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

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Summary

Background Olaparib, a novel, orally active poly(ADP-ribose) polymerase (PARP) inhibitor, induced synthetic lethality in *BRCA*-deficient cells. A maximum tolerated dose and initial signal of efficacy in *BRCA*-deficient ovarian cancers have been reported. We therefore assessed the efficacy, safety, and tolerability of olaparib alone in women with *BRCA1* or *BRCA2* mutations and advanced breast cancer.

Methods Women (aged ≥18 years) with confirmed *BRCA1* or *BRCA2* mutations and recurrent, advanced breast cancer were assigned to two sequential cohorts in a phase 2 study undertaken in 16 centres in Australia, Germany, Spain, Sweden, the UK, and the USA. The first cohort (n=27) was given continuous oral olaparib at the maximum tolerated dose (400 mg twice daily), and the second (n=27) was given a lower dose (100 mg twice daily). The primary efficacy endpoint was objective response rate (ORR). This study is registered with ClinicalTrials.gov, number NCT00494234.

Findings Patients had been given a median of three previous chemotherapy regimens (range 1–5 in cohort 1, and 2–4 in cohort 2). ORR was 11 (41%) of 27 patients (95% CI 25–59) in the cohort assigned to 400 mg twice daily, and six (22%) of 27 (11–41) in the cohort assigned to 100 mg twice daily. Toxicities were mainly at low grades. The most frequent causally related adverse events in the cohort given 400 mg twice daily were fatigue (grade 1 or 2, 11 [41%]; grade 3 or 4, four [15%]), nausea (grade 1 or 2, 11 [41%]; grade 3 or 4, four [15%]), vomiting (grade 1 or 2, three [11%]; grade 3 or 4, three [11%]), and anaemia (grade 1 or 2, one [4%]; grade 3 or 4, three [11%]). The most frequent causally related adverse events in the cohort given 100 mg twice daily were nausea (grade 1 or 2, 11 [41%]; none grade 3 or 4) and fatigue (grade 1 or 2, seven [26%]; grade 3 or 4, one [4%]).

Interpretation The results of this study provide positive proof of concept for PARP inhibition in *BRCA*-deficient breast cancers and shows a favourable therapeutic index for a novel targeted treatment strategy in patients with tumours that have genetic loss of function of *BRCA1*-associated or *BRCA2*-associated DNA repair. Toxicity in women with *BRCA1* and *BRCA2* mutations was similar to that reported previously in those without such mutations.

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Introduction

Breast cancer is one of the main causes of cancer-associated deaths in women. For most women, breast cancer arises after menopause, and the cause is probably related to a complex association of environmental[1,2] and polygenic genetic factors.[3] For less than 5% of women, the disease arises in association with mutations in two highly penetrant breast and ovarian cancer predisposition genes—*BRCA1*[4] and *BRCA2*.[5] The indicators include an early onset and a family history of several close relatives who are affected with breast, ovarian, prostate, or pancreatic cancer. Inheritance of one mutated *BRCA1* or *BRCA2* allele leads to a lifetime risk of breast cancer that is as high as 80%.[6] Genetic counselling and testing programmes have been established that enable women to assess their risk and consider surveillance and risk-reducing surgical strategies.[6] There has been great interest in the conversion of the rapid increase in elucidation of the function of the *BRCA1* and *BRCA2* genes into improved clinical management of breast cancer associated with mutations in these genes. The products of the *BRCA1* and *BRCA2* genes have roles in a highly specialised form of DNA repair—ie, homologous recombination.[7–9] When the remaining wild-type allele is lost in a tumour precursor cell, this repair mechanism does not work, and the consequent rapid onset of genome instability[10–12] is sufficient to enable tumour development.[13–16] Studies of invasive primary breast tumours in individuals with *BRCA1* and *BRCA2* mutations confirm loss of the remaining wild-type allele.[17–19]

The homologous recombination DNA repair defect might be a target for therapy.[20] Indeed, the idea of synthetic lethality has been revisited[21] and investigated in preclinical model systems with constitutive defects in BRCA1-dependent or BRCA2-dependent homologous recombination in combination with drug-induced inhibition of DNA repair mechanisms for single-strand breaks that were dependent on poly(ADP-ribose) polymerase (PARP)-1, resulting in highly selective cell

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killing.[22,23] We therefore postulated that inhibitors of PARP-1 would have significant antitumour efficacy and low toxicity when used in individuals with *BRCA1* and *BRCA2* mutations and advanced malignant disease. Olaparib (AZD2281) is a novel, small-molecule, orally active PARP inhibitor with up to 1000-fold selective potency in isogenic preclinical models.[22] In the first-in-human phase 1 study of this drug in patients with advanced solid tumours, olaparib 400 mg twice daily was identified as the maximum tolerated dose.[24] Pharmacodynamic activity in tumour biopsy samples, peripheral blood mononuclear cells, and hair follicles seemed to be maximum at doses greater than 60 mg twice daily.[24] An expansion cohort of 22 patients with *BRCA1* or *BRCA2* mutations, and advanced treatment-refractory malignant disease from various primary tumour sites were recruited in this study, and an initial indication of antitumour efficacy was noted at doses of olaparib greater than 100 mg twice daily.[24] We now report the results of a multicentre proof-of-concept phase 2 study designed to assess the efficacy and safety of oral olaparib at the maximum tolerated dose and at a lower dose that was pharmacodynamically active at phase 1 assessment,[24] in women with *BRCA1* and *BRCA2* mutations and advanced breast cancer.

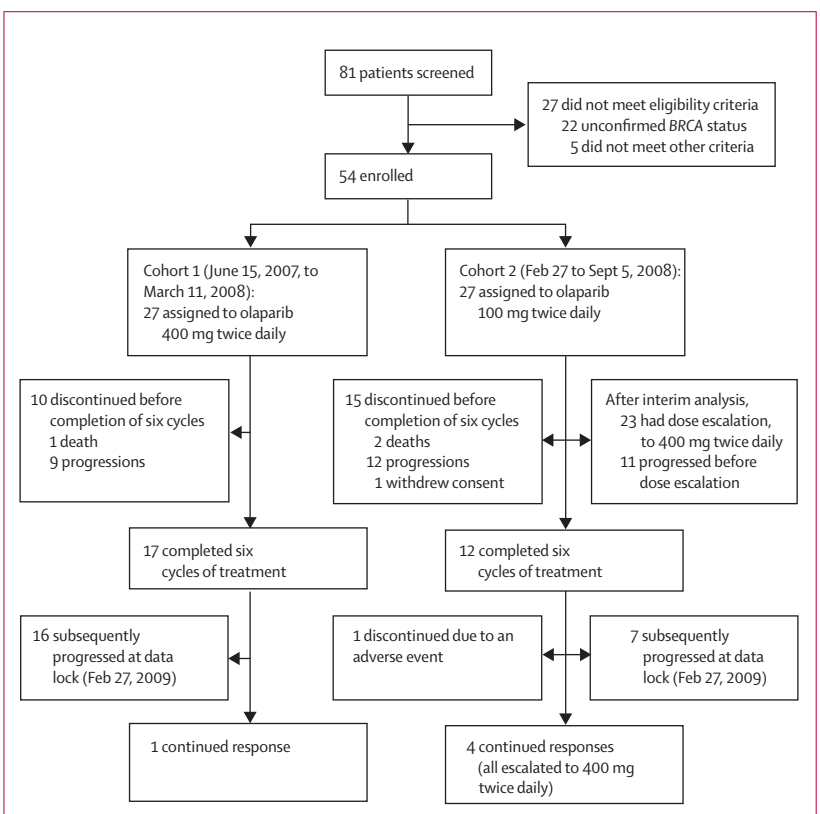

Figure 1: **Trial profile**
Cohort 1 (olaparib 400 mg twice daily) was recruited until 27 patients had been enrolled followed by cohort 2 (olaparib 100 mg twice daily). Patients were therefore not allocated to simultaneous cohorts by randomisation.

Methods

Study design

The study had a non-randomised, sequential cohort design, and was undertaken prospectively in 16 centres in Australia, Germany, Spain, Sweden, the UK, and the USA. The first cohort was enrolled from June 15, 2007, to March 11, 2008; and the second cohort was enrolled from Feb 27 to Sept 5, 2008. The first cohort of patients (cohort 1) was treated at the phase 1 maximum tolerated dose (400 mg twice daily).[24] A second sequential cohort (cohort 2) was given the lower PARP inhibitory dose (100 mg twice daily), which showed activity in the phase 1 study.[24]

Patients

Eligible women were aged 18 years or older and had locally advanced breast cancer (not amenable to curative surgery or radiation) or metastatic breast cancer (stage IIIB/IIIC or IV according to the American Joint Committee on Cancer Criteria) with one or more measurable lesions according to the Response Evaluation Criteria In Solid Tumours (RECIST).[25]

All patients were required to have a germline *BRCA1* or *BRCA2* mutation that was confirmed to be deleterious by analysis at an external central reference laboratory (Myriad Genetic Laboratories, Salt Lake City, UT, USA). All patients had been given at least one chemotherapy regimen, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had an estimated life expectancy of at least 16 weeks. Patients whose tumours were hormone-receptor positive had been given at least one regimen of hormonal therapy.

Patients were excluded if they had taken any anticancer therapy within 28 days of the first day of treatment; had brain or CNS metastases that were progressive or symptomatic, had not been previously resected or irradiated, or were the only site of measurable disease; had any other malignant disease that had been active or treated within the past 5 years (except adequately treated stage 1 or 2 ovarian cancer without any suspicion of recurrent disease); had persistent grade 2 or greater toxicities (Common Terminology Criteria for Adverse Events [CTCAE], version 3) caused by previous therapy. The concomitant use of bisphosphonates was allowed.

All patients provided written informed consent. The study was approved by the independent ethics committee for each trial centre, and done in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

Before starting treatment, patients underwent a physical examination, identification of ECOG performance status, full blood count, chemistry panel, and CT scan. Image assessments with CT scan were repeated every

two cycles (56 days) until there was confirmation of disease progression.

Study treatments

Olaparib was administered at 400 mg in the morning and evening (cohort 1) and 100 mg in the morning and evening (cohort 2), with a dosing interval of about 12 h. Patients were defined as completing a full study schedule if they received olaparib for up to and including 168 days.

Management of toxicity

If the National Cancer Institute's CTCAE grade 3 or 4 adverse events occurred, which the investigator thought were treatment related, olaparib was interrupted until the toxicity had reverted to CTCAE grade 1 or baseline grade. Repeat dose interruptions were allowed as required, for a maximum of 28 days on each occasion. If toxicity recurred following rechallenge with olaparib, and if further dose interruptions were inadequate for management of toxicity, then the patient could have a dose reduction (cohort 1 only) or discontinue olaparib. A maximum of two dose reductions was allowed (to 200 mg twice daily and then to 100 mg twice daily) after which, if toxicity persisted, the patient was withdrawn.

Study endpoints

The primary endpoint was objective response rate (ORR) assessed by use of RECIST, with responses confirmed with CT scan and RECIST after at least 28 days.

Secondary endpoints included efficacy of olaparib in terms of clinical benefit defined as the percentage of patients with complete response, partial response, and stable disease for at least 23 weeks (allowing for a 1-week window around the scheduled 24-week assessment), progression-free survival, and duration of response (defined as the time the measurement criteria for complete or partial response are met until progression according to RECIST). Safety and tolerability assessments included adverse events and changes in laboratory indices according to CTCAE.

Statistical analysis

All patients taking at least one dose of study drug were included in the primary analysis of response rate according to the principle of intention to treat. To achieve sufficient patient exposure, up to 27 patients had to be treated in each cohort to ensure at least 20 patients were available for the RECIST assessment after four cycles of treatment (unless they had previously progressed). As a measure of study precision, and an assumption that ORR was 20%, inclusion of 20 patients would ensure that the lower and upper limits of the 95% CIs were no more than 12% and 21% from the noted value. However, the study was not sufficiently sized to precisely estimate the treatment effect. Individuals with *BRCA1* and *BRCA2* mutations were to be recruited, and at least six patients of each genotype would receive olaparib in each cohort to ensure that the study hypothesis could be assessed for both patient groups.

The intention-to-treat population was all enrolled patients with confirmed germline mutations, who took at least one dose of olaparib. The per-protocol population was all enrolled patients with confirmed *BRCA* mutation, without any major deviations to the protocol. The population for analysis of olaparib safety was all patients who were given at least one dose of olaparib. An independent data monitoring committee reviewed safety data.

The first patient was enrolled on June 15, 2007, and the study database was locked on Feb 27, 2009. Statistical analyses were done by the Biostatistics Department at Parexel and AstraZeneca with SAS (version 9.1.3). 95% CIs were calculated by use of the Wilson score method as recommended by Newcombe and Altman.[26] Kaplan-Meier plots of progression-free survival are presented by treatment group. Patients assigned to

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Age (years; median, range)	44 (32–72)	41 (28–67)
Race		
White	25 (92%)	26 (96%)
Black or African American	1 (4%)	0
Asian	1 (4%)	1 (4%)
Recorded ethnic origin		
Ashkenazi Jewish	5 (19%)	2 (7%)
Hispanic or Latino	2 (7%)	2 (7%)
Time since diagnosis (months; median, range)	62 (11–253)	66 (16–344)
BRCA mutation genotype		
BRCA1	18 (67%)	15 (56%)
BRCA2	9 (33%)	11 (41%)
BRCA1 and *BRCA2*	0	1* (4%)
ECOG performance status		
0	12 (44%)	16 (59%)
1	13 (48%)	10 (37%)
2	2 (7%)	1 (4%)
Previous chemotherapy regimens (adjuvant and metastatic)		
Median (range)	3 (1–5)	3 (2–4)
Taxane and anthracycline	25 (93%)	19 (70%)
Taxane, anthracycline, and capecitabine	10 (37%)	11 (41%)
Platinum	6 (22%)	8 (30%)
Hormonal status†		
Triple negative	13/26 (50%)	16/25 (64%)
ER+ HER2–	11/27 (41%)	4/26 (15%)
ER+ HER2+	1/27 (4%)	4/26 (15%)
ER– HER2+	1/27 (4%)	1/26 (4%)

Data are number (%) or n/N (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. HER=human epidermal growth factor receptor. *Patient's mutation status before providing consent for participation in study was *BRCA1 Q563/X* and *BRCA2 C1573Y* (a variant of undetermined significance); she was excluded from the per-protocol analysis because she was only on treatment for 28 days and therefore did not have any follow-up data according to the Response Evaluation Criteria In Solid Tumours. †Patients with unknown hormone-receptor status were not included in the demographic information.

Table 1: **Patient characteristics**

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

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

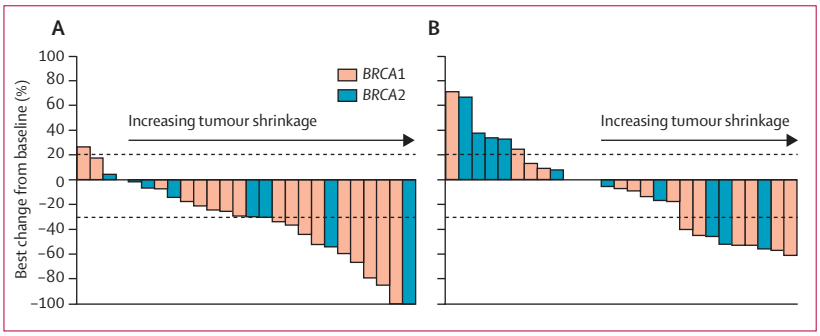

Figure 2: **Best percentage change from baseline in target lesion size by *BRCA* mutation genotype in the intention-to-treat population**
(A) Olaparib 400 mg twice daily. (B) Olaparib 100 mg twice daily. Reference lines indicate boundaries for progressive disease (20%) and partial response (–30%).

olaparib 100 mg twice daily were not censored at the time of dose increase in the absence of progression, that followed the interim analyses described below, to avoid the introduction of informative censoring. The principle of intention to treat was applied, and any progression after a switch to olaparib 400 mg twice daily was counted as an event in the cohort given olaparib 100 mg twice daily. Some patients who progressed on the lower dose were switched to the higher dose. The progression was judged to be the progression event, and the patients were given the higher dose outside of the trial.

See Online for webappendix

Interim analysis

The time to treatment withdrawal (or dose escalation for the cohort assigned to 100 mg twice daily) was compared between cohorts by use of the log-rank test to detect discrepancy in the activity of the two doses with a prespecified 5% significance level (two-sided) for the difference in withdrawal rates. These interim analyses were undertaken in October and December, 2008. Both consecutive analyses achieved the prespecified 5% significance level (two-sided) for the difference in withdrawal rates in favour of the cohort assigned to 400 mg twice daily (p=0·008 for the analysis done in October and p=0·003 for the analysis done in December). At interim analysis, the median times to withdrawal or dose escalation were 3·5 months in the cohort assigned to 100 mg twice daily, and 6·0 months in the cohort assigned to 400 mg twice daily. Therefore, patients in cohort 2 were offered the option to dose escalate to 400 mg twice daily after a repeat RECIST response assessment at this point. Dose escalation could be offered irrespective of response status, at the investigator's discretion. 11 of 23 patients who had their dose increased from 100 mg twice daily to 400 mg twice daily had progressed before dose escalation and were treated at the higher dose outside of the study protocol. Of the 12 patients whose disease had not progressed before dose escalation, seven had received less than 4 months of treatment at the time of dose escalation.

This study is registered with ClinicalTrials.gov, number NCT00494234.

Role of the funding source

The sponsor designed the study in collaboration with the ICEBERG investigators. The sponsor and Parexel did the statistical analyses. The sponsor did not participate in data collection. All authors had access to all the data through AstraZeneca and Parexel statisticians, and contributed to the decision to submit for publication.

Results

Figure 1 shows the trial profile. The enrolled patients were given at least one dose of olaparib. 25 (46%) of 54 patients discontinued treatment before being given the planned six cycles. The remaining 29 patients (54%) completed the full study schedule.

At the time the study database was locked, five patients were still taking olaparib with more patients still on study drug in cohort 2 as a result of the sequential nature of enrolment to the two cohorts. Four patients had protocol deviations—inclusion or exclusion criteria breached (n=1), drug non-compliance (n=2), and taking a disallowed medication (n=1)—and so were excluded from the per-protocol analysis. Table 1 shows the baseline characteristics of all enrolled patients. There were 34 women with *BRCA1* mutations and 20 with *BRCA2* mutations (webappendix p 1). Founder mutations in *BRCA1* and *BRCA2* are particularly prevalent in women of Ashkenazi ancestry. Although we noted a few patients with an Ashkenazi ethnic background, founder mutations at any particular locus in either *BRCA1* or *BRCA2* genes were not predominant, and therefore, the results could be generalised for mutation loci. Patients in both cohorts had been given a median of three previous chemotherapy regimens, taxanes and anthracyclines in most cases (table 1). The context of previous chemotherapy is provided in the webappendix (pp 2–6). There were some patients in both cohorts with a breast cancer phenotype that was oestrogen-receptor negative, progesterone-receptor negative, and HER2 (also known as ERBB2)-receptor negative (triple negative); most had *BRCA1* mutations (11 of 13 in cohort assigned to 400 mg, and 11 of 16 in cohort assigned to 100 mg). Most patients with oestrogen-receptor-positive tumours also had *BRCA2* mutations

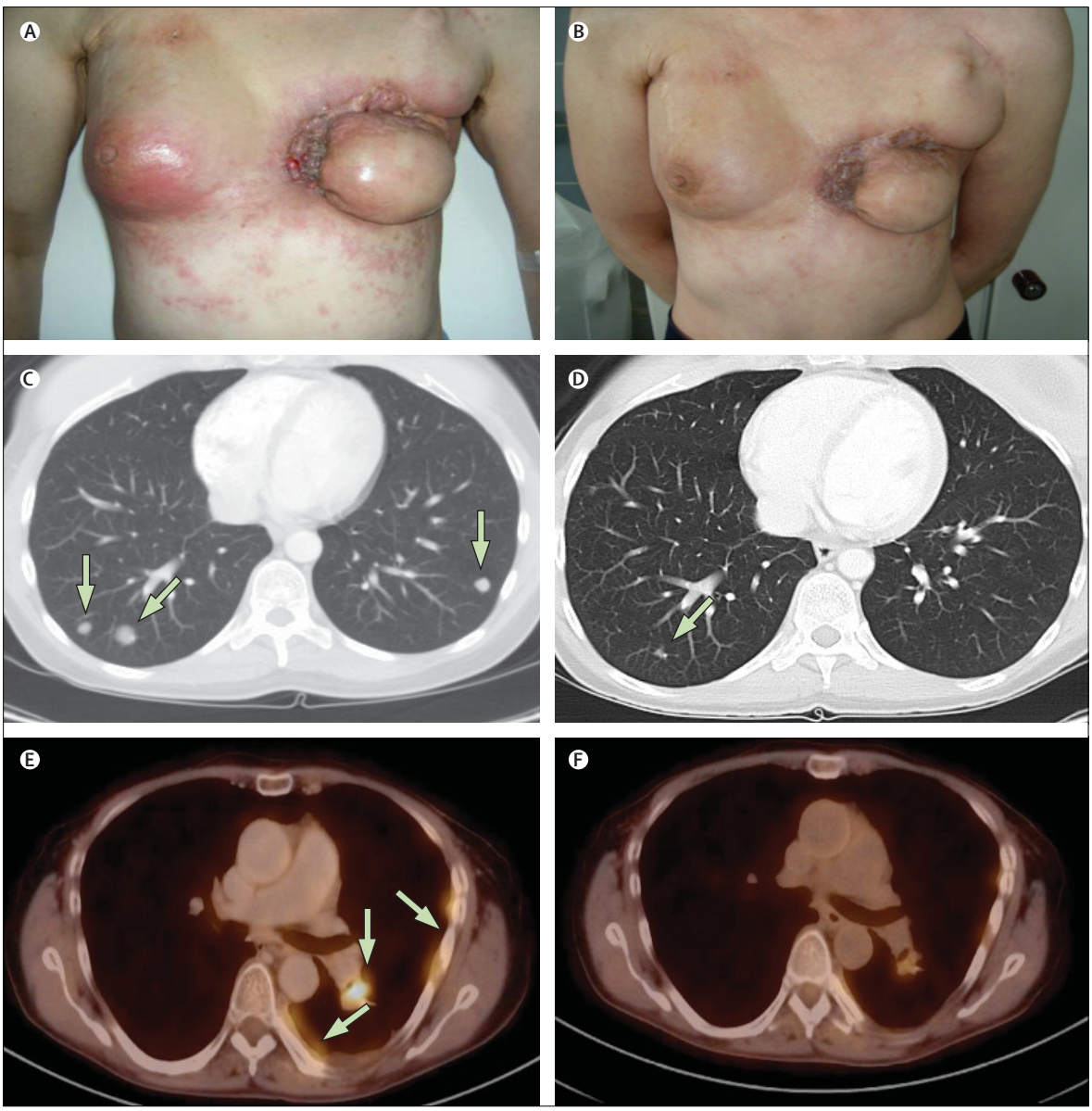

Figure 3: **Tumour response to olaparib**
(A) Photograph of a woman with a *BRCA1* mutation and bilateral inflammatory triple-negative breast cancer recurrence before starting olaparib (Jan 9, 2008); and (B) after 2 months (March 5, 2008) of olaparib 400 mg twice daily. (C) Image of axial thoracic CT scan of another patient with a *BRCA1* mutation, triple-negative breast cancer, and pulmonary metastases (yellow arrows) before treatment with olaparib; and (D) after 180 days of olaparib 400 mg twice daily. Previous therapy included adjuvant dose-dense sequential doxorubicin, cyclophosphamide, and paclitaxel with capecitabine and bevacizumab at metastatic relapse, and vinorelbine and bevacizumab at second progression. Olaparib was started on June 12, 2007, and at database lock (Feb 27, 2009), this patient was still receiving olaparib without progression. (E) Axial thoracic ^{18}F-fluorodeoxyglucose (FDG) PET-CT image of a patient with a *BRCA1* mutation and triple-negative breast cancer showing ^{18}F-FDG uptake in a left hilar lymph node and pleural disease (yellow arrows) before treatment with olaparib; and (F) after one cycle of olaparib 400 mg twice daily. The patient achieved a partial response in accordance with the Response Evaluation Criteria In Solid Tumours, and was free from progression for 6 months.

(seven of 12 in high-dose cohort, and five of eight in low-dose cohort), and the incidence of HER2-positive breast cancer was uncommon (seven of 54: four with *BRCA1* mutations, and three with *BRCA2* mutations); these findings were in accord with results of other studies.[27,28] Four patients with HER2-positive breast cancer had progressed despite previous treatment with trastuzumab.

Efficacy data are reported for the patients in the intention-to-treat analysis, unless otherwise specified. The confirmed ORR was higher in cohort 1 than in cohort 2 (table 2). All, except one, confirmed responses occurred within the first four cycles of olaparib treatment; the remaining patient showed a response after eight cycles. In the per-protocol analysis, the ORR was

	Olaparib 400 mg twice daily (n=27)				Olaparib 100 mg twice daily (n=27)			
	BRCA1 (n=18)	*BRCA2* (n=9)	Triple negative (n=13)	Non-triple negative (n=14)	*BRCA1* (n=16)	*BRCA2* (n=11)	Triple negative (n=16)	Non-triple negative (n=11)
Objective response	9 (50%)	2 (22%)	7 (54%)	4 (29%)	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Complete response	1 (6%)	0	0	0	0	0	0	0
Partial response	8 (44%)	2 (22%)	7 (54%)	4 (29%)	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Stable disease	7 (39%)	5 (56%)	4 (31%)	8 (57%)	9 (56%)	3 (27%)	7 (44%)	4 (36%)
Progressive disease	2 (11%)	2 (22%)	2 (15%)	2 (14%)	4 (25%)	5 (45%)	5 (31%)	5 (45%)

Data are number (%).

Table 3: **Best overall confirmed tumour response status (intention-to-treat population) by *BRCA* mutation status and hormonal status**

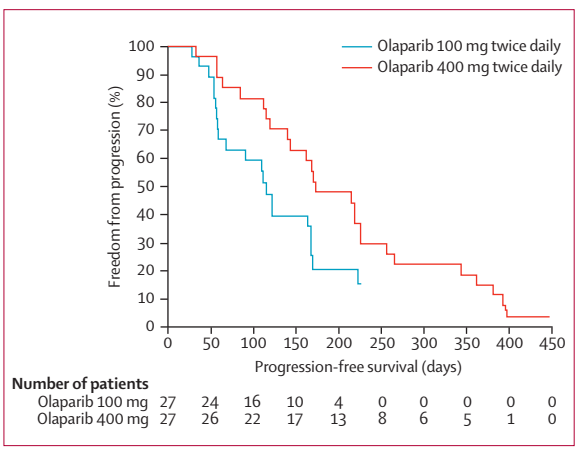

Figure 4: **Kaplan-Meier curves of progression-free survival for the intention-to-treat population**

confirmed in 11 of 26 patients (42%, 95% CI 26–61) in cohort 1 and six of 24 (25%, 12–45) in cohort 2. The median best percentage change (reduction) in tumour size from baseline was –30% (range –100% to 27%) in cohort 1 and –7% (–69% to 71%) in cohort 2 (figure 2). Figure 3 shows examples of objective responses.

In the exploratory analyses, objective responses were noted in individuals with *BRCA1* and *BRCA2* mutations (table 3), and in those with triple-negative and hormone-receptor-positive disease. Olaparib showed activity even in heavily pretreated patients who had been exposed to the most active licensed chemotherapy drugs for breast cancer. Of those patients who had received at least three (median) previous chemotherapy regimens, eight of 17 patients in cohort 1 had a response showing activity in this heavily pretreated population (webappendix pp 2–6). Previous chemotherapy regimens and best objective response to olaparib are shown in the webappendix (p 7). 12 of 14 patients had been given a platinum salt for advanced disease, seven of these had responded to that treatment. These responses were defined on the basis of a report of case records, and rigorous assessment against RECIST was not applied. One of these 14 patients, treated in cohort 1, had a subsequent response to olaparib.

Median duration of objective response was 144 days (range 92–393) in cohort 1 and 141 days (55–175) in cohort 2. The clinical benefit rate was 52% for cohort 1 and 26% for cohort 2. Median progression-free survival was 5·7 months (95% CI 4·6–7·4) for cohort 1 and 3·8 months (1·9–5·5) for cohort 2 (figure 4). Progression-free survival events were noted in 21 of 27 patients in the cohort given 100 mg twice daily, and in 26 of 27 patients in the cohort given 400 mg. More patients in the cohort given 100 mg twice daily remained on study at the data cutoff point because these patients were recruited later and therefore had less time in which to progress. Of the 23 patients who had their dose increased to 400 mg twice daily after the interim analysis, 11 of these patients had prior disease progression, eight had stable disease, and four had partial response according to RECIST at CT assessment at or within 4 weeks of the start of dose escalation. Drug dose was increased to 400 mg twice daily, without evidence of progression, in two of six patients with confirmed responses in cohort 2 in the intention-to-treat analysis, with the responses first recorded at 24 days and 34 days after the dose increase.

The toxicities associated with taking olaparib were generally manageable. Treatment-related adverse events were reported in 44 patients (81%) but were mainly CTCAE grade 1 or 2 (table 4). Overall, 13 (24%) patients had events that were CTCAE grade 3 or 4 and were attributed to study medication. In total, grade 3 or 4 CTCAEs were reported in 11 [41%] of 27 patients (21 events) in the cohort assigned to olaparib 400 mg twice daily, and in nine [33%] of 27 patients (17 events) in the cohort assigned to olaparib 100 mg twice daily. Grade 4 events occurred in three patients and included treatment-related anaemia (one patient in each cohort). One patient in the high-dose cohort had CTCAE grade 4 thrombocytopenia, which developed 4 weeks after stopping olaparib and while the patient was taking carboplatin, and was not thought to be related to olaparib. There were no CTCAE grade 5 events.

In the cohort assigned to olaparib 400 mg twice daily, no patients discontinued because of adverse events, although one patient withdrew after convulsions with evidence of new cerebral metastasis. Only one patient in the low-dose cohort discontinued treatment because of treatment-related dizziness, seizures, and syncope following dose escalation to 400 mg twice daily after the

interim analysis. Imaging investigations subsequently identified brain metastases in this patient. Dose interruptions and reductions due to adverse events were unusual. Ten patients had a dose interruption, ten had a dose reduction, and nine had both dose reductions and interruptions. The dose interruptions were for a median of 2 days (range 1–47) in cohort 1, and 3 days (1–41) in cohort 2 (table 5).

Discussion

This trial was designed to test the safety and efficacy of a monotherapy PARP inhibitor strategy in women with *BRCA1* and *BRCA2* mutations with advanced metastatic breast cancer. The results of this phase 2 study show that the oral PARP inhibitor olaparib at 400 mg twice daily was active even in women with *BRCA1* or *BRCA2* mutations and advanced breast cancer that was resistant to conventional chemotherapy. These findings provide proof of concept for the clinical usefulness of tumour-specific targeting of loss of *BRCA1*-associated or *BRCA2*-associated homologous recombination repair in patients with breast cancer. We noted an acceptable safety and tolerability profile, similar to that reported in the initial phase 1 study in which most patients did not have mutations.[24] Despite the 50% gene dosage for *BRCA1* or *BRCA2* in the normal tissues of the heterozygous patients, we did not note any evidence of increased toxic effects on normal tissue with olaparib, confirming the predictions of preclinical data with related compounds.[22] A similarly high therapeutic ratio was also reported in a companion phase 2 trial in patients with *BRCA1* or *BRCA2* mutations and advanced chemotherapy-refractory ovarian cancer.[29] The ORR and progression-free survival also seemed to be lower in the cohort assigned to olaparib 100 mg twice daily than in the cohort assigned to 400 mg twice daily in our patients. The results of a phase 1 trial had indicated that olaparib at 100 mg twice daily achieved drug concentrations that were sufficient to saturate inhibition of the target in peripheral blood mononuclear cells, resulting in downstream DNA-replication-fork arrest in hair follicle cells.[24] These results were the reason why we chose to use olaparib 100 mg twice daily. Although this result must be interpreted with caution, because treatment was not randomly assigned and there might have been an imbalance of unknown factors relevant to olaparib response, this and the similar result in the companion study of patients with ovarian cancer suggest that olaparib 100 mg twice daily might have inferior antitumour activity when given alone.[29] The target expression levels, drug concentration, and target inhibition achieved within the tumour might differ from that achieved in surrogate tissues, such as peripheral blood mononuclear and hair follicle cells. Although this explanation is logical, confirmation would require serial biopsy samples to be taken from deep tumour tissues, which was unacceptable according to patients and investigators in this study. Importantly, there was no apparent excess toxicity with olaparib at the higher dose, which allows consideration of the use of this dose in future studies.

Currently, the presence of mutations in *BRCA1* or *BRCA2* does not inform systemic therapy recommendations for women with breast cancer, but the results of this and subsequent studies might change established

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Nausea		
1 or 2	11 (41%)	11 (41%)
3 or 4	4 (15%)	0
Fatigue		
1 or 2	11 (41%)	7 (26%)
3 or 4	4 (15%)	1 (4%)
Vomiting		
1 or 2	3 (11%)	4 (15%)
3 or 4	3 (11%)	0
Anaemia*		
1 or 2	1 (4%)	2 (7%)
3 or 4	3 (11%)	2 (7%)
Anorexia		
1 or 2	3 (11%)	3 (11%)
3 or 4	0	1 (4%)
Diarrhoea		
1 or 2	3 (11%)	2 (7%)
3 or 4	0	0
Constipation		
1 or 2	2 (7%)	4 (15%)
3 or 4	0	0
Headache		
1 or 2	2 (7%)	3 (11%)
3 or 4	0	0
Abdominal pain†		
1 or 2	2 (7%)	3 (11%)
3 or 4	0	0
Dyspepsia		
1 or 2	2 (7%)	1 (4%)
3 or 4	0	0
Gastro-oesophageal reflux disease		
1 or 2	2 (7%)	1 (4%)
3 or 4	0	0
Flatulence		
1 or 2	2 (7%)	0
3 or 4	0	0
Arthralgia		
1 or 2	0	3 (11%)
3 or 4	0	0

Data are number (%). Adverse events were at least possibly, probably, and definitely related to olaparib in the opinion of the investigator in the safety population. No grade 5 adverse events were reported at the time of this analysis. *Includes Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of reduced anaemia and haemoglobin. †Includes MedDRA preferred terms of abdominal pain and low abdominal pain.

Table 4: **Olaparib-related adverse events, according to grade, arising in two or more patients**

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Discontinuations	0	1 (4%)
Dose interruption	8 (30%)	2 (7%)
Dose reduction	9 (33%)	1 (4%)

Data are number (%).

Table 5: **Dose interruptions and reductions due to adverse events**

practice. Currently full screening of *BRCA1* and *BRCA2* can take a long time in some countries, and the lack of availability of a genetic test result at oncological assessment can hamper the recruitment of patients into trials specifically designed to test specific interventions. If we are to use *BRCA* mutation status to direct treatment selection or recruit patients to clinical trials, in the way we already use hormone and *HER2* status, new clinical practice models for case selection and timely genetic testing will have to be developed. Data from single-group therapy trials have suggested substantial activity of cisplatin in patients with *BRCA1* mutations.[30,31] Data from a retrospective study suggests that the activity of anthracycline or cyclophosphamide chemotherapy might also be higher in women with *BRCA2* mutations than in sporadic control cases.[32] Randomised clinical trials are in progress to investigate the activity of carboplatin and docetaxel in patients with advanced breast cancer and *BRCA* mutations (registered with ClinicalTrials.gov as NCT00321633 for breast cancer with *BRCA* mutations, and as NCT00532727 for *BRCA* mutated or triple-negative breast cancer).

In this study, the 41% ORR and tolerability of olaparib at 400 mg twice daily compares favourably with expected levels of activity (20–30% or less) and toxicity reported for most licensed chemotherapy agents used in patients previously treated with anthracycline and taxane chemotherapy.[33–35] The degree of response to olaparib is particularly notable because of the high proportion of tumours with hormone-receptor-negative and HER2-negative phenotype. The efficacy and toxicity of a targeted PARP-inhibitor strategy will need to be compared with standard of care DNA-damaging chemotherapy. Notably, the response to olaparib was not restricted to those patients who had been given the least number of types of previous chemotherapy, suggesting a lack of overlap in resistance between most chemotherapy and PARP inhibitors. Although formal assessment of the association between olaparib response and previous platinum chemotherapy was not a planned analysis and was based on a retrospective chart review by investigators, a post-hoc exploratory analysis of overall response was undertaken for those patients who had been given platinum-based chemotherapy. Preclinical data indicated that resistance to PARP inhibitors can arise in women with mutations through restoration of the open reading frame of *BRCA1* or *BRCA2* by intragenic deletion with the selective pressure of therapy.[36–39] Furthermore patients developing resistance to platinum-based chemotherapy for ovarian cancer showed a similar genetic restoration of the reading frame for *BRCA1* and *BRCA2* gene products.[36–39] In the expanded cohort of patients with *BRCA1* or *BRCA2* mutations and ovarian cancer in the phase 1 trial, data suggested an association between early progression after platinum chemotherapy and a low rate of olaparib response.[40] Notably, those patients in our study who had progressed after platinum chemotherapy rarely had a confirmed response to olaparib. Since numbers of patients were small and platinum-based therapies were used at a late treatment stage, with consequent induction of many possible resistance mechanisms, we cannot conclude there is a specific cross resistance between olaparib and platinum salts in *BRCA1*-associated and *BRCA2*-associated breast cancer on the basis of these data.

In conclusion, the results of this study have shown that knowledge of cancer predisposition gene function can be translated from the laboratory to successfully test clinical treatment hypotheses for this rare group of women with hereditary breast cancer. The results of this study support further investigation of an approach that combines inhibition of a DNA repair target with an inherent residual loss of function of specialised DNA repair in many of these tumours. Whether this approach might also show efficacy in a broader group of sporadic breast and ovarian cancers that might have inactivation of the homologous recombination repair pathway[41] will be tested in future trials.

Contributors

AT, MR, JNW, GM, HE, MW, and JC were involved in the design of the trial. AT, MR, JEG, SMD, MWA, JNW, MF, BA, NL, RKS, AW, GM, and HE recruited patients and gathered data at their centres. AT, MR, JEG, SMD, MWA, JNW, MF, BA, NL, RKS, AW, GM, HE, MW, and JC were involved in data analysis and interpretation. AT 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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Conflicts of interest

AT has received a payment from the Institute of Cancer Research Rewards to inventors programme for work on use of PARP inhibitors to target *BRCA1*-associated and *BRCA2*-associated cancers; and support for travel to investigators' meetings and an honorarium, funded by AstraZeneca, for an academic lecture. MR has received research grants, support for travel to investigators' meetings and funding for patient payment to undertake study from AstraZeneca, and has received honoraria as a clinical advisory board member for Pfizer. JEG has received funding support for the trial and is a co-investigator for clinical trials for a PARP inhibitor. SMD has received funding support for the trial and for travel to investigators' meetings. MWA has received honoraria for consultancy from AstraZeneca and Myriad Genetics. MF has received honoraria as a clinical advisory board member and support for travel to meetings from AstraZeneca. BA has received a grant from AstraZeneca for a research study. NL has received funding support for the conduct of the trial. RKS has received funding support for the conduct of the trial and for travel to investigators' meetings. AW has received speaking honoraria (including speakers' bureau) and research funding from AstraZeneca. GM has received support for travel to investigators' meetings and funding for patient payment to undertake study from AstraZeneca. MW and JC are employees of AstraZeneca, and JC holds AstraZeneca stock options. JNW and HE declare that they have no conflicts of interest.

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