG platinum sensitive	13	26.0
	Platinum sensitive	7	14.0
Prior platinum regimens	1 prior regimen	16	32.0
	2 prior regimens	28	56.0
	3 prior regimens	6	12.0
BRCA mutation	*BRCA1*	39	78.0
	BRCA2	11	22.0

* "Platinum-resistant" patients are those in whom disease has progressed within 6 months of completing platinum-based therapy. "Overall Platinum Sensitive" is the sum of "GOG Platinum-sensitive" patients, which comprises those in whom disease recurrence was documented between 6 and 12 months following completion of the last platinum-based therapy and "Platinum-Sensitive" patients are those in whom disease recurrence was documented more than 12 months from completion of the last platinum-based therapy.

Table 2
Maximum grade adverse events observed on trial (N = 50).

AE category	0	1	2	3	4	5	Total
Leukopenia	30	14	5	1	0	0	50
Thrombocytopenia	41	8	0	0	1	0	50
Neutropenia	35	9	5	1	0	0	50
Anemia	26	17	7	0	0	0	50
Other investigations	34	11	2	3	0	0	50
Ear and labyrinth	45	4	1	0	0	0	50
Eye	46	4	0	0	0	0	50
Nausea	7	18	23	2	0	0	50
Vomiting	21	20	9	0	0	0	50
Other gastrointestinal	17	24	9	0	0	0	50
General and administration site	16	18	13	3	0	0	50
Infections/infestations	48	0	2	0	0	0	50
Metabolism/nutrition	26	18	5	1	0	0	50
Musculoskeletal/connective tissue	38	12	0	0	0	0	50
Peripheral sensory neuropathy	48	2	0	0	0	0	50
Nervous system	27	17	6	0	0	0	50
Psychiatric	35	11	4	0	0	0	50
Renal/urinary	49	0	1	0	0	0	50
Reproductive/breast	49	1	0	0	0	0	50
Respiratory/thoracic/mediastinal	45	4	1	0	0	0	50
Skin/subcutaneous	42	7	1	0	0	0	50
Vascular disorders	45	4	1	0	0	0	50

Other investigations included laboratory parameters such as increased alanine aminotransferase (N = 1 grade 3, N = 4 grade 1) and aspartate aminotransferase (N = 4 grade 1, N = 1 grade 2), and weight loss (N = 2, grade 1).

Table 3
Treatment outcome parameters (N = 50).

Characteristic	Category	No. cases	% cases
Response	Complete response	2	4.0
	Partial response	11	22.0
	Stable disease[1]	24	48.0
	Increase disease	7	14.0
	Indeterminate	6	12.0
PFS > 6 months	No	23	46.0
	Yes	27	54.0
EFS > 6 months	No	28	56.0
	Yes	22	44.0
Cycles of treatment	1	8	16.0
	2	6	12.0
	4	8	16.0
	5	2	4.0
	6	7	14.0
	9+	19	38.0
Off study	No[1]	4	8.0
	Yes	46	92.0
Why off study	On study/unspecified	4	8.0
	Disease progression	31	62.0
	Refused further treatment	4	8.0
	Toxicity	11	22.0
Alive		29	58.0
Dead	From disease	19	38.0
	Undetermined	2	4.0

[1] Two patients with stable disease are still on study therapy and could respond. However, all of these patients have been on study for at least 6 months.

neutropenia and one grade 4 thrombocytopenia, both of which resolved with dose delay and dose reduction. As expected, the most common non-hematological event was gastrointestinal-related. While there were no grade 4 events, 25 (50%) of the cohort reported grade 2 (N = 23), or grade 3 (N = 2) nausea and nine (18%) had grade 2 vomiting. These were most problematic in the first cycle (nausea, N = 41; vomiting, N = 24) and easily controlled with brief dose interruption and/or dose reduction. However, 32 (78%) and 9 (38%) of these patients had nausea or vomiting, respectively, in subsequent cycles. Antiemetic use was not captured in this cohort. In addition, 16 patients (grade 2, N = 13, grade 3, N = 3) reported fatigue. In all, 11 evaluable patients (22%) were removed from study due to toxicity after a median 2 cycles (range 1–6, Table 3). Overall, there were 11 patients who experienced dose delays over 22 total cycles. Most of these delays were due to scheduling issues, however, 2 cycles were delayed due to adverse events. Thirty-one patients (N = 95 total events) underwent dose reductions, predominately for GI toxicity (N = 33 events) and hepatic toxicity (N = 2 events).

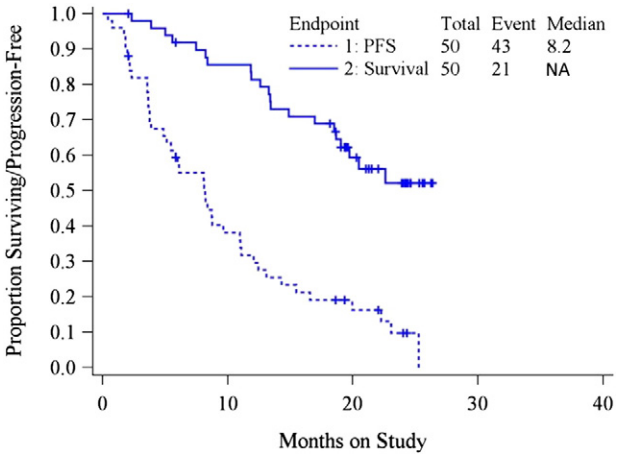

Fig. 1. Progression-free survival and overall survival are presented for the evaluable cohort (N = 50). Median PFS is 8.11 months and ranges from 0.43 to 19.55 months; median OS is 19.7 and ranges (to date) from 2.3 to 19.7 months.

3.3. Clinical activity

Table 3 details further clinical efficacy parameters. More than 424 monthly doses of veliparib were administered to this cohort with the median number of cycles being 6 (Inner Quartile Range (IQR):2–12 cycles). There were two complete and 11 partial responses producing an overall response rate of 26% (90% Confidence Interval (CI):16%–38%). Stable disease was observed in 24 other patients (48%), and includes 2 patients still on study treatment for more than 6 months. The most common reason for treatment discontinuation was disease progression, occurring in 31 (62%) of participants. Twenty-seven patients were progression-free at six months (PFS_6: 54%; 90% CI: 41%–66%). Fig. 1 presents the Kaplan–Meier survival PFS and OS curves for evaluable patients; median PFS is 8.18 months and median OS is not estimable at this time (likely >26 months). PFS based on CA125 (GCIG) criteria is presented in Supplementary Fig. 3. The median PFS was 23.4 months, but this analysis is considered unreliable due to the low number of events (n = 14) and the potential for non-random censoring.

Since PARP inhibitor clinical efficacy has been proportionally associated with platinum-sensitivity we analyzed this variable (defined as progression on or within 6 months of completion of the last platinum-based regimen) relative to veliparib response. As can be appreciated in Table 4, veliparib demonstrated objective responses in both patients with platinum-resistant (N = 6/30, 20%; 90% CI: 9%–36%) and platinum-sensitive (N = 7/20, 35%; 90%CI: 18%–56%) recurrent disease; this difference was not significantly different (Fisher's Exact P = 0.33). Similarly, the proportion responding between BRCA1 and BRCA2 mutation carriers was similar (26% and 27%, respectively) as was the PFS (Fig. 2). Finally, since up to 3 prior lines of therapy were allowed, we analyzed the frequency of cases responding by the number of prior regimens. The proportion responding was 43%, 22% and 17% for 1, 2, and 3 prior lines of therapy respectively. The Cochran–Armitage trend test was borderline suggestive (0.05 < exact one-sided p-value < 0.10). Spearman's correlation coefficient was −0.23 (asymptotic 95% CI −0.50–0.04).

4. Discussion

This multicenter, open-label phase II clinical trial demonstrated single agent activity of veliparib among women with BRCA-mutation positive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer and represents the first such study with veliparib. The trial was conducted in this setting to provide rationale for further clinical development. The observed objective response rate of 26% met our primary endpoint, which was established by outlining a sufficient level of clinical activity to distinguish veliparib from other ineffective therapies evaluated in recurrent ovarian cancer patients. Of interest, veliparib produced a 20% response rate in patients with platinum-resistant disease, and despite a trend toward lower response rates following each line of subsequent therapy, veliparib was associated with responses across a broad spectrum of patients with recurrent disease. This may be due to disassociation of mechanisms inducing platinum resistance that do not

Table 4
Best clinical response and progression-free survival by platinum-sensitivity status.

	Platinum sensitivity	
Response	Resistant N (% of category)	Sensitive N (% of category)
Complete	0	2 (10)
Partial	6 (20)	5 (25)
Stable disease	6 (53)	8 (40)
Progression	6 (20)	1 (5)
Indeterminate	2 (7)	4 (20)
PFS median	5.8 months	11.0 months
Total	0	20

PFI: platinum-free interval. PFS: progression-free survival.

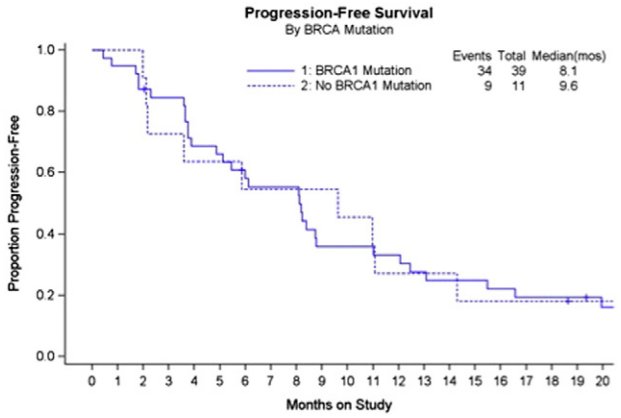

Fig. 2. Progression-free survival is illustrated by genotype in the evaluable cohort (N = 50). There was no significant difference in PFS between these cohorts with the median PFS in BRCA1 and BRCA2 patients being 8.1 and 5.8 months, respectively.

similarly define PARP inhibitor activity. In addition, an induced platinum-resistance phenotype may revert under stem cell clonal expansion with subsequent lines of non-platinum therapy [26,27]. Previous studies have also suggested that PFS and OS may be better for gBRCA2 carriers reflecting greater vulnerability to platinum-based chemotherapy. Although a small sample, we observed similar progression-free survival hazard rates in gBRCA1 and gBRCA2 carriers. Based on these observations, neither selection parameter appears definitive to dissuade use of veliparib in these settings [28].

Veliparib use produced several adverse events, particularly gastrointestinal. However, its toxicity profile is similar to other PARP inhibitors, including olaparib, the most extensively studied agent in this class [10,12]. Compared to olaparib, veliparib appears to have similar rates of nausea but less hematologic toxicity (e.g., 2% grade 3 or 4 neutropenia versus 9% with olaparib in a similar setting) [23]. As noted, the median dose intensity was 17,525 mg/cycle and 78% of patients had dose modification, predominately for nausea and vomiting. As an orally administered agent, these adverse events can be troubling in maintaining compliance with dose administration. We sought to aggressively institute preemptive nausea control interventions, as well as, intracycle dose reduction. This appears to have significantly improved tolerance without significant additional treatment delay. In addition, while there was frequent dose modification in this trial due to nausea, it appeared to abate after the first two weeks of treatment. Although, no dose re-escalations were allowed in this trial, we would recommend future trials of single agent veliparib initiate therapy at 400 mg p.o. b.i.d. but allow later dose re-escalation for a nausea-induced reduction.

PARP inhibitors have been of great interest in patients who carry a germline mutation in the BRCA genes (gBRCA) based on the preclinical synthetic lethality seen in this setting [7,8]. Subsequent reports have identified that somatic deletion in BRCA (sBRCA) also confers sensitivity to this class of agent [11,29]. A recent update of the randomized phase II olaparib maintenance trial provided an expanded analysis (79% of randomized population) of gBRCA or sBRCA status. In this analysis 136 of 265 patients carried either gBRCA or sBRCA. Relative to control, those patients receiving olaparib maintenance had a reduction in the hazard of progression by 82% (HR: 0.18, 95% CI: 0.1–0.31). Since only approximately 15% of ovarian cancer patients carry gBRCA, the expansion of the potential target audience by demonstrating efficacy among those with sBRCA, as well as somatic events impairing other genes governing homologous recombination (HR) could greatly expand the target population. It is estimated that an additional 35% of primary ovarian cancer patients develop such somatic events and could achieve objective benefit from this class of therapy [30,31].

Given the strong connection between HR deficiency and response due to PARP inhibitors, it is unclear why patients, particularly gBRCA carriers, are either primarily resistant to PARP inhibition or develop resistance on therapy. In our study of gBRCA carriers, 14% were primarily resistant to veliparib and 28% ultimately progressed on therapy. Previous preclinical work has suggested that relative to primary ovarian tumors, metastatic cells may be less sensitive PARP inhibition [32]. Understanding these processes would help predict those most likely to benefit from this line of therapy. At least 4 different mechanisms of innate or acquired PARP resistance have been postulated [33]. The best defined has been the discovery of a secondary mutation in the BRCA gene that either restores it to wild-type status or restores BRCA gene functionality via alterations in its open reading frame (ORF) [34–36]. This aberration in the ORF nearly always encodes the C-terminal RAD51 binding domain thus promoting protein translation. The frequency to which mutational restoration of the ORF occurs is not well known, but may be related in part to primary platinum-refractory disease and those who develop secondary platinum-resistance [35]. A second resistance mechanism related to *BRCA1* lies in the loss of 53BP1, a gene that regulates and promotes non-homologous end joining (NHEJ) [37]. Under normal circumstances, PARP inhibition would promote this error-prone repair mechanism leading to cancer cell cytotoxicity. However, it has been recently shown that loss of 53BP1 expression promotes HR competency in g*BRCA1*-mutated cells. Of interest, this loss promoted sensitivity to DNA crosslinking agents, such as platinum and if confirmed could be used as a new treatment paradigm [37,38]. Third, cellular transport mechanisms that impact intracellular drug accumulation may also act to export PARP inhibitors before initiating cytotoxicity. It has been shown that PARP inhibitor responses are altered by ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp) [39]. Preclinical studies pharmacologically inhibiting of P-gp (e.g. verapamil) restored PARP inhibitor response. These observations support clinical investigation of concomitant administration or P-gp and PARP inhibitors, as well as, pharmaceutical development of PARP inhibitors that are not P-gp substrates. Finally, levels of PARP expression may influence activity of these agents and may implicate differential activity among PARP inhibitors. While both single strand breaks and DNA–PARP complexes are cytotoxic, the later may be more so. Trapping PARP–DNA complexes at the site of DNA damage appears to confer greater cytotoxicity, thus less enzymatic activity from decreased intrinsic or acquired PARP expression may impact an agent's cytotoxicity [40]. The overall impact in exploring each of these mechanisms is establishing better patient–drug matching and developing new avenues of treatment based on acquired events from treatment. Since there is potential for prolonged and repeated therapy with this class of agent alone and in combination with cytotoxic therapy, careful assessment of attendant and emergent toxicity will need to be conducted to fully understand their therapeutic ratio.

In summary, veliparib demonstrated significant treatment effects (objective response and delay in progression) with an acceptable toxicity profile in women with gBRCA mutant epithelial ovarian cancer. We acknowledge that an open-label single arm trial has limitations in assessing magnitude of effect and toxicity against control comparators [41], and can be subject to investigator bias. However, our intent was exploratory in a well-defined genotyped population and we established parameters of desired clinical activity from similarly treated patients on other GOG trials. In this regard, the trial met its pre-specified level of clinical activity to warrant further investigation, which is already underway as veliparib now joins several other PARP inhibitors (e.g. olaparib NCT01844986, NCT01874353, niraparib NCT 01847274, rucaparib NCT01968213) being studied in the phase III setting among patients with ovarian cancer.

Future analysis of response characteristics relative to alterations in the genes governing homologous recombination will provide additional support to further hone patient selection in coming clinical investigations.

Conflict of interest

The authors wish to disclose that there are no conflicts of interest with the exception of Dr. Robert Coleman, Dr. Carol Aghajanian and Dr. Thomas Rutherford as detailed below. Dr. Coleman reports that he has received funding from Clovis as well as non-financial support from AstraZeneca and Merck. Dr. Coleman also reports funding from Merck, Janssen, Amgen, Novartis, Merrimack, Millennium, OncoMed, Array, and EMD Serono, Inc. Dr. Carol Aghajanian received an honorarium as a one-time ad board member in addition to travel expenses. Additionally, Dr. Aghajanian received funding for travel from Abbvie for clinical trial planning meetings. Dr. Thomas Rutherford reports that he is a member of GOG#280 clinical trial at Yale University.

Acknowledgments

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical and Data Center (CA 37517). This was also supported, in part, by NIH grant P50 CA098258.

The following Gynecologic Oncology Group member institutions participated in this study: Duke University Medical Center, Florida Hospital Cancer Institute Protocol Office, Johns Hopkins University, Cancer Care Northwest — Spokane South, Tacoma General Hospital, Pacific Gynecology Specialists, Providence Regional Cancer Partnership, Seattle Cancer Care Alliance, Northwest Hospital, Abramson Cancer Center of The University of Pennsylvania, Norton Health Care Pavilion — Downtown, Hope Women's Cancer Centers-Ashville, Stanford University Hospitals and Clinics, Cleveland Clinic Cancer Center/Fairview Hospital, Washington University School of Medicine, Memorial Sloan Kettering Cancer Center, Ohio State University Medical Center, M D Anderson Cancer Center, University of Oklahoma Health Sciences Center, Baylor All Saints Medical Center at Fort Worth, University of Chicago, Loyola University Medical Center, Summa Akron City Hospital/Cooper Cancer Center, Yale University, John Muir Medical Center-Concord Campus, Northside Hospital, UCSF-Mount Zion, Mercy Hospital — Coon Rapids, Memorial Medical Center, Christiana Care Health System-Christiana Hospital, McFarland Clinic PC-William R Bliss Cancer Center.

Dr. Coleman is supported in part by the Ann Rife Cox Chair in Gynecology. We also acknowledge Abbvie (North Chicago, Ill) for providing the investigational drug.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.03.042.

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