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ORIGINAL REPORT

# Phase II, Open-Label, Randomized, Multicenter Study Comparing the Efficacy and Safety of Olaparib, a Poly (ADP-Ribose) Polymerase Inhibitor, and Pegylated Liposomal Doxorubicin in Patients With *BRCA1* or *BRCA2* Mutations and Recurrent Ovarian Cancer

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## ABSTRACT

### Purpose
Olaparib (AZD2281), an orally active poly (ADP-ribose) polymerase inhibitor that induces synthetic lethality in *BRCA1*- or *BRCA2*-deficient cells, has shown promising clinical efficacy in nonrandomized phase II trials in patients with ovarian cancer with *BRCA1* or *BRCA2* deficiency. We assessed the comparative efficacy and safety of olaparib and pegylated liposomal doxorubicin (PLD) in this patient population.

### Patients and Methods
In this multicenter, open-label, randomized, phase II study, patients with ovarian cancer that recurred within 12 months of prior platinum therapy and with confirmed germline *BRCA1* or *BRCA2* mutations were enrolled. Patients were assigned in a 1:1:1 ratio to olaparib 200 mg twice per day or 400 mg twice per day continuously or PLD 50 mg/m$^2$ intravenously every 28 days. The primary efficacy end point was Response Evaluation Criteria in Solid Tumors (RECIST) –assessed progression-free survival (PFS). Secondary end points included objective response rate (ORR) and safety.

### Results
Ninety-seven patients were randomly assigned. Median PFS was 6.5 months (95% CI, 5.5 to 10.1 months), 8.8 months (95% CI, 5.4 to 9.2 months), and 7.1 months (95% CI, 3.7 to 10.7 months) for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no statistically significant difference in PFS (hazard ratio, 0.88; 95% CI, 0.51 to 1.56; $P = .66$) for combined olaparib doses versus PLD. RECIST-assessed ORRs were 25%, 31%, and 18% for olaparib 200 mg, olaparib 400 mg, and PLD, respectively; differences were not statistically significant. Tolerability of both treatments was as expected based on previous trials.

### Conclusion
The efficacy of olaparib was consistent with previous studies. However, the efficacy of PLD was greater than expected. Olaparib 400 mg twice per day is a suitable dose to explore in further studies in this patient population.

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## INTRODUCTION

Despite our increased understanding of the pathophysiology of *BRCA1*- or *BRCA2*-mutated ovarian cancer (collectively referred to here as *BRCA1/2*),[1-6] specific treatments for this disease have not yet been established. However, loss of BRCA1/2 function has recently been identified as offering potential therapeutic advantage through the application of synthetic lethality involving single-agent treatment with the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib (AZD2281; AstraZeneca, Wilmington, DE). Proof-of-concept studies in preclinical models have shown that inhibition of PARP-1 activity could

lead to a potentially wide therapeutic index by causing error-prone DNA repair and cell death selectively in cells that lose BRCA1/2 protein function.[7-10]

Olaparib is an orally active PARP inhibitor, selective for homologous recombination–deficient cells, such as those with homozygous *BRCA1/2* deficiency.[10] In a previously reported phase I study of olaparib monotherapy, the maximum-tolerated dose was identified as 400 mg twice per day.[11] In the expansion phase of the study, in patients with *BRCA1/2*-mutated advanced ovarian cancer treated with olaparib 200 mg twice per day, the radiologic response rate was 28% (14 of 50 patients), with a response duration of 7 months.[12] In a subsequent nonrandomized multicenter study in patients with *BRCA1/2*-mutated advanced ovarian cancer treated with olaparib 100 mg twice per day, an objective response rate (ORR) of 13% (three of 24 patients) with a similar median response duration (8.8 months) was observed, whereas patients treated with olaparib 400 mg twice per day had an ORR of 33% (11 of 33 patients) and a median response duration of 9.5 months.[13]

Pegylated liposomal doxorubicin (PLD) represents one approved option for the treatment of patients whose disease has progressed or recurred after the use of a platinum-based chemotherapy regimen. In a randomized phase III study of PLD versus topotecan, 239 patients with recurrent ovarian cancer treated with PLD achieved an overall ORR of 20% and a median progression-free survival (PFS) time of 16 weeks.[14] The efficacy of PLD in patients with *BRCA1/2*-mutated ovarian cancer has not been separately studied but was expected to be similar to that observed in patients with nonhereditary ovarian cancer.

Given this background, we tested the primary hypothesis that olaparib is more effective than the current standard of care, PLD, in patients with *BRCA1/2*-mutated advanced ovarian cancer with an interval of less than 12 months after previous platinum-based chemotherapy. An additional aim was to establish the most appropriate dose of olaparib for use in future clinical studies. Hence, two dose levels (olaparib 200 and 400 mg twice per day) were incorporated to provide more information on their relative efficacies. However, this study was not powered to detect a statistical difference between these doses.

## PATIENTS AND METHODS

### Patients

Women age ≥ 18 years with histologically or cytologically confirmed recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma and one or more measurable lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) were enrolled.[15] Patients had a confirmed germline *BRCA1/2* mutation, disease that recurred or progressed within 12 months of the most recent platinum-based chemotherapy regimen (another non-PLD chemotherapy after this was permitted), an Eastern Cooperative Oncology Group performance status of 0 to 2, and estimated life expectancy of ≥ 16 weeks. Additional eligibility criteria included adequate bone marrow, renal, and hepatic function.

Exclusion criteria included prior anthracyclines or PARP inhibitors in the treatment of ovarian cancer; known brain metastases; a history of another active malignant disease within the preceding 5 years; persistent toxic effects of previous treatment; left ventricular ejection fraction less than 50%; and for patients who received non-PLD or epirubicin for treatment of prior breast cancer, a cumulative anthracycline dose of more than 240 mg/m$^2$ or more than 480 mg/m$^2$, respectively. Other chemotherapy, endocrine therapy, biologic therapy, or high-dose radiotherapy during the course of the study or up to 28 days before the start of the study was not permitted.

All patients provided written informed consent. This study was approved by local institutional review boards and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

### Study Design and Treatment

This prospective, multicenter, open-label, randomized, phase II study evaluated twice-daily continuous olaparib at doses of 200 or 400 mg versus intravenous infusions of PLD 50 mg/m$^2$ every 28 days (ClinicalTrials.gov identifier: NCT00628251). Olaparib was given orally at least 2 hours before or 1 hour after food, approximately 12 hours apart. Patients were randomly assigned sequentially using an Interactive Voice Response System. The random assignment list was computer-generated using the Global Randomization system (GRand; AstraZeneca). A blocked random assignment approach was used to assign patients to each of the treatment groups in a 1:1:1 ratio; all centers used the same list to minimize any imbalance. Patients were stratified according to *BRCA1* or *BRCA2* status and platinum sensitivity (patients whose tumor responded to the most recent platinum-containing chemotherapy with a treatment-free interval of > 6 months were classified as sensitive; patients experiencing relapse ≤ 6 months after platinum-based treatment were classified as resistant). Cross-over from PLD to olaparib 400 mg was permitted after centralized ascertainment of disease progression. Treatment continued until disease progression, unacceptable toxicity (adverse events [AEs]), death, or discontinuation for other reasons. As necessary, olaparib doses were reduced in a stepwise manner from 400, to 200, to 100 mg, whereas PLD doses were allowed to be reduced once by 25%.

### End Points and Assessments

The primary end point was investigator-assessed PFS for olaparib versus PLD, defined as the time interval from random assignment to RECIST-defined progression or death.[15] Secondary end points included ORR (RECIST-defined complete or partial response); duration of treatment response for each treatment group; tumor size; overall survival (OS); safety and tolerability; and health-related quality of life (HRQoL), which was measured by three indices/scores of the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) questionnaire (FACT-O Symptom Index, Trial Outcome Index, and total FACT-O score). CA-125 responses were assessed according to Gynecologic Cancer Intergroup (GCIG) criteria.[16] All end points were analyzed for olaparib doses combined and individually versus PLD.

Disease assessments were performed at baseline and every 8 weeks until progression, using computed tomography and/or magnetic resonance imaging and serum CA-125 measurements. Patients who discontinued treatment before disease progression had disease assessments until progression or initiation of an alternative anticancer treatment. Centrally reviewed tumor assessments for all patients with RECIST scans were used for sensitivity analyses. Safety and tolerability were evaluated at baseline and at least every 4 weeks, as assessed by AEs and changes in laboratory parameters according to Common Terminology Criteria for Adverse Events (CTCAE).[17]

### Statistical Assessments

The study had 80% power to demonstrate a promising difference in favor of olaparib (one-sided $P < .1$) if the true hazard ratio (HR) for the olaparib groups combined versus PLD was 0.55. A total of 57 PFS events were required. All analyses were carried out on an intent-to-treat basis. PFS curves were derived using the Kaplan-Meier method. PFS was analyzed using a Cox proportional hazards model with factors for treatment (olaparib *v* PLD), *BRCA1* or *BRCA2* status, and platinum sensitivity (sensitive or resistant/refractory). An HR of 0.56 or better would be required to be observed with 57 events to achieve a $P < .02$ (one-sided). In the event of nonsignificance in the combined comparison, each olaparib dose was to be compared separately with PLD using a closed testing procedure and type I error rate of 0.005 (one-sided). The overall type I error for declaring a statistically significant difference in favor of olaparib was to be no more than 2.5% (one-sided). ORR was compared between olaparib (combined and separately) and PLD using logistic regression, adjusting for the same set of factors as for PFS. Effect of treatment was estimated using the adjusted odds ratio. Changes from baseline in target tumor size were assessed using analysis of covariance. OS was assessed using a Cox

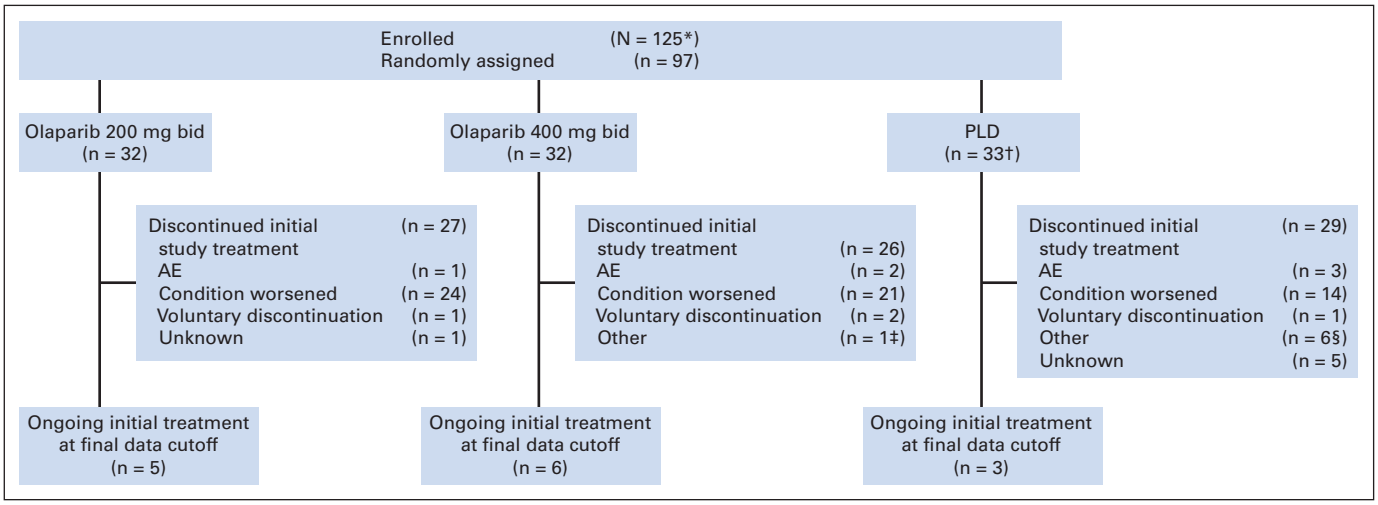


**Fig 1.** CONSORT flowchart showing disposition of enrolled patients at the time of data cutoff. Twenty-eight patients were not randomly assigned. (*) Of these, 21 patients were incorrectly enrolled, two patients voluntarily discontinued, and five patients discontinued for other reasons. (†) Of the 97 patients who were randomly assigned, one patient in the pegylated liposomal doxorubicin (PLD) group voluntarily discontinued from the study before receiving study treatment. (‡) Clinical deterioration, pain, leg edema, and CA-125 elevation. (§) One patient each discontinued as a result of investigator criteria, lifetime PLD dose reached, progressive disease was confirmed with a computed tomography scan (the patient crossed over to olaparib 400 mg), and PLD treatment was stopped according to local practice (benefit of treatment was questioned); two patients discontinued because they had completed six cycles of PLD (full treatment dosage according to local treatment protocol). AE, adverse event.



proportional hazards model, and FACT-O data were assessed using logistic regression. All of these analyses used factors as for PFS. There were two data cutoffs for this study, September 15, 2009, for the PFS analysis and April 30, 2010, for the final OS analysis. After the first data cutoff, patients were observed for survival and core safety assessments.

## RESULTS

### Patients

Ninety-seven patients were randomly assigned to the treatment groups; 32 patients (33%) were assigned to olaparib 200 mg, 32 (33%) were assigned to olaparib 400 mg, and 33 (34%) were assigned to PLD (Fig 1). Demographics and disease characteristics were well balanced between the groups (Table 1). Nineteen patients remained on olaparib treatment at the time of the final data cutoff for the analysis of OS; 11 patients had initially been randomly assigned to olaparib, and eight had crossed over from the PLD group. The proportions of patients who had dose reductions as a result of AEs were 6.3% in the olaparib 200-mg group, 31.3% in the olaparib 400-mg group, and 28.1% in the PLD group, with median dose-intensities of 99% (range, 49% to 100%), 94% (range, 53% to 100%), and 82% (range, 33% to 105%), respectively.

### PFS

Fifty-nine RECIST-defined progression events were documented. Median PFS times were 6.5 months (95% CI, 5.5 to 10.1 months), 8.8 months (95% CI, 5.4 to 9.2 months), and 7.1 months (95% CI, 3.7 to 10.7 months) for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no statistically significant difference in PFS between the olaparib (combined or individual doses) and PLD groups (Figs 2A and 2B). Centrally reviewed tumor assessments were generally consistent with investigator-assessed analyses for sensitivity analyses.

### ORRs and Duration of Response

RECIST-assessed ORRs were 25%, 31%, and 18% in the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively, with no statistically significant differences between the olaparib and PLD groups; the mean odds ratios were 1.90 (95% CI, 0.55 to 7.01; $P = .31$), 2.69 (95% CI, 0.81 to 9.76; $P = .11$), and 2.27 (95% CI, 1.13 to 4.79; $P = .13$) for olaparib 200 mg, olaparib 400 mg, and both doses combined, respectively. Median durations of response were 6.0, 6.8, and 5.5 months in the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. Stable disease for $\geq$ 8 weeks (minimum 8-week assessment period) was reported in 47%, 59%, and 52% of patients receiving olaparib 200 mg, olaparib 400 mg, and PLD, respectively. By GCIG (CA-125) criteria, response rates were 34%, 56%, and 33% for olaparib 200 mg, olaparib 400 mg, and PLD, respectively; the difference in CA-125 response was significant between the olaparib 400 mg and PLD groups (odds ratio, 3.26; 95% CI, 1.15 to 9.76; $P = .025$), although this should be interpreted cautiously because there was no correction for multiple testing in the analyses of secondary end points. Combined response rates (ie, RECIST and/or GCIG) were 38%, 59%, and 39% in the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively, with odds ratios of 0.98 ($P = .97$), 2.76 ($P = .05$), and 1.64 ($P = .27$), for olaparib 200 mg, olaparib 400 mg, and both doses combined versus PLD, respectively.

### Changes in Tumor Size

Median best percentage changes from baseline in target tumor size were −15.9%, −24.6%, and −14.3% in the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively, with no statistically significant differences observed (Fig 3). A lower percentage of patients developed new lesions in the olaparib 200 mg and olaparib 400 mg groups (28.1% and 34.4%, respectively) than in the PLD group (45.5%).

**Table 1.** Baseline Patient Demographics and Tumor Characteristics

| Demographic or Tumor Characteristic | Olaparib 200 mg Twice per Day (n = 32) | | Olaparib 400 mg Twice per Day (n = 32) | | PLD (n = 33) | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Age, years | | | | | | |
| Mean | 57.2 | | 53.8 | | 54.3 | |
| Standard deviation | 8.53 | | 8.77 | | 9.32 | |
| Median | 58.5 | | 53.5 | | 53.0 | |
| Range | 45-77 | | 35-76 | | 43-81 | |
| *BRCA* status | | | | | | |
| *BRCA1* | 26 | 81.3 | 28 | 87.5 | 27 | 81.8 |
| *BRCA2* | 6 | 18.8 | 4 | 12.5 | 6 | 18.2 |
| Organ of origin of primary tumor | | | | | | |
| Ovary | 23 | 71.9 | 27 | 84.4 | 31 | 93.9 |
| Fallopian tube | 3 | 9.4 | 1 | 3.1 | 1 | 3.0 |
| Primary peritoneal | 6 | 18.8 | 3 | 9.4 | 1 | 3.0 |
| Not known | 0 | 0 | 1 | 3.1 | 0 | 0 |
| Histology subtype | | | | | | |
| Serous | 25 | 78.1 | 24 | 75.0 | 26 | 78.8 |
| Transitional-cell carcinoma | 0 | 0 | 1 | 3.1 | 0 | 0 |
| Endometrioid | 2 | 6.3 | 6 | 18.8 | 3 | 9.1 |
| Mixed epithelial | 0 | 0 | 0 | 0 | 1 | 3.0 |
| Primary peritoneal | 3 | 9.4 | 1 | 3.1 | 0 | 0 |
| Other | 2 | 6.3 | 0 | 0 | 3 | 9.1 |
| Tumor grade | | | | | | |
| 1 | 0 | 0 | 1 | 3.1 | 1 | 3.0 |
| 2 | 5 | 15.6 | 6 | 18.8 | 5 | 15.2 |
| 3 | 26 | 81.3 | 21 | 65.6 | 26 | 78.8 |
| Not known | 1 | 3.1 | 4 | 12.5 | 1 | 3.0 |
| FIGO stage at diagnosis | | | | | | |
| I | 1 | 3.1 | 0 | 0 | 1 | 3.0 |
| II | 1 | 3.1 | 0 | 0 | 2 | 6.0 |
| III | 18 | 56.3 | 22 | 68.8 | 23 | 69.7 |
| IV | 12 | 37.5 | 9 | 28.1 | 7 | 21.2 |
| Not known | 0 | 0 | 1 | 3.1 | 0 | 0 |
| ECOG PS | | | | | | |
| 0 | 16 | 50.0 | 19 | 59.4 | 19 | 57.6 |
| 1 | 13 | 40.6 | 13 | 40.6 | 13 | 39.4 |
| 2 | 3 | 9.4 | 0 | 0 | 1 | 3.0 |
| Platinum-resistant disease | | | | | | |
| Yes | 18 | 56.3 | 16 | 50.0 | 14 | 42.4 |
| No | 14 | 43.8 | 15 | 46.9 | 19 | 57.6 |
| Not known | 0 | 0 | 1 | 3.1 | 0 | 0 |
| Platinum therapy immediately before entry* | | | | | | |
| Yes | 27 | 84.4 | 19 | 59.4 | 24 | 72.7 |
| No | 5 | 15.6 | 13 | 40.6 | 9 | 27.3 |
| No. of lines of previous cancer therapy at baseline | | | | | | |
| 1 | 6 | 18.8 | 1 | 3.1 | 7 | 21.2 |
| 2 | 7 | 21.9 | 6 | 18.8 | 9 | 27.3 |
| 3 | 8 | 25.0 | 15 | 46.9 | 8 | 24.2 |
| 4 | 7 | 21.9 | 8 | 25.0 | 6 | 18.2 |
| ≥ 5 | 4 | 12.5 | 2 | 6.3 | 3 | 9.1 |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; PLD, pegylated liposomal doxorubicin.

*No other chemotherapy administered for progression or recurrence of disease between the most recent platinum regimen and enrollment onto the study.

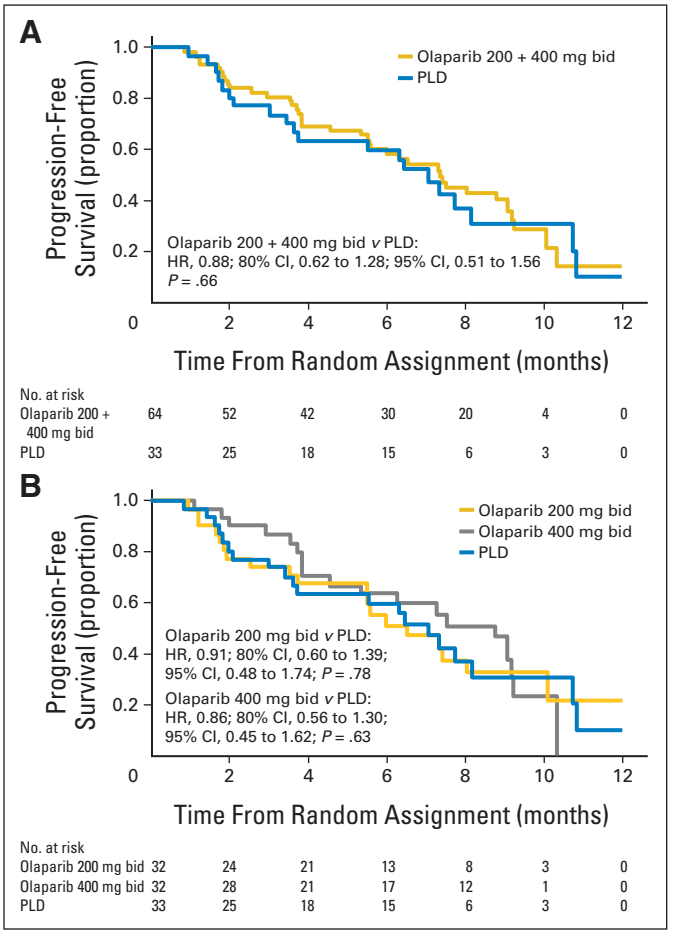


**Fig 2.** Kaplan-Meier plots of progression-free survival in patients receiving (A) olaparib (two doses combined) versus pegylated liposomal doxorubicin (PLD) and (B) olaparib 200 mg twice per day and 400 mg twice per day versus PLD. HR, hazard ratio.

### *OS*

At the final analysis of OS, 9, 11, and 13 deaths had occurred in the olaparib 200 mg, olaparib 400 mg, and PLD arms, respectively. HR versus PLD for olaparib 200 mg and 400 mg were 0.66 (95% CI, 0.27 to 1.55) and 1.01 (95% CI, 0.44 to 2.27), respectively.

### *AE Profile and HRQOL*

The AEs occurring in ≥ 30% of patients (regardless of causality) are listed in Table 2. The most common AEs in the olaparib groups were generally CTCAE grade ≤ 2 fatigue, GI symptoms, anemia, and rash; these were seen more commonly at olaparib 400 mg (Table 2). The most commonly reported AEs in the PLD group were nausea, stomatitis, and fatigue. The incidence of CTCAE grade 3 or 4 events was low; they were more frequent in patients receiving PLD and included stomatitis, palmar-plantar erythrodysesthesia, and rash, although grade 3 anemia was seen more frequently in patients receiving olaparib 400 mg (13%). One patient in the olaparib 200-mg group died as a result of a severe AE (cerebrovascular accident), which was considered to be possibly related to olaparib treatment. However, factors including deep vein thrombosis and concurrent anticoagulation treatment may have contributed. One patient receiving olaparib 200 mg died as a result of an AE of myelodysplastic syndrome considered by the investigator to be related to olaparib; however, this patient had received extensive chemotherapy. Overall, the AEs reported in the

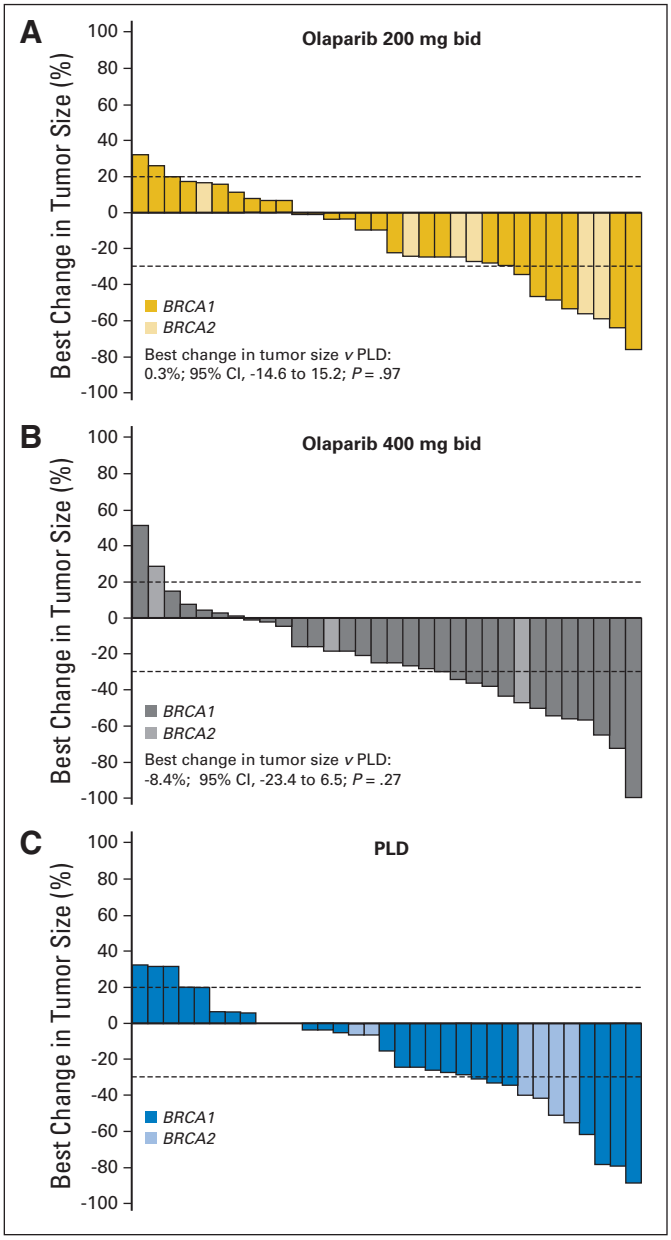


**Fig 3.** Waterfall plots of best percentage changes in target tumor size in patients receiving (A) olaparib 200 mg twice per day, (B) olaparib 400 mg twice per day, and (C) pegylated liposomal doxorubicin (PLD).



three treatment groups were compatible with previously reported toxicity profiles.

There were no significant differences in improvement or worsening rates between the olaparib treatment groups and the PLD group for the FACT-O Symptom Index and Trial Outcome Index scores. However, a higher improvement rate was noted for olaparib 400 mg compared with PLD for the total FACT-O score (odds ratio, 7.23; 95% CI, 1.09 to 143.3; $P = .039$).

## DISCUSSION

This phase II study compared the efficacy of olaparib 200 mg twice per day and 400 mg twice per day with that of PLD in patients with *BRCA1/2*-mutated advanced ovarian cancer and disease progression within 12 months of previous platinum-based chemotherapy. No significant difference was seen in the primary end point of PFS between the olaparib and PLD groups, although the ORR for olaparib 400 mg (31%) was consistent with previous studies in patients with ovarian cancer and *BRCA1/2* mutations (28%[11] and 33%[13]). The median PFS of 7.1 months in the PLD group studied here exceeded that seen in a previous, large, randomized trial of patients with unknown *BRCA1/2* status who received PLD (PFS of 4 months) with similar proportions of patients with platinum-resistant and platinum-sensitive relapsed disease.[14]

RECIST-assessed ORRs and duration of response were not statistically different between the olaparib and PLD groups. Both the CA-125–assessed ORR and the combined RECIST and/or GCIG response rates were observed to be higher in the olaparib 400-mg group than in the olaparib 200-mg group and the PLD group; there were no adjustments for multiple comparisons. These findings concur with observations from earlier phase I and II studies of patients with advanced ovarian cancer and *BRCA1/2* mutations[11,13] and suggest the existence of a dose-response relationship; however, this study was not formally powered to address this. Because only 33 deaths (26%) had occurred at the time of data cutoff, the OS results are inconclusive.

The longer than anticipated median PFS observed in the PLD group, when compared with the findings from the previous phase III study by Gordon et al,[14] likely impacted on the power of the study to detect a difference in PFS between olaparib and PLD. However, the efficacy of PLD in the current study is consistent with a recent retrospective analysis that suggested a potential link between germline *BRCA1/2* status and greater clinical benefit achieved with PLD in this disease setting.[18] Moreover, a study by Graeser et al[19] suggested a likely correlation between functional homologous recombination deficiency (defined using a RAD51 focus formation assay) and clinical benefit from the use of neoadjuvant anthracycline-based chemotherapy in sporadic breast cancer. Hence, it is conceivable that patients with homologous recombination–deficient tumors, including those with germline *BRCA1/2* mutations, may derive more benefit from anthracycline-based treatments than unselected patients, and this clearly has implications for the design of further trials in this patient population.

Olaparib was generally well tolerated. The incidence of AEs and dose reductions in patients treated with olaparib were slightly higher at the 400-mg dose level than the 200-mg dose level, but dose-intensity remained more than 90%. The toxicity profile of olaparib is distinct from that of PLD. Nausea, fatigue, and vomiting were the most common AEs related to olaparib treatment, whereas AEs related to PLD treatment were stomatitis and palmar-plantar erythrodysesthesia. Anemia was also more commonly seen with olaparib, particularly at 400 mg twice per day. Olaparib is administered orally as a capsule (although a new tablet formulation is in development), whereas PLD, in common with other cytotoxics, is given intravenously. Both PARP inhibitors and PLD are likely to play important roles in the management of patients with recurrent advanced ovarian cancer and *BRCA1/2* mutations, and differences in the tolerability and route of administration will be of importance in individualizing their treatment. There were no significant differences in HRQoL between the

**Table 2.** Summary of the Most Commonly Reported AEs by Grade in Each Treatment Arm

| AE | Olaparib 200 mg Twice per Day (n = 32) | | | | Olaparib 400 mg Twice per Day (n = 32) | | | | PLD (n = 32)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 or 2 | | Grade 3 or 4 | | Grade 1 or 2 | | Grade 3 or 4 | | Grade 1 or 2 | | Grade 3 or 4 | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Nausea | 18 | 56 | 1 | 3 | 23 | 72 | 2 | 6 | 16 | 50 | 2 | 6 |
| Fatigue | 12 | 38 | 1 | 3 | 18 | 56 | 3 | 9 | 12 | 38 | 3 | 9 |
| Abdominal pain | 10 | 31 | 2 | 6 | 8 | 25 | 0 | 0 | 10 | 31 | 2 | 6 |
| Vomiting | 11 | 34 | 0 | 0 | 15 | 47 | 1 | 3 | 9 | 28 | 1 | 3 |
| Constipation | 7 | 22 | 2 | 6 | 5 | 16 | 0 | 0 | 12 | 38 | 0 | 0 |
| Diarrhea | 6 | 19 | 0 | 0 | 12 | 38 | 0 | 0 | 8 | 25 | 2 | 6 |
| Asthenia | 5 | 16 | 1 | 3 | 11 | 34 | 0 | 0 | 3 | 9 | 1 | 3 |
| Urinary tract infection | 5 | 16 | 0 | 0 | 11 | 34 | 0 | 0 | 3 | 9 | 1 | 3 |
| Anemia | 2 | 6 | 2 | 6 | 6 | 19 | 4 | 13 | 1 | 3 | 0 | 0 |
| Rash | 3 | 9 | 0 | 0 | 3 | 9 | 0 | 0 | 11 | 34 | 3 | 9 |
| Palmar-plantar erythrodysesthesia syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 25 | 12 | 38 |
| Stomatitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 17 | 53 | 2 | 6 |

Abbreviations: AE, adverse event; PLD, pegylated liposomal doxorubicin.
*One patient was randomly assigned to PLD but did not receive it.



treatment groups, apart from a higher improvement rate in the olaparib 400-mg group compared with the PLD group in the total FACT-O score ($P = .039$). However, in these HRQoL analyses, the presence of patients with nonevaluable data, small sample size for each group, lack of adjustment for multiple comparisons, and open-label trial design preclude definitive interpretation.

A recent key development is the detection of a clear efficacy signal for olaparib in patients with sporadic high-grade serous ovarian cancer with a RECIST-based ORR of 24%.[20] The collective incidence of somatic mutations and epigenetic loss of *BRCA1/2* in patients with high-grade serous ovarian cancer is reportedly as high as 55%.[21] Another series reported somatic *BRCA1/2* mutations in 44 (19%) of 235 unselected patients with ovarian cancer, with somatic origin being demonstrated in 11 (23%) of 28 patients for whom germline DNA samples were also available.[22] These results suggest that the potential scope of application for this class of agents may be considerably broadened. In this context, predictive biomarkers of clinical benefit are being developed, including functional assessments of homologous recombination deficiency,[19] as well as *BRCA1/2* promoter hypermethylation and array-based assays that detect BRCAness.[23,24]

To conclude, our data show that the efficacy of olaparib in patients with *BRCA1/2* mutation and advanced ovarian cancer after a platinum-free interval of ≤ 12 months is not statistically different from that of PLD. Whereas the response rate and PFS of olaparib 400 mg twice per day were consistent with previous studies, for PLD, these exceeded previously published data in patients with recurrent ovarian cancer. The toxicity profile of olaparib differs significantly from PLD; as a well-tolerated oral monotherapy, olaparib continues to represent a potential step forward in the treatment of patients with *BRCA1/2*-mutated cancers. Eight of 25 patients in this study who have crossed over from PLD have continued on treatment with olaparib, indicating the potential for continued benefit in patients with *BRCA1/2*-mutated ovarian cancer and suggesting that future trials in PLD-treated patients would be of interest. Our data, together with data from previous studies, suggest that monotherapy with olaparib 400 mg twice per day is a suitable dose to explore in further studies in patients with *BRCA1/2*-mutated cancers. These studies could include evaluation of olaparib in combination with PLD because a feasible schedule has been recently identified in a phase I trial.[25]

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## Glossary Terms

**BRCA1:** A tumor suppressor gene, the breast cancer 1 susceptibility gene is known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risks of developing breast or ovarian cancer.

**BRCA2:** Known as breast cancer 2 early onset gene, BRCA2 is a tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from BRCA1, BRCA2 has cellular functions similar to BRCA1. BRCA2 binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents.

**Eastern Cooperative Oncology Group performance status:** Criteria used by doctors and researchers to define the progression of a patient's disease, assessing how the disease affects daily living habits, and to assist in the determination of the appropriate treatment and prognosis.

**Homologous recombination:** Genetic recombination whereby nucleotide sequences are exchanged between two similar or identical strands of DNA to facilitate accurate repair of DNA double-strand breaks.

**Olaparib:** A highly potent, orally active PARP inhibitor in clinical development for the treatment of cancer. Formerly known as AZD2281 and KU-0059436.

**Pegylated liposomal doxorubicin (PLD):** A unique formulation of conventional doxorubicin (commonly used in the treatment of a wide range of cancers) in which a polyethylene glycol layer surrounds the doxorubicin-containing liposome via a process termed pegylation. Pegylation protects the liposomes from detection by the reticuloendothelial system and increases the plasma half-life of the compound compared with conventional doxorubicin.

**Poly (ADP-ribose) polymerase (PARP):** The PARP family of nuclear enzymes facilitate DNA repair via poly (ADP-ribose)ylation of histones and DNA repair enzymes.

**Response Evaluation Criteria In Solid Tumors (RECIST):** The Response Evaluation Criteria Group proposed a model by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment.

**Synthetic lethality:** A situation that occurs when a DNA repair pathway is inhibited in cells already compromised in a second repair pathway. This prevents repair of DNA breaks, thereby leading to cell death.