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Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial



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Summary

Background Olaparib is a novel, orally active poly(ADP-ribose) polymerase (PARP) inhibitor that induces synthetic lethality in homozygous *BRCA*-deficient cells. We aimed to assess the efficacy and safety of olaparib for treatment of advanced ovarian cancer in patients with *BRCA1* or *BRCA2* mutations.

Methods In this international, multicentre, phase 2 study, we enrolled two sequential cohorts of women (aged ≥ 18 years) with confirmed genetic *BRCA1* or *BRCA2* mutations, and recurrent, measurable disease. The study was undertaken in 12 centres in Australia, Germany, Spain, Sweden, and the USA. The first cohort (n=33) was given continuous oral olaparib at the maximum tolerated dose of 400 mg twice daily, and the second cohort (n=24) was given continuous oral olaparib at 100 mg twice daily. The primary efficacy endpoint was objective response rate (ORR). This study is registered with ClinicalTrials.gov, number NCT00494442.

Findings Patients had been given a median of three (range 1–16) previous chemotherapy regimens. ORR was 11 (33%) of 33 patients (95% CI 20–51) in the cohort assigned to olaparib 400 mg twice daily, and three (13%) of 24 (4–31) in the cohort assigned to 100 mg twice daily. In patients given olaparib 400 mg twice daily, the most frequent causally related adverse events were nausea (grade 1 or 2, 14 [42%]; grade 3 or 4, two [6%]), fatigue (grade 1 or 2, ten [30%]; grade 3 or 4, one [3%]), and anaemia (grade 1 or two, five [15%]; grade 3 or 4, one [3%]). The most frequent causally related adverse events in the cohort given 100 mg twice daily were nausea (grade 1 or 2, seven [29%]; grade 3 or 4, two [8%]) and fatigue (grade 1 or 2, nine [38%]; none grade 3 or 4).

Interpretation Findings from this phase 2 study provide positive proof of concept of the efficacy and tolerability of genetically targeted treatment with olaparib in *BRCA*-mutated advanced ovarian cancer.

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Introduction

Poly(ADP-ribose) polymerase (PARP) has an important role in base excision repair of single-strand DNA breaks. Inhibition of PARP leads to accumulation of single-strand DNA breaks, which can cause formation of double-strand DNA breaks after stalling and collapse of progressing DNA replication forks.¹ These double-strand DNA breaks are usually repaired by the error-free homologous recombination repair pathway, of which the tumour-suppressor genes *BRCA1* and *BRCA2* are key components.^{2–6} About 10% of women with ovarian cancer carry a *BRCA1* or *BRCA2* mutation,⁷ which confers a high risk of development of breast and ovarian cancer.⁸ Although women with *BRCA*-associated ovarian cancer might have higher response rates to chemotherapy and improved survival rates than do those with sporadic ovarian cancer, most with stages III and IV will ultimately relapse and die despite available therapies.⁹ Up until now, knowledge of a *BRCA* mutation has not affected the selection of treatment for ovarian cancer.

Tumour models with compromised ability to repair double-strand DNA breaks by the homologous recombination repair pathway, such as those with *BRCA1*

and *BRCA2* mutations, are highly sensitive to blockade of the repair of single-strand DNA breaks via PARP inhibition, which provides the basis for a novel synthetic lethal approach to cancer therapy.¹⁰ Such synthetic lethality occurs when there is a potent and lethal synergy between two otherwise non-lethal events: in this case, PARP inhibition induces a DNA lesion which is lethal when combined with tumour-restricted genetic loss of function for the DNA repair pathway (ie, the homologous recombination repair pathway). PARP inhibition is selectively potent against cells with biallelic *BRCA1* or *BRCA2* deficiency, so treatment via PARP inhibition could be particularly useful for *BRCA*-mutated tumours. This approach would keep toxic effects on healthy cells to a minimum, and would allow these cells to retain normal homologous recombination function.^{11–13} Evidence to support the treatment of *BRCA*-deficient tumours with PARP inhibitors has been shown in several in-vitro and in-vivo studies.^{14–18}

Olaparib (AZD2281) is a novel, orally active PARP inhibitor that induces synthetic lethality in homozygous *BRCA*-mutated cells.¹⁷ In a phase 1 study in patients with advanced solid tumours, olaparib 400 mg twice daily was

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identified as the maximum tolerated dose.¹⁹ However, tumour biopsies, peripheral blood mononuclear cells, and hair follicles seemed to have maximum pharmacodynamic activity at doses of more than 60 mg twice daily.^{19,20} In this phase 1 study, the first clinical response was seen at a dose of 100 mg twice daily.¹⁹ During dose escalations, further responses were recorded at twice daily doses of 200 mg and 400 mg. To gain additional data on toxic effects and identify any sign of efficacy, the protocol then allowed continued recruitment to expand the cohort at the dose of 200 mg twice daily, with recruitment limited to patients with genetic *BRCA* mutations. Olaparib was also well tolerated: the most frequently reported adverse events were grade 1 or 2 nausea and fatigue, according to the Common Terminology Criteria for Adverse Events (CTCAE, version 3).

In this phase 2, multicentre, international study, we aimed to assess the efficacy and safety of oral olaparib

monotherapy at the maximum tolerated dose (400 mg twice daily), and separately at a pharmacodynamically active lower dose (100 mg twice daily), for treatment of recurrent ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations.^{19,20}

Methods

Study design

This prospective, multicentre, phase 2 study was undertaken in a rare population of patients with recurrent ovarian cancer and known germline mutations who had been pretreated with at least one of several types of chemotherapy regimens. The study had a sequential cohort design: patients in the first cohort were enrolled and treated continuously with oral olaparib 400 mg twice daily in 28-day cycles until disease progression; and participants in the second cohort were recruited after successful recruitment of the first cohort, and given continuous oral olaparib 100 mg twice daily, which was the lowest PARP inhibitory dose with clinical activity.^{19,20} Patients were enrolled and treated at 12 centres in Australia, Germany, Spain, Sweden, and the USA between June 11, 2007, and Dec 3, 2007, for the first cohort, and between Oct 16, 2007, and March 14, 2008, for the second cohort.

Patients

Women (aged ≥ 18 years) were enrolled if they had recurrent epithelial ovarian cancer, primary peritoneal or fallopian tube carcinoma, and one or more measurable lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST).²¹ All patients needed to have a germline *BRCA1* or *BRCA2* mutation that was confirmed by analysis at an external central reference laboratory (Myriad Genetic Laboratories, Salt Lake City, UT, USA). All patients needed to have tumours that had recurred after a previous chemotherapy regimen, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and an estimated life expectancy of at least 16 weeks. Other chemotherapy, endocrine therapy, antibody-based therapy, or high-dose radiotherapy was not permitted during the study or for 28 days before the start of the study.

We obtained a thorough history of previous platinum treatment, including response and relapse dates, to distinguish between platinum-resistant and platinum-sensitive patients, with platinum resistance defined as recurrence or progression while on or within 6 months of platinum therapy. However, patients were not stratified at study entry by previous platinum response. Patients were excluded if they had: brain or CNS metastases that were progressive or symptomatic within 28 days of starting study treatment; a history of any other malignant disease that had been active or treated within the past 5 years; or persistent toxic effects of CTCAE grade 2 or greater (excluding alopecia) caused by previous treatment.

All patients provided written informed consent. The study was done in accordance with International Conference on Harmonisation Good Clinical Practice

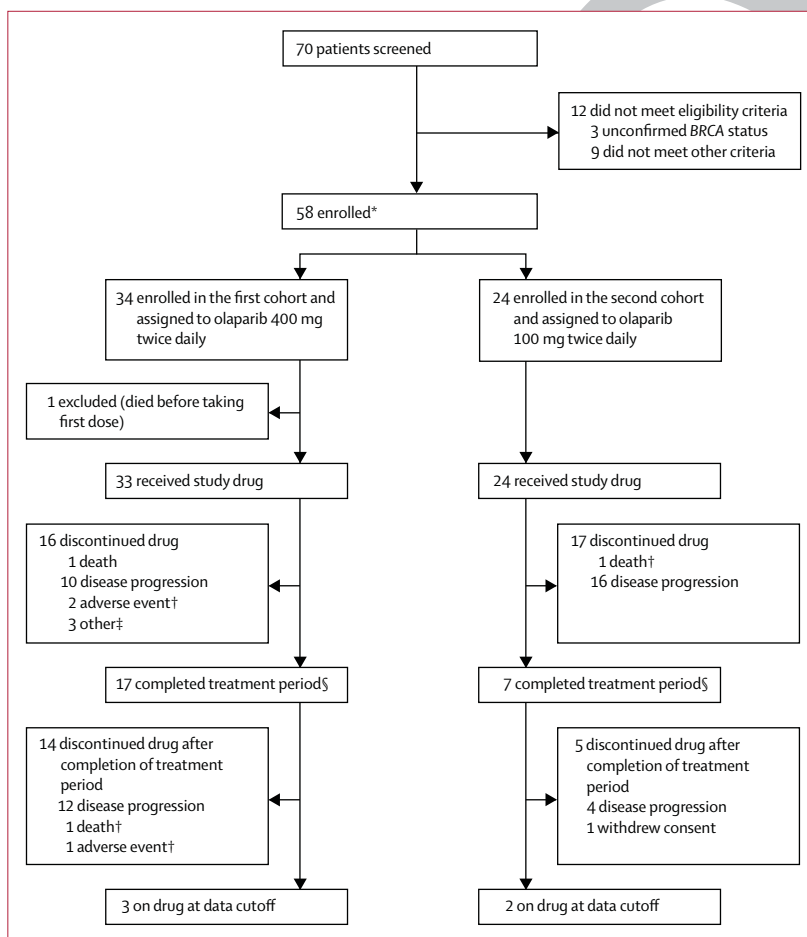


Figure 1: Trial profile

*Patients were not recruited and randomly assigned to treatment; 33 patients were enrolled into the first cohort (olaparib 400 mg twice daily), then recruitment began for the second cohort (olaparib 100 mg twice daily). †These five patients discontinued treatment due to adverse events. ‡Investigator discretion due to rising CA-125 concentrations, intercurrent illness, or non-compliance. §Completed the full study schedule of 168 days' treatment.

guidelines and the Declaration of Helsinki, and was approved by the independent ethics committee or institutional review board in every trial centre.

Study endpoints

The primary endpoint was objective tumour response rate (ORR) according to RECIST, with confirmation of response at least 28 days apart by CT scan and RECIST. Tumour assessments according to RECIST were done at baseline and at the end of every two cycles (28 days per cycle), up to and including the withdrawal visit. Secondary endpoints included: progression-free survival; clinical benefit rate; and duration of response from complete response or partial response until progression, according to RECIST. Clinical benefit rate was defined in the protocol as the proportion of patients with confirmed RECIST response of complete response, partial response, or stable disease for 8 weeks or more. However, we report data for complete response, partial response, or stable disease for 15 weeks or more (four treatment cycles), because these data were judged to be more clinically relevant. Safety and tolerability were assessed by adverse events and changes in laboratory parameters, including clinical chemistry, haematology, and urinalysis, according to CTCAE.

Statistical analysis

A sample size of up to 27 patients per cohort was needed to ensure that at least 20 patients were available for the RECIST assessment after four cycles (unless they had previously progressed). As a measure of study precision, with the assumption that ORR was 20%, 20 patients would ensure that the lower and upper limits of the 95% CIs were no more than 12% and 21% from the recorded value. However, the study size was not sufficient to estimate the treatment effect precisely. We aimed to recruit carriers of *BRCA1* and *BRCA2* mutations, and to treat at least six patients of each genotype in each cohort to ensure that the study hypothesis could be assessed for both patient groups.

The safety population comprised all patients who received at least one dose of olaparib. The intention-to-treat population (full analysis set) comprised all enrolled patients with positive *BRCA* status who took at least one dose of olaparib, irrespective of whether they completed the trial schedule and treatment regimen. Efficacy data are reported for the intention-to-treat analysis population unless otherwise specified. The first patient was enrolled on June 11, 2007, and the study database was locked on March 17, 2009. Statistical analyses were done by the sponsor and Parexel (Biostatistics Department) with SAS (version 9.1.3). Patients with a best RECIST response of complete response or partial response had to have a confirmed response at least 28 days later. 95% CIs were calculated with the Wilson score method, as recommended by Newcombe and Altman.²² Kaplan-Meier plots of progression-free survival are presented by treatment cohort.

	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
Age (years)	54 (35–74)	56 (39–69)
Ethnic origin		
White	31 (94%)	22 (92%)
Ashkenazi Jewish	9 (27%)	2 (8%)
Black	1 (3%)	0
Asian	1 (3%)	2 (8%)
Time since diagnosis (months)	40 (15–193)	46 (14–134)
<i>BRCA</i> mutation genotype		
<i>BRCA1</i>	21 (64%)	19 (79%)
<i>BRCA2</i>	12 (36%)	5 (21%)
ECOG performance status		
0	21 (64%)	15 (63%)
1	12 (36%)	6 (25%)
2	0	3 (13%)
Previous chemotherapy regimens	3 (1–10)	4 (1–16)

Data are median (range) or number (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: Patient characteristics

	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
Objective response	11 (33%, 20–51)	3 (13%, 4–31)
Complete response	2 (6%, 2–20)	0
Partial response	9 (27%, 15–44)	3 (13%, 4–31)
Stable disease	12 (36%, 22–53)	7 (29%, 15–49)
Progressive disease	10 (30%, 17–47)	14 (58%, 39–76)
Duration of response (days)	290 (126–506)	269 (169–288)*

Data are number (%; 95% CI) or median (range). *These data might be underestimated because time up to data cutoff is included for patients who responded but had not yet progressed.

Table 2: Best overall confirmed tumour response status (intention-to-treat population)

In April, 2008, the study investigators raised concerns that the frequency of early progression in patients receiving the dose of olaparib 100 mg twice daily was higher than in those receiving olaparib 400 mg twice daily. This was confirmed in a review of data in May, 2008, when the frequency of progression at 16 weeks was 15 (65%) of 23 patients in the olaparib 100 mg twice daily cohort compared with 11 (33%) of 33 in the olaparib 400 mg twice daily cohort. At that point, one patient in the 100 mg twice daily cohort had not completed 16 weeks' treatment. These findings led to a protocol amendment: all patients in the 100 mg twice daily cohort were offered the option to continue receiving olaparib 100 mg twice daily, or to increase to olaparib 400 mg twice daily immediately or at the time when the investigator believed disease progression had occurred. During October, 2008, an unscheduled interim analysis of the time to withdrawal (or dose escalation for the cohort assigned to 100 mg twice daily) was compared between the cohorts by use of the log-rank test to support the earlier decision to allow dose escalation ($p=0.0017$).

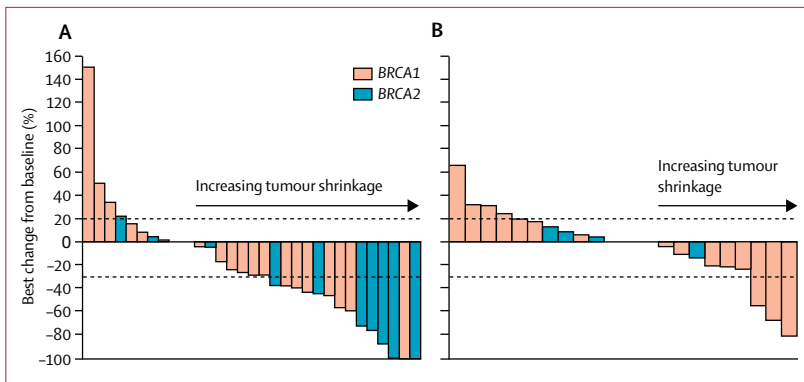


Figure 2: Best percentage change from baseline in target lesion size by BRCA mutation genotype in the intention-to-treat population

(A) Olaparib 400 mg twice daily. (B) Olaparib 100 mg twice daily. Two patients on olaparib 400 mg twice daily and one patient on olaparib 100 mg twice daily have been excluded because they died before Response Evaluation Criteria In Solid Tumors assessment. Reference lines indicate boundaries for progressive disease (20%) and partial response (-30%).

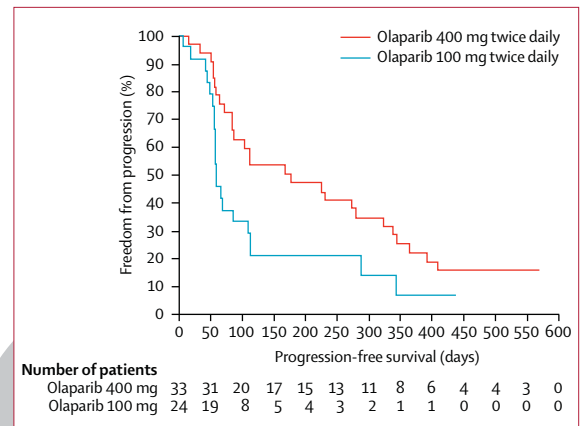


Figure 3: Kaplan-Meier curves of progression-free survival for the intention-to-treat population

Progression-free survival is shown for each of the two cohorts, which ran in sequence.

This study is registered with ClinicalTrials.gov, number NCT00494442.

Role of the funding source

The sponsor designed the study in collaboration with the ICEBERG investigators. The sponsor did not participate in data collection. The sponsor and Parexel did the statistical analyses, and the sponsor participated in data interpretation and review of the report. The corresponding author had full access to all the data in the study, and MWA and AT had final responsibility for the decision to submit for publication.

Results

70 patients with ovarian cancer and a confirmed BRCA mutation were screened for eligibility, of whom 58 (83%) were enrolled and 57 (81%) received at least one dose of olaparib (figure 1). One patient was enrolled and allocated to receive olaparib 400 mg, but died before receiving the first dose of treatment. 24 patients successfully completed the full study schedule (up to and including 168 days of treatment).

Table 1 shows the baseline characteristics of patients. In total, 40 patients had the BRCA1 mutation and 17 had the BRCA2 mutation (webappendix p 1 shows individual mutation genotype for all evaluable patients). Patients had been heavily pretreated, with a median of three (range 1–16) previous chemotherapy regimens (webappendix pp 2–7 show the context of previous chemotherapy regimens). All patients had received previous platinum and taxane therapy, and some patients had received a variety of other chemotherapies and targeted treatments, including gemcitabine (n=34, 60%), anthracycline (n=37, 65%), topotecan (n=17, 30%), and cyclophosphamide (n=15, 26%).

In six patients, the olaparib dose was escalated from 100 mg twice daily to 400 mg twice daily. For five patients, the dose escalations occurred between May 17 and May 30,

2008 (protocol amendment dated May 22, 2008), and for one patient, the dose was escalated on March 5, 2009, after a new lesion, indicative of progression, was recorded. Of the remaining 18 patients on olaparib 100 mg twice daily, 17 had progressed before the protocol amendment and one continued on the 100 mg dose.

In analysis of efficacy, comparisons between cohorts should be made with caution because the two cohorts were recruited sequentially and allocation was not randomised. Table 2 shows the confirmed ORRs and duration of response for the two cohorts. The median duration of response might be underestimated for the 100 mg cohort because one patient was continuing to respond at data cutoff. In patients on olaparib 400 mg twice daily, objective response was confirmed in five of 21 patients (24%) with BRCA1 mutations and six of 12 patients (50%) with BRCA2 mutations. In those on olaparib 100 mg twice daily, objective response was confirmed in three of 19 patients (16%) with BRCA1 mutations and none of five patients with BRCA2 mutations. Furthermore, objective response was confirmed in five of 13 (38%) platinum-sensitive patients and six of 20 (30%) platinum-resistant patients on olaparib 400 mg twice daily, but in only three of six (50%) platinum-sensitive patients on olaparib 100 mg twice daily.

The median best percentage change (maximum reduction or minimum increase in the absence of a reduction) in tumour size from baseline was 29% (range -100 to 150) in the olaparib 400 mg cohort, and 0% (-88 to 66) in the olaparib 100 mg cohort (figure 2). Median progression-free survival was 5.8 months (95% CI 2.8–10.6) in the olaparib 400 mg cohort, and 1.9 months (1.8–3.6) in the olaparib 100 mg cohort (figure 3). The clinical benefit rate was 52% (n=17) in the olaparib 400 mg cohort and 21% (n=5) in the olaparib 100 mg cohort for the modified intention-to-treat population.

All patients, except one in the olaparib 100 mg cohort, had at least one adverse event. The most frequently

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reported adverse events were nausea and fatigue, and most events were mild in intensity (CTCAE grade 1 or 2). CTCAE grade 3 or 4 events were reported in 17 of 33 patients (52%; 38 events) in the olaparib 400 mg cohort and in 14 of 24 patients (58%; 29 events) in the olaparib 100 mg cohort. Two CTCAE grade 5 events occurred: congestive cardiac failure in a patient on olaparib 100 mg twice daily, and intestinal perforation in a patient on olaparib 400 mg twice daily. Table 3 shows the most frequently reported treatment-related adverse events. In total, five patients discontinued treatment due to adverse events, but only one patient in the olaparib 400 mg cohort discontinued treatment due to a treatment-related adverse event (nausea; table 4).

Overall, eight patients (24%) in the olaparib 400 mg cohort had both a dose interruption and dose reduction due to an adverse event, and an additional four had dose interruptions alone (table 4). 11 patients on olaparib 400 mg twice daily and ten on olaparib 100 mg twice daily died during the study. Nine deaths in each cohort were due to disease progression. Of the remaining two deaths in the olaparib 400 mg cohort, one was due to both disease progression and an adverse event (intestinal perforation of CTCAE grade 5), and the other was in a patient who died due to a second malignant disease (acute myeloid leukaemia) about 9 months after discontinuation of olaparib. This patient had a *BRCA1* mutation (3819del5) and had received 21 previous cycles of chemotherapy in three separate courses (six cycles of carboplatin and paclitaxel, five cycles of intraperitoneal cisplatin, and ten cycles of topotecan). The remaining death in the olaparib 100 mg cohort was due to both disease progression and an adverse event (congestive cardiac failure of CTCAE grade 5, and respiratory failure of CTCAE grade 3). The patient had a medical history of hypothyroidism and high cholesterol, and had lymph node metastases at entry to the study. After 63 days' treatment, the patient was admitted to hospital for congestive cardiac failure and respiratory failure. The investigator judged these events to be unrelated to olaparib. Treatment was permanently stopped and the patient died on day 68. The causes of death were recorded as congestive heart failure, ovarian cancer, and respiratory failure. None of the adverse events reported in the patients who died was judged by the investigator to be related to treatment.

Discussion

The results of this phase 2 study show that the oral PARP inhibitor olaparib, given as monotherapy at a dose of 400 mg twice daily, has antitumour activity in heavily pretreated carriers of *BRCA1* or *BRCA2* mutations who have recurrent ovarian cancer. Olaparib 100 mg twice daily also had clinical activity in this population, but this dose seems to be less efficacious than the 400 mg twice daily dose. However, the allocation of patients to these doses was not randomised and the olaparib 100 mg

cohort had poorer prognostic features than did the 400 mg cohort. Response to olaparib was seen in all patient groups, including patients defined to be platinum sensitive or platinum resistant. Although the study was not designed to compare differences in response between these patient populations, these results are consistent with a previous report¹⁹ and would suggest that the mechanisms of resistance to olaparib might only partly overlap those for platinum salts.

	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
Nausea		
1 or 2	14 (42%)	7 (29%)
3 or 4	2 (6%)	2 (8%)
Fatigue		
1 or 2	10 (30%)	9 (38%)
3 or 4	1 (3%)	0
Anaemia*		
1 or 2	5 (15%)	4 (17%)
3 or 4	1 (3%)	0
Diarrhoea		
1 or 2	5 (15%)	3 (13%)
3 or 4	0	0
Vomiting		
1 or 2	3 (9%)	0
3 or 4	1 (3%)	0
Neutropenia		
1 or 2	0	0
3 or 4	3 (9%)	0
Rash		
1 or 2	3 (9%)	2 (8%)
3 or 4	0	0
Gastro-oesophageal reflux disease		
1 or 2	3 (9%)	0
3 or 4	0	1 (4%)
Abdominal pain†		
1 or 2	3 (9%)	0
3 or 4	0	0
Dyspepsia		
1 or 2	2 (6%)	3 (13%)
3 or 4	0	0
Dizziness		
1 or 2	2 (6%)	2 (8%)
3 or 4	0	0
Headache		
1 or 2	2 (6%)	1 (4%)
3 or 4	0	0
Asthenia		
1 or 2	2 (6%)	0
3 or 4	0	0
Gastritis		
1 or 2	2 (6%)	0
3 or 4	0	0

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	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
(Continued from previous page)		
Peripheral neuropathy		
1 or 2	1 (3%)	2 (8%)
3 or 4	0	0
Constipation		
1 or 2	1 (3%)	2 (8%)
3 or 4	0	0
Haemoglobin urine		
1 or 2	0	3 (13%)
3 or 4	0	0
Lymphopenia		
1 or 2	0	1 (4%)
3 or 4	0	1 (4%)

Data are number (%). Adverse events are graded according to the Common Terminology Criteria for Adverse Events (version 3); no grade 5 adverse events were reported at the time of this analysis. *Includes Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of anaemia and haemoglobin decreased. †Includes MedDRA preferred terms of abdominal pain and abdominal pain lower. ‡Adverse events at least possibly, probably, and definitely related to olaparib in the opinion of the investigator in the safety population.

Table 3: Olaparib-related adverse events‡, according to grade, arising in two or more patients

	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
Discontinuation	4 (12%)	1 (4%)
Dose interruption	12 (36%)	4 (17%)
Dose reduction	8 (24%)	0

Data are number (%).

Table 4: Dose interruptions and reductions due to adverse events

We judged the possibility that the response to olaparib was restricted to patients with either *BRCA1* or *BRCA2* mutations to be unlikely, and our hypothesis was substantiated with objective responses reported in both *BRCA*-mutant populations. Furthermore, ORRs did not seem to differ between patients with *BRCA1* versus *BRCA2* mutations, but the patient numbers are small and the study is not powered to make formal comparisons. Of the 11 Ashkenazi Jewish patients, six achieved a partial response. Conversely, not all carriers of *BRCA1* or *BRCA2* mutations had a response to olaparib. Potential resistance mechanisms to PARP inhibitor therapy have been described on the basis of genetic reversion in tumour subclones.^{23,24} However, the frequency of this event is unknown and has not been examined in this study. Other potential resistance mechanisms remain to be defined and explored in this group of patients and will be the subject of future analyses.

These findings support the results of the phase 1 assessment of olaparib in patients with *BRCA1* or *BRCA2* mutations who have ovarian cancer,¹⁹ and the phase 2 study of carriers of *BRCA1* or *BRCA2* mutations who

have advanced breast cancer.²⁵ Taken together, these studies support the selection of cancers for specific targeted therapy on the basis of the presence of a common underlying genetic defect, rather than organ of origin.²⁶

Olaparib was associated with predominantly mild-to-moderate adverse events. The most frequently reported adverse events were nausea, fatigue, and clinical diagnoses of haematological events, which are known to be associated with olaparib treatment. A few dose interruptions and reductions occurred due to toxic effects, and only five patients discontinued olaparib due to adverse events. The adverse events reported in these individuals with a *BRCA1* or *BRCA2* mutation who have ovarian cancer were similar to those reported in non-carriers, and in patients with a *BRCA1* or *BRCA2* mutation who have ovarian cancer¹⁹ and breast cancer.²⁵ The absence of unique toxic effects in patients with and without *BRCA* mutations confirms the findings from in-vitro data of no synthetic lethality in cells heterozygous for *BRCA* mutations.¹⁵

In our study, results suggest that PARP inhibition has a wide therapeutic window and sufficient tumour cell selectivity to target ovarian cancers that have defects in DNA repair by homologous recombination. These findings support the hypothesis that *BRCA*-mutated tumours are susceptible to a synthetic lethal therapeutic approach. These data also support the identification of *BRCA1* or *BRCA2* mutations as a predictive biomarker for responsiveness to PARP inhibition, and raise the possibility that homologous recombination defects caused by loss of function of other genes with roles in this DNA repair process,^{11,27} or by epigenetic loss of *BRCA1* or *BRCA2*,²⁸ could predict similar responsiveness to PARP inhibition in a broad, genetically defined group of malignant diseases.

Contributors

MWA, JC, JNW, MW, RKS, and AT participated in the study design. MWA, RTP, MF, BP, KMB-M, CS, JNW, AO, NL, KL, RKS, and UM recruited patients and gathered data at their centres. All authors participated in data analysis and interpretation. MWA wrote the report. All authors reviewed and provided input on initial drafts of the report and have approved the final version.

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San Francisco, CA; Katherine Bell-McGuinn, Memorial Sloan-Kettering Cancer Center, New York, NY; Karen Lu, University of Texas MD Anderson Cancer Center, Houston, TX.

Conflicts of interest

MWA has received honoraria for consultancy from AstraZeneca and Myriad Genetic Laboratories, and funding support for travel to investigators' meetings for this study from AstraZeneca and to advisory board meetings from Myriad Genetic Laboratories. RTP has received honoraria and funding support for travel to investigators' meetings for this study from AstraZeneca, RTP's institution has received grants from AstraZeneca, and RTP has received funding support for travel to investigators' meetings from XXXX. MF has received honoraria as a clinical advisory board member and funding support for travel to investigators' meetings for this study from AstraZeneca. BP's institution has received funding support for patient care, and BP has received funding support for travel to an investigators' meeting for this study from AstraZeneca. KMB's institution has received study grants, and KMB has received funding support for travel to investigators' meetings for this study from AstraZeneca. CS has received funding support for travel to investigators' meetings for this study from AstraZeneca. NL's institution has received funding support for the conduct of the study and travel to investigators' meetings for this study from AstraZeneca, NL has received honoraria for lectures to patient groups that were organised and funded by AstraZeneca, and NL has received funding support for travel to investigators' meetings from XXXXXX. RKS's institution has received fees to cover study expenses, and RKS has received funding support for travel to investigators' meetings for this study from AstraZeneca. UM's institution has received fees to cover study expenses, and UM has received funding support for travel to investigators' meetings for this study from AstraZeneca. MW and JC are employees of AstraZeneca, and JC has AstraZeneca stock options. AT has received a payment from the UK Institute of Cancer Research's rewards to inventors programme for work on use of PARP inhibitors to target cancers associated with *BRCA1* and *BRCA2* mutations, and has received funding support for travel to investigators' meetings for this study and an honorarium for an academic lecture from AstraZeneca. AO, KL, and JNW declare that they have no conflicts of interest.

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