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Phase Ib with expansion study of olaparib plus weekly (Metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients

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HIGHLIGHTS

- Phase Ib with expansion study of olaparib plus weekly (metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients.
- Relapsed ovarian cancer with *BRCAm* or *BRCAwt*.
- Established maximum tolerated dose of olaparib tablets combined with metronomic chemotherapy.
- Complete remission 24%, partial response 30%, overall response 54%. Progression-free survival and overall survival significantly longer in *BRCAm*.

ABSTRACT

Objective Our goals were to: establish the maximum-tolerated dose of olaparib tablets combined with metronomic carboplatin and paclitaxel in patients with relapsed high-grade serous ovarian cancer; evaluate dose-limiting toxicities; and evaluate efficacy at the maximum tolerated dose.

Methods In this open-label, single-arm, investigator-initiated trial (ClinicalTrials.gov NCT01650376), patients with high-grade serous ovarian cancer who failed primary platinum and taxane therapy received oral olaparib tablets twice daily days 1–3 each week combined with fixed-dose metronomic carboplatin AUC2 and paclitaxel 60 mg/m^2 weekly for 3 out of 4 weeks. A 3 × 3 design was used to determine the olaparib maximum tolerated dose. Combination therapy continued until disease progression, but patients with partial or complete response were transitioned to olaparib maintenance therapy. All patients were included in the analysis.

Results The maximum tolerated dose of olaparib tablets was 150 mg twice daily with metronomic carboplatin and paclitaxel. 54 women were enrolled, 14 in phase Ib and 40 in the expansion phase. The median number of prior therapeutic regimens was 3. Response included 13 complete remission (24%) and 16 partial remission (30%) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for an overall response rate of 54% (95% CI 40% to 67%). Of 47 patients who underwent *BRCA* testing, 23 were *BRCA* mutation (*BRCAm*) and 24 *BRCA* wild type (*BRCAwt*). Progression-free survival for *BRCAm* was 12.1 months versus 4.8 for *BRCAwt* (p=0.0001). Median overall survival for *BRCAm* was 24.1 months versus 10.4 months for *BRCAwt* (p=0.02). 42 patients (78%) experienced grade 3–4 toxicities with combination therapy; the most common were hematologic. There were no treatment related deaths. Among 14 patients who received maintenance therapy, 7 experienced grade 1–2 non-hematologic toxicities.

Conclusions Olaparib 150 mg tablet twice daily can be safely administered in combination with metronomic carboplatin and paclitaxel in pre-treated relapsed ovarian cancer with 24% complete remission. *BRCAm* patients had statistically significant longer progression-free survival and overall survival than *BRCAwt*.

Trial registration number NCT01650376.

INTRODUCTION

Ovarian cancer is the leading cause of death among gynecologic malignancies. There will be an estimated 22 240 new cases of ovarian cancer in 2018 in the USA with 14 070 deaths.[1] Unfortunately, only 15% of ovarian cancers are confined to the primary site at diagnosis while 80% are either regional or distant. The incidence of advanced disease at diagnosis increases with age. Surgical cytoreduction and improved chemotherapies, such as carboplatin and paclitaxel, have resulted in a 47% 5 year survival.[2] However, while the majority of patients respond to initial therapy, only 23% of patients with stage III, and 5% with stage IV, survive to 10 years.[3] Improved treatment options are needed for patients with advanced and relapsed disease.

One exciting new target for therapy in ovarian cancer has been inhibition of poly (ADP-ribose) polymerase (PARP) enzymes. PARP enzymes are involved in base excision repair, the primary pathway for the repair of single strand DNA breaks. Farmer et al were the first to target the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy.[4]

Olaparib is an oral PARP inhibitor approved by the Food and Drug Administration in December 2014 for germline *BRCA*-mutated advanced ovarian cancer patients who failed three or more prior chemotherapy

regimens. In 2017 therapeutic indications were expanded to include maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy regardless of *BRCA* mutation status. Olaparib was recently approved in 2018 for use in patients with metastatic breast cancer and deleterious or suspected deleterious *BRCA* mutation.[5]

Studies demonstrate olaparib is effective across multiple tumor types in patients with *BRCA1/2* mutation.[6 7] Responses have been reported in breast, ovarian, pancreatic, and prostate cancers.[6 7] This anti-tumor activity correlates with platinum sensitivity.[8] Ledermann's study of olaparib in platinum-sensitive patients with high-grade serous ovarian cancer showed anti-tumor activity regardless of BRCA mutation status, though progression-free survival was longer in patients with *BRCA* mutation.[9–11]

Initial attempts to combine olaparib with standard chemotherapy regimens in ovarian cancer were disappointing. Several published reports concluded that olaparib given twice daily in combination with carboplatin and paclitaxel every 3 weeks produced an unacceptable toxicity profile.[12–15] The results of these phase I trials led the manufacturer (AstraZeneca) to consider discontinuing development of olaparib in 2011.[16] However, due to the promising anti-tumor activity observed in patients with *BRCA* mutations during phase I testing, dose and scheduling modifications were recommended for future investigations.[13]

Several studies have shown that weekly carboplatin and paclitaxel for the treatment of recurrent ovarian and fallopian tube cancers have been effective.[17–26] Norton et al recommended treating relapsed ovarian cancer with weekly paclitaxel.[27–29] Pignata et al (MITO-7 trial) compared a weekly schedule of carboplatin plus paclitaxel to the standard schedule of the same drugs every 3 weeks in patients with advanced ovarian cancer and no prior chemotherapy. Findings revealed similar progression-free survival between the two groups. However, patients in the weekly treatment group experienced significantly better quality of life scores and fewer adverse events than the standard therapy group.[30] A more recent study, ICON8, compared three different schedules of administering carboplatin and paclitaxel including dose-dense, standard every 3 weeks, or weekly therapy. The progression-free survival results were the same for all three arms.[31]

Two randomized studies in breast cancer demonstrated weekly paclitaxel is superior to dosing every 3 weeks. Results of a randomized trial with 12 years of follow-up reported weekly paclitaxel was superior to every 3 weeks, with statistically-significant longer disease-free and overall survival in triple negative breast cancer patients.[32] The genetic abnormalities in triple negative breast cancer have been shown to be similar to those in high-grade serous ovarian cancer.[33] A separate study comparing weekly paclitaxel to every-3-week dosing in patients with clinical stage I–IIIA breast cancer resulted in similar clinical response rates. However, the pathologic complete response was higher in the weekly paclitaxel group (28.2% vs 15.7%; P=0.02), with improved breast conservation (P=0.05).[34]

Our experience of adding a small molecule inhibitor to weekly carboplatin and paclitaxel led us to select a similar metronomic schedule for investigating olaparib combination therapy in women with heavily pre-treated ovarian cancer.[35]

This is the first study using metronomic chemotherapy combined with olaparib tablets for treatment in ovarian cancer. The primary purpose of the study was to establish the olaparib maximum tolerated dose and evaluate dose-limiting toxicities when combined with metronomic carboplatin and paclitaxel. We also evaluated the response, safety, and tolerability of this regimen with olaparib tablets at MTD in relapsed ovarian cancer.

METHODS AND ANALYSIS

This open-label, single-arm, phase Ib with expansion, investigator-initiated study was conducted at the Swedish Cancer Institute in Seattle, WA (ClinicalTrials.gov NCT01650376). Six additional sites within the Swedish network, plus Providence Regional Cancer Partnership (Everett, Washington), joined the expansion phase to enroll 40 additional patients. The Western Institutional Review Board approved the study for each site. Patients provided written informed consent before study entry.

Outcomes

The primary objective was to determine the maximum tolerated dose of olaparib tablets twice daily weekly days 1–3 in combination with metronomic carboplatin and paclitaxel administered day 1 every 3 of 4 weeks in women with relapsed serous ovarian cancer. Secondary objectives included preliminary assessments of safety and tolerability, overall response rate, progression-free survival, and overall survival. Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[36] Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.02.[37] Pre-specified exploratory objectives included a comparison of clinical outcomes between: (a) patients whose tumor had *BRCA1/2* mutations (*BRCAm*) versus patients with wild-type tumors (*BRCAwt)*; and (b) platinum-sensitive versus platinum-resistant/refractory patients. In addition, an exploratory analysis was performed to compare clinical outcomes between patients who failed 1–3 prior chemotherapy regimens versus patients who failed ≥4.[36 37]

Participants

Eligible patients had histologically or cytologically confirmed advanced serous ovarian cancer that relapsed after primary platinum and taxane treatment. Patients were platinum-sensitive (relapsed at least 6 months following treatment), platinum-refractory (experienced disease progression on treatment), or platinum-resistant (relapsed within 6 months of treatment). There was not an upper limit to the allowed number of previous treatments. Additional eligibility requirements included: age 18 or older, able to swallow and retain oral medication, life expectancy ≥16 weeks, ECOG (Eastern Cooperative Oncology Group) performance status of 0–2, normal organ and bone marrow function, and at least one measurable disease lesion per RECIST 1.1.[36] Testing for germline *BRCA1/2* mutation was performed when possible, but was not required for study entry. The major exclusion criteria were prior use of a PARP inhibitor, myelodysplastic syndrome, acute myeloid leukemia, or uncontrolled brain metastases.

Table 1 Patient characteristics

	n=54	
	n	%
Age (years)		
Median (range)	58 (26–77)	
Body mass index (kg/m^2)		
Median (range)	24.9 (15.0–46.1)	
Race		
White	49	91%
Asian	4	7%
Other	1	2%
BRCA status		
Wild type	24	44%
Mutant	23	43%
Unknown	7	13%
Platinum sensitivity		
Refractory	1	2%
Resistant	12	22%
Sensitive	41	76%
Number of prior therapies		
Median (range)	3 (1–15)	
1	4	7%
2	9	17%
3	18	33%
4	9	17%
5	6	11%
6+	8	15%
Number of prior platinum therapies		
Median (range)	2 (1–5)	
1	13	24%
2	20	37%
3	9	17%
4	6	11%
5	5	9%
Unknown	1	2%
Prior bevacizumab		
No	26	48%
Yes	26	48%
Unknown	2	4%
Prior intraperitoneal chemotherapy		
No	42	78%
Yes	12	22%
Months between last prior therapy and start of protocol therapy*		
Median (range)	1.9 (0.3–57)	
Years between diagnosis and start of protocol therapy		
Median (range)	3.7 (0.3–11.2)	

*One patient is missing date of last previous chemotherapy.

Study Treatment

The investigational agent olaparib (AstraZeneca, Merck & Co, Inc) was supplied as 25 mg and 100 mg tablets. Commercially available carboplatin and paclitaxel were obtained from the Swedish Investigational Drug Services.

Trial Design: Phase Ib

A standard 3-by-3 dose escalation design was utilized to determine the maximum tolerated dose of olaparib oral tablet when combined with metronomic carboplatin and paclitaxel. The starting dose of olaparib was 50 mg administered twice daily on days 1–3 each week of a 4 week cycle. Planned dose escalations were in 50 mg increments ranging from 100 mg to 400 mg twice daily on days 1–3 of each week. Patients completing three cycles of treatment in their assigned cohort were allowed to advance to the next open cohort dose level.

In conjunction with olaparib, patients received a fixed dose of carboplatin area under the curve (AUC2) by the Calvert formula[38] intravenously and paclitaxel 60 mg/m^2 IV on day 1 weekly for 3 out of 4 weeks.

Dose-limiting toxicities were evaluated during the first cycle of treatment and were defined as grade 4 thrombocytopenia or grade 3 other hematologic adverse events; grade 2 renal or immune system disorder; any pneumonitis (grade 1 pulmonary); any other grade 3 non-hematologic adverse event (except elevated alkaline phosphatase); or any adverse event unrelated to disease progression, inter-current illness, or concomitant medication that caused an inability to administer three doses of olaparib within a treatment cycle. A patient was considered evaluable for dose-limiting toxicity on completion of cycle 1. Patients who were removed from treatment before completion of cycle 1, and who did not experience a dose-limiting toxicity, were considered not evaluable for dose-limiting toxicity and replaced. Dose escalations continued until two patients within a cohort experienced a dose-limiting toxicity indicating the maximum tolerated dose had been exceeded, establishing the maximum tolerated dose as the previous cohort in which no more than two out of six (or one out of three) experienced a dose-limiting toxicity.

Trial Design: Expansion Phase

Following determination of the maximum tolerated dose, responding patients continued treatment and 40 additional patients were enrolled to the expansion phase in order to calculate preliminary estimates of efficacy endpoints (response rate, progression-free survival, overall survival) and evaluate toxicity at the maximum tolerated dose. Olaparib was administered at the maximum tolerated dose on days 1–3 weekly simultaneously with carboplatin AUC2 and paclitaxel 60 mg/m^2 IV day 1 weekly for 3 weeks out of the 4 week cycle. Subjects were monitored closely for toxicities because they were receiving weekly chemotherapy. Dose reductions of olaparib were allowed in the expansion phase. If clinically indicated, filgrastim for neutropenia rescue was allowed at the standard dose and schedule according to good clinical practice.[39]

Table 2 Grade 3-4 adverse events possibly or probably related to protocol treatment worst severity grade reported per patient (n=54)

	Grade 3		Grade 4		Total	
Adverse event	**No. patients**	**%**	**No. patients**	**%**	**Total no. patients**	**Total %**
Lymphopenia	21	38.9%	4	7.4%	25	46.3%
Leucopenia	15	27.8%	2	3.7%	17	31.5%
Neutropenia	12	22.2%	3	5.6%	15	27.8%
Anemia	5	9.3%	4	7.4%	9	16.7%
Thrombocytopenia	3	5.6%	2	3.7%	5	9.3%
Fatigue	2	3.7%	0	0.0%	2	3.7%
Hypomagnesemia	2	3.7%	0	0.0%	2	3.7%
Diarrhea	1	1.9%	0	0.0%	1	1.9%
Febrile neutropenia	1	1.9%	0	0.0%	1	1.9%
Fever	1	1.9%	0	0.0%	1	1.9%
Hypocalcemia	1	1.9%	0	0.0%	1	1.9%
Myalgia (chest wall, neck)	1	1.9%	0	0.0%	1	1.9%
Nocturia	1	1.9%	0	0.0%	1	1.9%
Pancytopenia	1	1.9%	0	0.0%	1	1.9%
Peripheral neuropathy	1	1.9%	0	0.0%	1	1.9%
Pneumonia	0	0.0%	1	1.9%	1	1.9%
Septic shock	0	0.0%	1	1.9%	1	1.9%
Any adverse event	**28**	**51.9%**	**14**	**25.9%**	**42**	**77.8%**

Maintenance Therapy

Subjects who attained a complete remission or partial response per RECIST criteria during phase Ib or the expansion received two additional cycles followed by a CT scan to confirm response. Patients with confirmed complete remission or partial response discontinued combination therapy and transitioned to maintenance olaparib administered twice daily until disease progression. The original olaparib maintenance dose was 400 mg twice daily. During the course of the study, the manufacturer changed the recommended maintenance dose to 300 mg twice daily and the protocol was amended accordingly.[40–42]

Statistical Methods

Overall survival was defined as the duration between treatment start date and the date of death due to any cause. Patients last known to be alive were censored at their date of last contact. Progression-free survival was defined as the duration between treatment start date and the date of first documentation of progression/relapse or death due to any cause. During protocol treatment, disease assessments were performed every 8 weeks for the first 2 years, then every 3 months. Disease assessments were discontinued once a patient came off protocol treatment. Patients who were missing at least one disease assessment were censored for progression-free survival at the date of their last known disease assessment. Overall survival and progression-free survival estimates were calculated using the method of Kaplan-Meier[43] and confidence intervals for the medians were constructed using the method of Brookmeyer-Crowley.[44] All p values reported from comparisons performed come from a two-sided log-rank test. Exact confidence intervals were constructed for dichotomous variables, and comparisons were made using a two-sided Fisher's exact test. Missing values were excluded and not imputed in any way. All analyses were performed using SAS software version 9.2 or later (SAS Institute Inc, Cary, NC, USA).

RESULTS

A total of 54 patients with relapsed serous ovarian cancer were enrolled in this trial, 14 in phase Ib and 40 in the expansion phase. Enrollment began on August 22, 2012 for phase Ib with the expansion phase beginning May 20, 2013. The final patient was enrolled October 14, 2014. Median age was 58 years (range 26–77) and 91% were Caucasian. The median number of prior regimens was three (range 1–15) and the median number of platinum regimens was two (range 1–5). In addition, 22% of patients failed intraperitoneal therapy, and 48% progressed on bevacizumab. Forty-seven patients underwent genetic *BRCA* testing indicating 23 *BRCAm* and 24 *BRCAwt* (Integrated BRACAnalysis assay, Myriad Genetics, Inc, Salt Lake City, UT). Baseline characteristics are shown in Table 1.

Patients enrolled into the olaparib dose-escalation cohorts 1–3 (50 mg, 100 mg, 150 mg) did not experience any dose-limiting toxicities and enrollment began in the 200 mg cohort. Two patients in the 200 mg cohort did not complete the first cycle of treatment due to disease progression and were replaced per protocol guidelines. Thus, a total of five patients were enrolled in the 200 mg cohort. Two of three evaluable patients developed

Table 3 Adverse events related to olaparib maintenance

	Grade 0		Grade 1		Grade 2		Grade ≥3	
Adverse event								
Arthralgia	13	93%	1	7%	0	0%	0	0%
Constipation	13	93%	1	7%	0	0%	0	0%
Diarrhea	13	93%	1	7%	0	0%	0	0%
Dyspareunia	13	93%	0	0%	1	7%	0	0%
Emesis	13	93%	1	7%	0	0%	0	0%
Fatigue	12	86%	0	0%	2	14%	0	0%
Headaches	13	93%	1	7%	0	0%	0	0%
Hearing changes	13	93%	1	7%	0	0%	0	0%
Hematuria	13	93%	1	7%	0	0%	0	0%
Hot flashes	13	93%	0	0%	1	7%	0	0%
Insomnia	11	79%	3	21%	0	0%	0	0%
Mouth sores	13	93%	1	7%	0	0%	0	0%
Mucositis	13	93%	1	7%	0	0%	0	0%
Myalgia	13	93%	1	7%	0	0%	0	0%
Nausea	13	93%	1	7%	0	0%	0	0%
Neuropathy	11	79%	2	14%	1	7%	0	0%
Rash – macropapular	12	86%	2	14%	0	0%	0	0%
Taste disturbance	13	93%	1	7%	0	0%	0	0%
Vision changes	13	93%	1	7%	0	0%	0	0%
Maximum grade any adverse event	**7**	**50%**	**5**	**36%**	**2**	**14%**	**0**	**0%**

dose-limiting toxicity at 200 mg; both experienced grade 3 leucopenia, neutropenia, and fatigue. The MTD of olaparib was determined to be 150 mg twice daily when given in combination with metronomic carboplatin and paclitaxel.

Safety Profile

Adverse events experienced with combination therapy included 14 (26%) patients with grade 4 hematologic toxicity, including one patient who also had grade 4 pneumonia and septic shock (Table 2). Twelve patients did not experience any combination therapy-related adverse events greater than grade 2. Maintenance therapy adverse events were assessed following a 28 day washout from chemotherapy; they were non-hematologic in nature and did not exceed grade 2 (Table 3).

Treatment was well tolerated with only four of 54 patients stopping treatment due to toxicity per protocol guidelines. Forty-four patients discontinued treatment due to disease progression or relapse, and four for non-protocol reasons. Two *BRCAm* patients remain in complete remission and continue to receive olaparib maintenance therapy at 39 and 58 months, respectively. There were no treatment-related deaths with combination or maintenance therapy.

Response

Of the 54 patients, 13 (24%) had a complete remission, while 16 (30%) had a best response of partial response for an estimated overall response rate of 54% (95% CI 40% to 67%) (Figure 1). Nine of the patients who achieved complete remission had *BRCAm*, three were *BRCAwt*, and one was not assessed for *BRCA* status. Best response of the remaining patients included 11 (20%) stable disease and 14 (26%) progressive disease. The median duration of complete remission was 10.3 months (95% CI 6.2 to 18.8.). Patients with *BRCAm* and those with 1–3 prior therapies regardless of *BRCA* status had statistically significant superior overall survival and progression-free survival

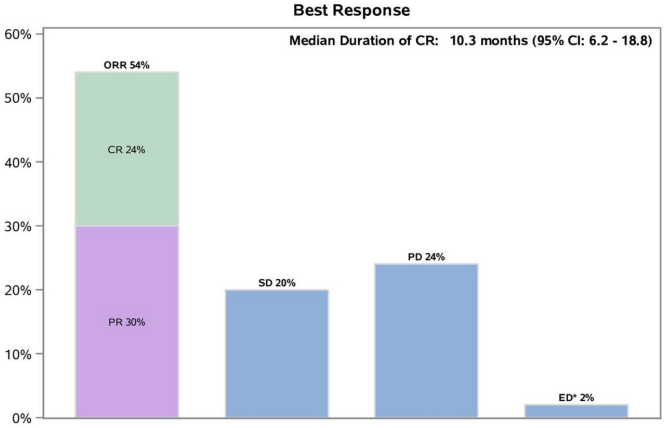

Figure 1 Best response.*One patient died from a pulmonary embolism before her first follow-up disease assessment.This patient is included in the denominator as a non-responder. CR, complete remission; ED, early death; ORR, overall response rate; PD, progressive disease; PR; partial response; SD, stable disease.

Table 4 Efficacy

Overall survival	N	Deaths	Median (months)	95% Confidence Interval		P-value
Overall study population	54	43	15.6	10.4	20.7	
BRCAm	23	15	24.1	16.8	48.4	
BRCAwt	24	21	10.4	7.8	16.1	0.02
1–3 prior therapies	31	22	20.7	15.1	39.5	
4+ prior therapies	23	21	10.4	4.6	13.8	0.01
Platinum resistant/refractory	13	13	16.1	7.0	16.8	
Platinum sensitive	41	30	15.6	10.4	35.6	0.08
BRCAm and platinum resistant/refractory	5	5	16.8	8.5	20.0	
BRCAm and platinum sensitive	18	10	35.6	20.3	48.4	0.07
Progression-free survival	**N**	**Events**	**Median (months)**	**95% Confidence Interval**		**P-value**
Overall study population	54	45	7.8	3.7	9.2	
BRCAm	23	17	12.1	9.4	16.7	
BRCAwt	24	21	4.8	2.3	6.2	0.0001
1–3 prior therapies	31	25	9.2	7.5	10.3	
4+ prior therapies	23	20*	3.7	2.6	6.2	0.03
Platinum resistant/refractory	13	11*	7.5	2.6	10.7	
Platinum sensitive	41	34	7.8	3.7	9.2	0.56
BRCAm and platinum resistant/refractory	5	5	10.7	1.6	12.6	
BRCAm and platinum sensitive	18	12	16.7	9.4	23.9	0.16
Response rate	**N**	**CR+PR**	**Rate**	**95% Confidence Interval**		**P-value**
Overall study population	54	29	54%	40%	67%	
BRCAm	23	20	87%	66%	97%	
BRCAwt	24	6	25%	10%	47%	0.00003
1–3 prior therapies	31	20	65%	45%	81%	
4+ prior therapies	23	9	39%	20%	61%	0.10
Platinum resistant/refractory	13	5	38%	14%	68%	
Platinum sensitive	41	24	59%	42%	74%	0.34
BRCAm and platinum resistant/refractory	5	4	80%	28%	99%	
BRCAm and platinum sensitive	18	16	89%	65%	99%	0.54

*Number of events less than number of deaths due to missing disease assessments.
CR, complete remission; PR, partial response.

(Table 4). Kaplan-Meier curves indicate significant median survival benefit for *BRCAm* versus *BRCAwt* for progression-free survival (12.1 months vs 4.8 months; p=0.0001) and overall survival (21.1 months vs 10.4 months; p=0.02) (Figure 2).

DISCUSSION

This is the first trial to determine the maximum tolerated dose of simultaneous olaparib tablets and metronomic carboplatin and paclitaxel in patients with extensively pre-treated ovarian cancer. We established olaparib tablets 150 mg twice daily weekly days 1–3 is the maximum tolerated dose to be safely administered in combination with metronomic carboplatin AUC2 and paclitaxel 60 mg/m^2 given weekly 3 out of 4 weeks in this population. Treatment resulted in 24% complete remission and 30% partial response for an overall response rate of 54%.

We selected a metronomic schedule because the half-life of carboplatin, paclitaxel, and olaparib are highest within the first 3 days of dosing.[5 45 46] Weekly paclitaxel has been shown to have significant anti-angiogenic effects compared with once every 3 weeks.[47] Carboplatin and olaparib are known DNA damaging agents. We hypothesized that adding a PARP inhibitor during this timeframe would increase DNA damage and increase cancer cell death.

Patients received combination therapy until they achieved a confirmed complete remission or partial response and then

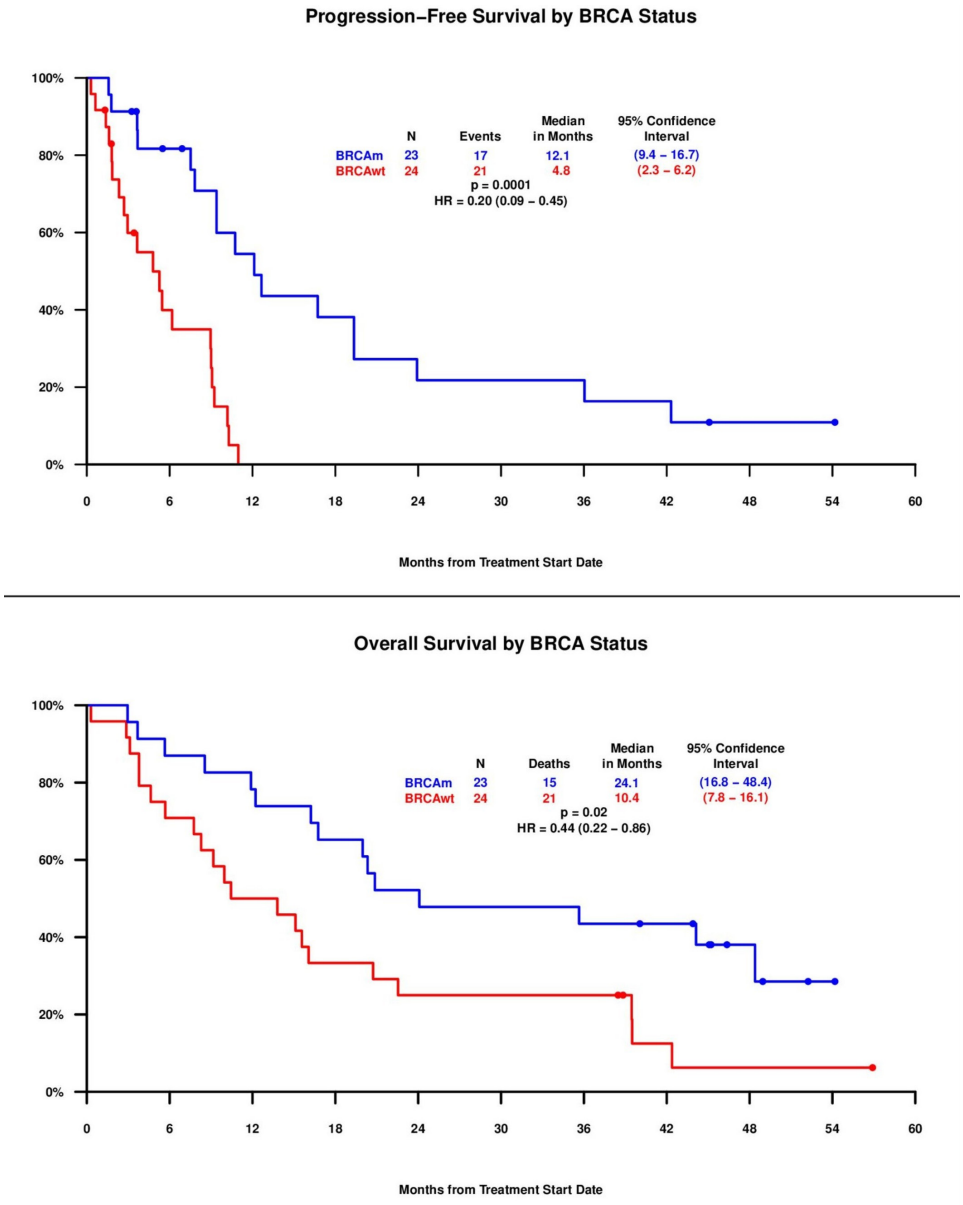

Figure 2 Progression-free and overall survival by *BRCA* status.

converted to maintenance olaparib 300 mg twice daily. We theorized olaparib would be most efficacious when the cancer load is at its lowest.

Fifty-one patients completed one or more cycles of combination therapy. Treatment was generally well tolerated throughout the study and there were no treatment related deaths. Only four patients were removed from further treatment for toxicity. The majority of adverse events during combination therapy were hematologic grade 3 or less. Compliance with the weekly schedule was extremely high in this group of patients.

Oza reported the largest trial to date comparing olaparib with every 3 week carboplatin and paclitaxel followed by maintenance olaparib to standard chemotherapy with carboplatin and paclitaxel without maintenance. The investigational arm utilized a reduced dose of carboplatin at AUC4 every 3 weeks with olaparib capsules 200 mg twice daily days 1–10. The progression-free survival for the olaparib arm was longer than the standard therapy arm (12.2 months compared with 9.6 months; p=0.0012) with the most benefit in *BRCAm* patients. The toxicity profile was manageable with no deaths due to toxicity. At publication there was no overall survival advantage even in the *BRCAm* patients.[48]

Two first-line trials looked at weekly chemotherapy in patients with ovarian cancer, MITO-7 and ICON8.[30 31] The MITO-7 trial is more mature and has long-term toxicity results. It compared standard therapy to carboplatin and paclitaxel weekly at the same dosage in our study, but it was given every week for 18 weeks. Median PFS was not significantly different between these two groups. Compared with the standard schedule, the weekly arm had better quality of life and less toxicity, with significantly less thrombocytopenia, hair loss, and neuropathy.[30] It was difficult to determine alopecia or neuropathy in our trial because the patients had undergone several previous therapies. The ICON8 trial compared standard therapy to dose-dense and weekly carboplatin and paclitaxel with similar toxicity across all arms.

A weekly regimen represents a practical model for combination with olaparib or other investigational agents.

Our trial tested for germline *BRCA*, but not other homologous recombination deficiencies. Median overall survival was significantly longer in *BRCAm*; however, three *BRCAwt* patients achieved complete remission. A recent report of a different PARP inhibitor in patients with platinum-sensitive ovarian cancer evaluated both germline and somatic *BRCA* mutations and other homologous recombination defects. It found longer progression-free survival in *BRCAm* and *BRCAwt* with high loss of heterozygocity suggesting assessment of loss of heterozygocity may be advantageous in identifying patients with *BRCAwt* who may benefit from PARP therapy.[49]

Future trials could incorporate our regimen in evaluating the benefit of combination chemotherapy in patients with platinum-sensitive ovarian cancer in first relapse. Assessment of additional HRD may help clarify the utility of our regimen in both *BRCAm* and *BRCAwt*.

Is chemotherapy necessary in patients with *BRCAm* ovarian cancer optimally debulked to no evidence of disease? Comparison could be made between olaparib alone versus standard chemotherapy followed by olaparib. This may determine whether chemotherapy is necessary by using an approach similar to SWOG 7827 that showed paclitaxel alone is comparable to chemotherapy.[50]

In summary, olaparib tablets can be safely administered simultaneously with a regimen of metronomic carboplatin with paclitaxel in heavily pre-treated relapsed ovarian cancer patients. This trial provides a reasonable option for this patient population and appears to be most efficacious in *BRCAm* patients.

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