Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study

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Summary

Background **Olaparib (AZD2281) is a small-molecule, potent oral poly(ADP-ribose) polymerase (PARP) inhibitor. We aimed to assess the safety and tolerability of this drug in patients without *BRCA1* or *BRCA2* mutations with advanced triple-negative breast cancer or high-grade serous and/or undifferentiated ovarian cancer.**

Methods **In this phase 2, multicentre, open-label, non-randomised study, women with advanced high-grade serous and/or undifferentiated ovarian carcinoma or triple-negative breast cancer were enrolled and received olaparib 400 mg twice a day. Patients were stratified according to whether they had a *BRCA1* or *BRCA2* mutation or not. The primary endpoint was objective response rate by Response Evaluation Criteria In Solid Tumors (RECIST). All patients who received treatment were included in the analysis of toxic effects, and patients who had measurable lesions at baseline were included in the primary efficacy analysis. This trial is registered at ClinicalTrials.gov, number NCT00679783.**

Findings **91 patients were enrolled (65 with ovarian cancer and 26 breast cancer) and 90 were treated between July 8, 2008, and Sept 24, 2009. In the ovarian cancer cohorts, 64 patients received treatment. 63 patients had target lesions and therefore were evaluable for objective response as per RECIST. In these patients, confirmed objective responses were seen in seven (41%; 95% CI 22–64) of 17 patients with *BRCA1* or *BRCA2* mutations and 11 (24%; 14–38) of 46 without mutations. No confirmed objective responses were reported in patients with breast cancer. The most common adverse events were fatigue (45 [70%] of patients with ovarian cancer, 13 [50%] of patients with breast cancer), nausea (42 [66%] and 16 [62%]), vomiting (25 [39%] and nine [35%]), and decreased appetite (23 [36%] and seven [27%]).**

Interpretation **Our study suggests that olaparib is a promising treatment for women with ovarian cancer and further assessment of the drug in clinical trials is needed.**

Funding **AstraZeneca.**

Introduction

Poly(ADP-ribose) polymerase (PARP) is an important new target in cancer therapy and is essential for the repair of single-strand DNA breaks via the base excision pathway. PARP inhibitors have shown preclinical efficacy in tumours with homologous DNA repair defects such as those arising in *BRCA1* or *BRCA2* mutation carriers with breast cancer and ovarian cancer.[1–3]

Olaparib (AZD2281) is a small-molecule, potent oral PARP inhibitor.[4] In a phase 1 study, responses were reported in an expanded cohort of *BRCA1* or *BRCA2* mutation carriers with ovarian cancer.[5,6] Subsequent phase 2 studies of *BRCA1* or *BRCA2* mutation carriers have confirmed the activity of olaparib monotherapy with objective response rates of 41% (11 of 27) in patients with advanced breast cancer and 33% (11 of 33) in those with ovarian cancer.[7,8]

Germline *BRCA1* and *BRCA2* mutations confer a high risk of breast cancer and ovarian cancer; the risk of breast cancer in *BRCA1* or *BRCA2* mutation carriers by age 70 years is 50–87% and in those with ovarian cancer is 10–40%.[9–12] Although 75% of *BRCA1*-mutated breast cancers are classed as triple-negative breast cancer as defined by the standard clinical parameters of oestrogen-receptor and progesterone-receptor negative and HER2 negative, this subtype of breast cancer also occurs without germline *BRCA1* mutations.[13] Researchers queried whether defects in homologous recombination repair could account for the development and behaviour of the aggressive triple-negative breast-cancer subtype, which has led to the concept of so-called BRCAness in these tumours.[14]

Likewise, women with *BRCA1* or *BRCA2* mutations have a tendency to develop high-grade serous ovarian cancer or poorly differentiated tubo-ovarian cancer, with more than 70% presenting with stage III or IV disease.[15] In studies of patients with high-grade serous ovarian cancer, about 55% had germline or somatic mutations or epigenetic silencing of *BRCA1* or *BRCA2* resulting in DNA repair defects.[16,17] As PARP inhibition was shown to

be effective in cancers with germline mutations,[7,8] we questioned whether sporadic cancers with similar genetic changes would also be responsive to drugs such as olaparib. We aimed to determine the role of *BRCA* mutations on the efficacy and safety of single-drug olaparib in women with advanced ovarian or breast cancer.

Methods

Patients

We undertook a phase 2, open-label, non-randomised study of patients from six centres in Canada. Patients aged 18 years or older were enrolled if they had histologically confirmed advanced metastatic or recurrent breast cancer (oestrogen-receptor, progesterone-receptor, or HER2 negative, or known *BRCA*-mutated breast cancer) or ovarian cancer (high-grade serous and/or undifferentiated and/or known *BRCA*-mutated ovarian and/or fallopian-tube or peritoneum cancer), a life expectancy of 16 weeks or more, an Eastern Co-operative Group (ECOG) performance status of 2 or less, acceptable haemoglobin concentrations (≥90 g/L), haematological (absolute neutrophil count ≥1500×10^6 cells per L, white-blood-cell count >3×10^9 cells per L, platelet count ≥100 000 cells per μL), hepatic (total bilirubin levels ≤1·5 times normal [<3 times upper limit of normal for patients with Gilbert's syndrome], aspartate aminotransferase and alanine aminotransferase concentrations ≤2·5 times normal [≤5 times upper limit of normal for patients with liver metastases]), and renal function (serum creatinine concentration of ≤1·5 times normal), and had been tested or were willing to undergo *BRCA1* and *BRCA2* mutation testing by the external reference library (Myriad Genetics, Salt Lake City, UT, USA).

Patients were ineligible if they had another malignancy within the past 3 years; symptomatic or uncontrolled brain metastases; uncontrolled infection, were immunocompromised, were currently having seizures, or had other severe illnesses (including hepatic disease); required treatment with inhibitors or inducers of CYP3A4; received chemotherapy, radiotherapy, or major surgery within 4 weeks of study entry; received anticancer treatment within 30 days of receiving study treatment (patients could receive bisphosphonates and corticosteroids if they were on a stable dose for at least 4 weeks before study entry); received any investigational drug within 28 days of study entry; persistent grade 2 or higher toxic effects (Common Terminology Criteria for Adverse Events [CTCAE; version 3.0])[18] caused by prior treatment (excluding alopecia); existing gastrointestinal disorders

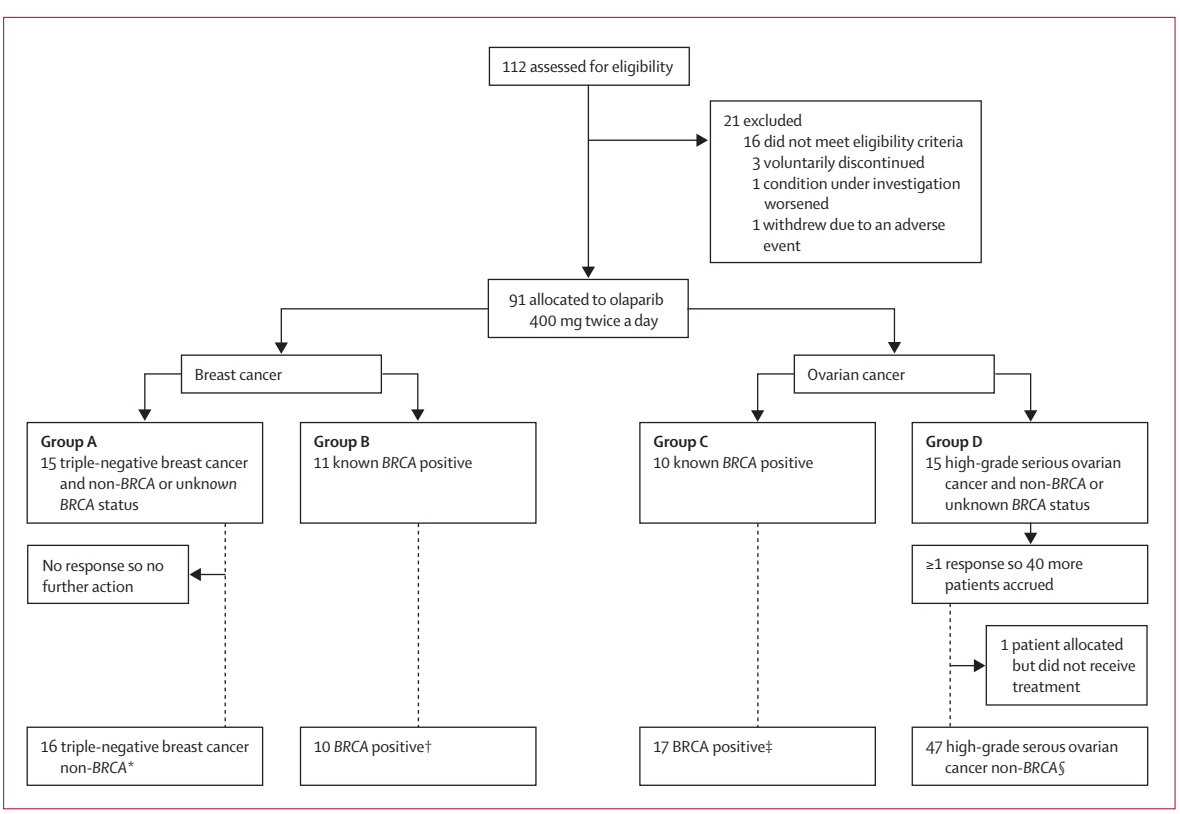

***Figure 1*: Trial profile**

BRCA classification errors might be due to reports from local laboratories of *BRCA* variants rather than *BRCA* mutations. *Includes two patients from the *BRCA*-positive cohort who were reclassified as non-*BRCA*. †Includes one patient from the non-*BRCA* or unknown-*BRCA*-status cohort who was *BRCA* positive. ‡Includes seven patients from non-*BRCA* or unknown-*BRCA*-status cohort who were *BRCA* positive. §Excludes seven patients from stage one who were shown to be *BRCA* positive and one who did not receive treatment.

that could interfere with absorption of the study drug; inability to swallow; and pregnancy.

All patients provided written informed consent. The study protocol was approved by Health Canada and the institutional review boards at the six participating sites.

See Online for webappendix

Procedures

The study included four patient cohorts that were treated and followed up in the same manner (webappendix p 1). The results of olaparib trials of patients with *BRCA*-mutation-associated ovarian

	Ovarian cancer			Breast cancer		
	BRCA (n=17)	Non-*BRCA* (n=47)	Total (n=64)	*BRCA* (n=10)	Non-*BRCA* (n=16)	Total (n=26)
Age						
Median (range)	52 (41–78)	59 (39–84)	58 (39–84)	46 (24–80)	48 (42–61)	47 (24–80)
Race						
White	14 (82%)	44 (94%)	58 (91%)	8 (80%)	10 (63%)	18 (69%)
Asian	3 (18%)	3 (6%)	6 (9%)	2 (20%)	2 (13%)	4 (15%)
Black	0	0	0	0	4 (25%)	4 (15%)
Ethnic origin						
Ashkenazi Jewish	3 (18%)	5 (11%)	8 (13%)	1 (10%)	0	1 (4%)
Sephardic Jewish	0	1 (2%)	1 (2%)	0	0	0
Other	1 (6%)	1 (2%)	2 (3%)	0	1 (6%)	1 (4%)
Unknown	13 (76%)	40 (85%)	53 (83%)	9 (90%)	15 (94%)	24 (92%)
BRCA status						
BRCA1	11 (65%)	0	11 (17%)	4 (40%)	0	4 (15%)
BRCA2	5 (29%)	0	5 (8%)	6 (60%)	0	6 (23%)
Both	1 (6%)	0	1 (2%)	0	0	0
Hormonal and HER2 receptor status						
ER negative	..	..	..	5 (50%)	0	5 (19%)
PR negative	..	..	..	8 (80%)	0	8 (31%)
HER2 negative	..	..	..	9 (90%)	0	9 (35%)
ER negative, PR negative, HER2 negative (TNBC)	..	..	..	5 (50%)	16 (100%)	21 (81%)
ECOG performance status*†						
0	5 (29%)	21 (45%)	26 (41%)	7 (70%)	9 (56%)	16 (62%)
1	11 (65%)	22 (47%)	33 (52%)	2 (20%)	7 (44%)	9 (35%)
2	1 (6%)	3 (6%)	4 (6%)	1 (10%)	0	1 (4%)
Prior chemotherapy regimens						
Median (range)	3 (1–10)	3 (1–8)	3 (1–10)	3 (2–7)	3 (1–6)	3 (1–7)

All data are n (%) unless otherwise indicated. ER=oestrogen receptor. PR=progesterone receptor. TNBC=triple-negative breast cancer. ECOG=Eastern Cooperative Oncology Group. *0=fully active, 1=restricted in physically strenuous activity, 2=ambulatory and capable of self-care. †ECOG status was not recorded at baseline for one patient in the non-*BRCA* serous ovarian group.

***Table 1*: Baseline patient and tumour characteristics**

	Ovarian cancer						Breast cancer					
	***BRCA* (n=17)**				Non-*BRCA* (n=46)	Total (n=63)	***BRCA* (n=8)**				Non-*BRCA* (n=15)	Total (n=23)
	BRCA1	*BRCA2*	Both	Total			*BRCA1*	*BRCA2*	Both	Total		
Confirmed objective response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)	0	0	0	0	0	0
Complete response	0	0	0	0	0	0	0	0	0	0	0	0
Partial response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)	0	0	0	0	0	0
Stable disease ≥8 weeks	5 (29%)	1 (6%)	0	6 (35%)	18 (39%)	24 (38%)	2 (25%)	3 (38%)	0	5 (63%)	2 (13%)	7 (30%)
Progressive disease	1 (6%)	1 (6%)	1 (6%)	3 (18%)	13 (28%)	16 (25%)	1 (13%)	2 (25%)	0	3 (38%)	12 (80%)	15 (65%)
Not evaluable	1 (6%)	0	0	1 (6%)	4 (9%)	5 (8%)	0	0	0	0	1 (7%)	1 (4%)

Data are only for those patients assessable for objective Response Evaluation Criteria in Solid Tumors response (measurable lesions at baseline). One patient with non-*BRCA* ovarian cancer (best response was progressive disease) and one patient with *BRCA1*, one with *BRCA2*, and one with non-*BRCA* breast cancer (all best responses were stable disease) were excluded from the table.

***Table 2*: Best objective response rates (Response Evaluation Criteria in Solid Tumors) for patients with ovarian cancer and breast cancer**

and breast cancers were not known at study conception. Therefore, patients with *BRCA1* or *BRCA2* mutations were enrolled as reference cohorts and to provide comparative tissue for translational studies.

Group A had patients with triple-negative breast cancer and negative or unknown *BRCA1* or *BRCA2* mutation status. Triple-negative disease was defined as oestrogen-receptor and progesterone-receptor Allred scores of less than 3 or oestrogen-receptor and progesterone-receptor score of 0 by immunohistochemistry, HER2 score by immunohistochemistry of 1+ or 0, or a negative fluorescence in-situ hybridisation (FISH) score (ratio ≥2·2 for positive or <1·8 for equivocal);[19] if HER2 score by immunohistochemistry was 2+, a negative FISH was required. Group B included patients with recurrent and advanced breast cancer with a documented germline mutation of *BRCA1* or *BRCA2*. Group C had patients with recurrent ovarian cancer with a documented germline mutation in *BRCA1* or *BRCA2*. Group D had patients with advanced recurrent high-grade serous ovarian cancer or poorly differentiated ovarian cancer with negative or unknown *BRCA1* or *BRCA2* mutation status.

A two-stage Simon design[20] was used for enrolment to the unknown *BRCA1* or *BRCA2* mutation associated cohorts (groups A [triple-negative breast cancer] and group D [ovarian cancer]). In the first stage, 15 patients with negative or unknown *BRCA1* or *BRCA2* mutation statuses were planned for inclusion into each of the breast-cancer and ovarian-cancer cohorts. One or more responses (assessed by RECIST) in either group led to progression to the second stage with further enrolment of 20–40 patients in each cohort to assess objective response. No set criteria were used to assess success in terms of response rate in the study, however; if the true objective response rate was 10%, with a 15 patient cohort a 21% chance would exist of stopping treatment incorrectly at the end of the first stage of the study (ie, if no response was reported).

All patients received olaparib 400 mg twice a day (supplied by AstraZeneca, Macclesfield, UK, as 50 mg oral capsules) on a continuous basis (treatment cycle was 4 weeks) until disease progression or other discontinuation criteria were met. At screening, patients underwent a history, physical examination, and baseline haematological and chemistry assessments, and CA-125 tests (in patients with ovarian cancer). Blood samples were taken for confirmatory *BRCA1* and *BRCA2* mutation analysis. Baseline CT and MRI scans and pretreatment biopsy samples were also taken. Patients were seen at the beginning of each 4-week cycle for haematological and chemistry assessment, analysis of tumour markers, physical examination, and history. Imaging was done every two cycles (8 weeks). Tumour biopsies were repeated at 8 weeks and at progression. For patients with toxic effects of CTCAE grade 3 or higher judged to be related to olaparib by the investigator, treatment was interrupted until resolution of the toxic effects to grade 1 or less.

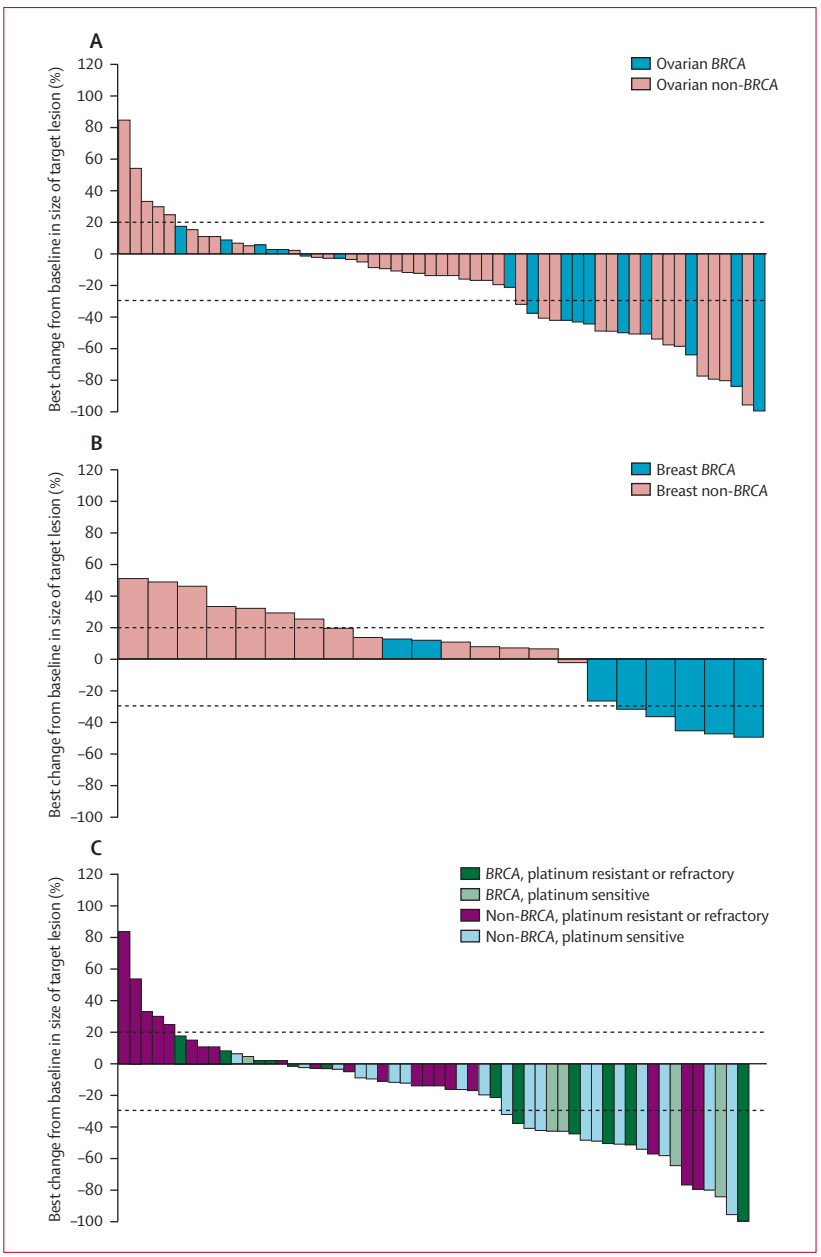

***Figure 2*: Waterfall plots of best percentage change from baseline in size of target tumour lesion**
Best change in target-lesion size is maximum reduction from baseline or minimum increase in absence of reduction. (A) Ovarian-cancer cohorts. (B) Breast-cancer cohorts. 23 patients were treated with target lesions identified at baseline. 22 had at least one follow-up assessment. One patient was not assessed because of missing or incomplete post-baseline assessments. (C) Ovarian-cancer cohorts by platinum sensitivity or resistance.

Repeat dose interruptions were allowed as required, for a maximum of 28 days on each occasion. If a toxic effect recurred after further treatment with olaparib, and if further dose interruptions were inadequate, drug-dose reduction or discontinuation was considered. A maximum of two dose reductions were allowed (to 200 mg twice a day and then 100 mg twice a day) after which, if toxic effects persisted, the patient was withdrawn. Investigators could use their discretion to interrupt olaparib treatment

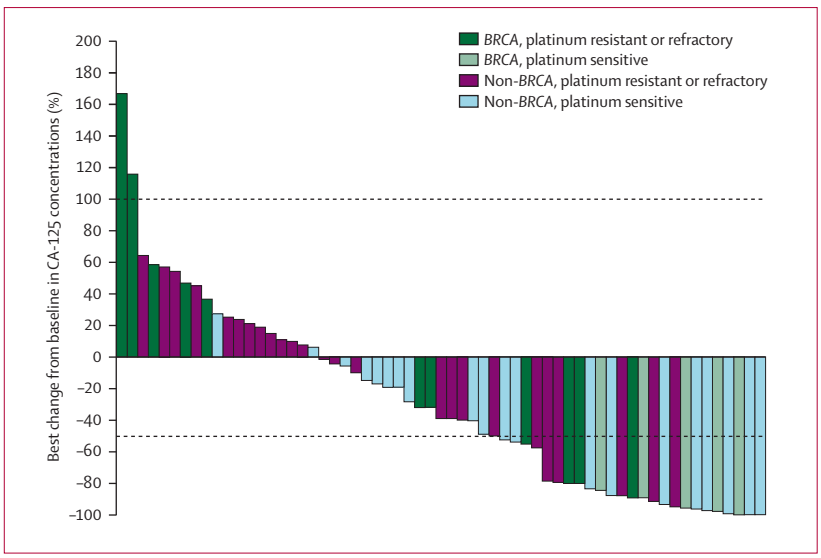

Figure 3: **Best percentage change from baseline in CA-125 concentrations in the ovarian-cancer cohorts, by platinum sensitivity and resistance**
Best change in CA-125 (U/mL) is maximum reduction from baseline or minimum increase in the absence of reduction.

for patients with lower than grade 3 toxic effects. Compliance with treatment was monitored by regular capsule counts by site pharmacy personnel.

The primary endpoint was objective response rate, defined as a complete response or partial response according to RECIST.[21] Secondary endpoints were disease-control rate (complete response, partial response, or stable disease according to RECIST), percentage change from baseline in target-tumour size, progression-free survival, and for patients with ovarian cancer, assessment of CA-125, according to Gynecologic Cancer InterGroup Criteria (GCIG).[22] No independent review of response assessments was done. An exploratory post-hoc analysis of efficacy by platinum sensitivity was undertaken. A masked review with recent GCIG Fourth Ovarian Consensus Conference criteria was used to assess time since last platinum-based treatment after reports of the possible predictive significance of prior platinum treatment.[6] Safety and laboratory assessments were undertaken throughout the study. Adverse events were graded according to the CTCAE.[18] Archival tissue and biopsy samples were centrally collected at the Centre for Translational and Applied Genomics at the British Columbia Cancer Agency (Vancouver, Canada) to assess and identify markers of olaparib activity.

Statistical analyses

Statistical analyses were done in accordance with the statistical plan with SAS (version 8.1). As planned, patients were analysed in cohorts defined by tumour type and confirmed *BRCA1* and *BRCA2* statuses from the baseline-blood sample, and not by the original enrolled cohorts based on historical *BRCA1* and *BRCA2* statuses. For the safety analysis, all patients who received at least one dose of olaparib were included. For the objective response (RECIST) assessment, all patients with measurable lesions (at least 10 mm by longest diameter measured by CT or 20 mm by standard imaging) at baseline were included.[21] Disease control rate was assessed, as defined per protocol, in the safety analysis set. For assessment of CA-125 response, all patients with CA-125 concentrations two or more times the upper limit of normal within 2 weeks before starting treatment were included.[22] CIs were calculated using the Wilson score method.[23] Kaplan-Meier plots of progression-free survival (assessed by RECIST) were created.

This trial is registered with ClinicalTrials.gov, number NCT00679783.

Role of the funding source

The study was designed by the principal investigator (KAG) in collaboration with the study sponsor. Data collection and analysis were undertaken by the study sponsor, and interpretation of the data was done by the investigators and the sponsor. All authors had access to the data and KAG, EM, JC, and AO had access to the full raw-data set. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We recruited patients between July 8, 2008, and Sept 24, 2009. The study database was locked on March 26, 2010. In the triple-negative breast cancer cohort (group A), no RECIST validated responses were reported at the first stage, so this cohort was closed. However, responses were recorded during the first stage of the study in the high-grade serous ovarian cancer cohort (group D), so an additional 40 patients were enrolled. There was a range of two to 42 patients enrolled at each centre. Table 1 shows baseline patient and tumour characteristics.

Before data analysis, patients were reclassified into cohorts on the basis of their confirmed *BRCA1* or *BRCA2* mutation status with baseline-blood samples (figure 1). In the ovarian-cancer cohorts with this classification, 13 (76%) of 17 women with *BRCA1* or *BRCA2* positive mutation status and 45 (94%) of 48 with negative *BRCA1* or *BRCA2* mutation status had serous ovarian cancer. The non-serous ovarian cancers were poorly differentiated carcinomas. In the breast-cancer cohorts, one (7%) of 15 women with triple-negative breast cancer had a *BRCA* mutation. Of the 11 patients initially recruited into the mutation-positive cohort, four (36%) had triple-negative breast cancer, five (45%) had non-triple-negative disease, and two (19%) were reclassified as *BRCA* negative after Myriad screening favoured genetic variants rather than mutations.

Patients with ovarian cancer had a median time from initial diagnosis to the first dose of study treatment of 35·3 (range 6–184) months: in the *BRCA* cohort, time from initial diagnosis to the first dose of study treatment was 41·4 (range 12–117) months and in the non-*BRCA* cohort 35·0 (6–184) months. The breast-cancer cohorts had a median time from initial diagnosis of 29·1 (range 3–129) months: in the *BRCA* cohort, time from initial diagnosis to the first dose of study treatment was 29·1 (3–106) and in the non-*BRCA* cohort 34·4 months (4–129).

In the ovarian-cancer cohorts, the median number of previous chemotherapies was three (range 1–10); 13 (76%) of 17 in the *BRCA* cohort and 24 (51%) of 47 in the non-*BRCA* cohort had three or more chemotherapy regimens before study enrolment (table 1). In the breast-cancer cohorts, the median number of previous chemotherapy regimens was three (range 1–7); seven (70%) of ten in the *BRCA* cohort and 12 (75%) of 16 in the non-*BRCA* cohort had exposure to three or more chemotherapy regimens (table 1).

13 (20%) of 65 patients with ovarian cancer discontinued the study prematurely (without confirmed radiological progression); three (5%) because of worsening disease, three (5%) because of an adverse event, two (3%) voluntarily discontinued, and five (8%) because of other reasons. One (4%) of 26 patients with breast cancer discontinued the study prematurely because of an adverse event. At the cutoff date of this analysis, 13 (20%) of 65 patients with ovarian cancer and one (4%) of 26 with breast cancer were still receiving olaparib.

63 patients with ovarian cancer and 23 with breast cancer had target lesions and were evaluable for objective response as per RECIST. The overall objective response rate in ovarian-cancer cohorts who were evaluable for RECIST response was 29% (95% CI 19–41; 18 of 63); the response rate for the positive *BRCA1* or *BRCA2* mutation cohort was 41% (22–64; seven of 17) and for the confirmed negative *BRCA1* or *BRCA2* cohort 24% (14–38; 11 of 46). All 18 responses were partial responses. Best objective responses are shown in table 2. The CA-125 response rate in 54 evaluable patients was 31% (95% CI 21–45; 17 responders). Of these, 13 (24%) had a normalisation of CA-125 and four (7%) had an incomplete marker response. The combined objective response rate (assessed by RECIST) and CA-125 response rate in 64 evaluable patients was 36% (95% CI 25–48; 23 responders). In the ovarian-cancer cohort without *BRCA1* or *BRCA2* associated mutations, a CA-125 response rate of 26% (95% CI 15–42; ten of 38) and a combined RECIST or CA-125 response rate of 30% (95% CI 19–44; 14 of 47) was recorded. All responders in the *BRCA1* or *BRCA2* negative cohort assessed with either criteria had high-grade serous ovarian cancer. Of the total population of patients with ovarian cancer, the disease-control rate (partial response plus stable disease at 8 weeks) was 66% (42 of 64): in *BRCA1* or *BRCA2* negative mutation cohorts the disease-control rate was 76% (13 of 17) and in *BRCA1* or *BRCA2* positive cohorts it was 62% (29 of 47).

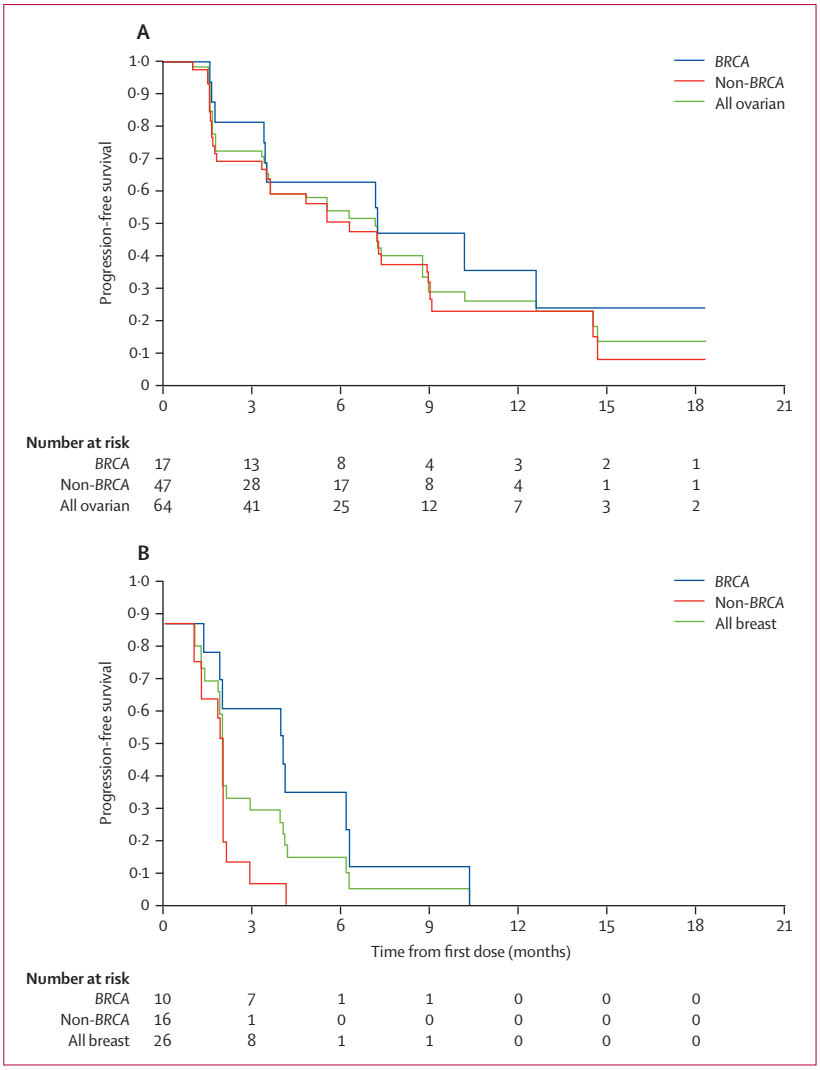

Figure 4: **Kaplan-Meier curves of progression-free survival in the ovarian-cancer cohorts (A) and breast-cancer cohorts (B)**

In post-hoc exploratory analyses, the objective response rate in patients with platinum-sensitive ovarian cancer was 50% (ten of 20) in the *BRCA1* or *BRCA2* negative cohort and 60% (three of five) in the *BRCA1* or *BRCA2* positive mutation cohort. Platinum-resistant ovarian-cancer responses were seen in 33% (four of 12) of those in the mutation-positive cohort, but in only 4% (one of 26) of those in the *BRCA1* or *BRCA2* negative cohort. When the platinum-sensitive group was reviewed for CA-125 response similar results were recorded, with 40% (six of 15) of the *BRCA1* or *BRCA2* negative cohort and 100% (five of five) of the *BRCA*-mutation-associated cohort showing a CA-125 response. In patients with platinum-resistant ovarian cancer, responses were seen in 17% (four of 23) of the *BRCA1* or *BRCA2* negative cohort and 18% (two of 11) of the *BRCA*-mutation-associated cohort.

None of the patients with breast cancer had an objective response. Disease-control rate at 8 weeks was 38% (95% CI 22–57; ten of 26); 70% (40–89; seven of ten) in the positive *BRCA1* or *BRCA2* cohort and 19% (7–43; three of 16) in mutation-negative cohorts. Target lesions in five (50%) patients with *BRCA1* or *BRCA2* mutations reduced in size by more than 30%, but they were not confirmed objective responders (assessed by RECIST) because of absence of confirmation at the next visit (three patients) or progression of non-target or new lesions at the same visit (two patients).

The median best percentage change from baseline in target-tumour size (defined as maximum reduction from baseline or minimum increase in the absence of reduction) for the overall population was a reduction of 14·2% (range –100 to 83) in the ovarian-cancer cohort (figure 2A) and an increase of 10·1% (–50 to 50) in the breast-cancer cohort (figure 2B). For the ovarian-cancer cohort, the best percentage change from baseline in target-tumour size (figure 2C) and CA-125 concentrations (defined as maximum reduction from baseline or minimum increase in the absence of reduction) by platinum sensitivity or resistance are also shown (figure 3).

In the ovarian-cancer cohort, median progression-free survival (assessed by RECIST) in patients with *BRCA* mutation was 221 (95% CI 106–383) days, in those without *BRCA* mutation 192 (109–267) days, and in all those with ovarian cancer 219 (110–273) days (figure 4A). In the breast-cancer cohort, progression-free survival in patients with *BRCA* mutation was 109 (95% CI 53–168) days, in those without *BRCA* mutation 54 (49–54) days, and in all those with breast cancer 54 (51–106) days (figure 4B).

Median exposure to olaparib treatment was 157 days (range 11–595) in the ovarian-cancer cohort and 56 days (range 20–288) in the breast-cancer cohort. 30 (47%) of 64 patients in the ovarian-cancer cohort and three (12%) of 26 patients in the breast-cancer cohort received six or more cycles (168 days) of treatment. Dose adherence was about 99% in both cohorts. 19 (30%) patients with ovarian cancer and eight (31%) with breast cancer had dose modifications (dose reduction or interruption).

All 64 patients in the ovarian-cancer cohort and 25 (96%) of 26 in the breast-cancer cohort had at least one adverse event. The most common adverse events, which occurred in 20% or more of patients, were fatigue, nausea, vomiting, decreased appetite, and abdominal distension in the ovarian-cancer cohort, and nausea, fatigue, vomiting, and decreased appetite in the breast-cancer cohort (table 3; webappendix pp 2–3).

56 (88%) of 64 patients with ovarian cancer had an adverse event that was judged to be causally related to olaparib and 23 (36%) of 64 had CTCAE events grade 3 or higher (webappendix p 4). Ten (16%) of 64 patients had CTCAE events grade 3 or higher, which were judged to be causally related to olaparib. Five (8%) of 64 patients had adverse events that led to treatment discontinuation; in two patients adverse events were attributed to olaparib.

	Ovarian cancer									Breast cancer								
	BRCA (n=17)			Non-BRCA (n=47)			Total (n=64)			BRCA (n=10)			Non-BRCA (n=16)			Total (n=26)		
	Any Grade	Grade 1–2	Grade 3–4	Any Grade	Grade 1–2	Grade 3–4	Any Grade	Grade 1–2	Grade 3–4	Any Grade	Grade 1–2	Grade 3–4	Any Grade	Grade 1–2	Grade 3–4	Any Grade	Grade 1–2	Grade 3–4
Nausea	12 (71%)	12 (71%)	..	30 (64%)	29 (62%)	1 (2%)	42 (66%)	41 (64%)	1 (2%)	8 (80%)	7 (70%)	1 (10%)	8 (50%)	8 (50%)	..	16 (62%)	15 (58%)	1 (4%)
Fatigue	16 (94%)	13 (77%)	3 (18%)	29 (62%)	25 (53%)	4 (9%)	45 (70%)	38 (59%)	7 (11%)	6 (60%)	6 (60%)	..	7 (44%)	7 (44%)	..	13 (50%)	13 (50%)	..
Vomiting	6 (35%)	6 (35%)	..	19 (40%)	19 (40%)	..	25 (39%)	25 (39%)	..	5 (50%)	4 (40%)	1 (10%)	4 (25%)	4 (25%)	..	9 (35%)	8 (31%)	1 (4%)
Decreased appetite	9 (53%)	9 (53%)	..	14 (30%)	13 (28%)	1 (2%)	23 (36%)	22 (34%)	1 (2%)	3 (30%)	3 (30%)	..	4 (25%)	4 (25%)	..	7 (27%)	7 (27%)	..
Abdominal distension	5 (29%)	5 (29%)	..	11 (23%)	11 (23%)	..	16 (25%)	16 (25%)	..	..	..	..	1 (6%)	1 (6%)	..	1 (4%)	..	..
Diarrhoea	4 (24%)	4 (24%)	..	11 (23%)	8 (17%)	3 (6%)	15 (23%)	12 (19%)	3 (5%)	..	..	..	..	..	..	..	..	..
Dysgeusia	5 (29%)	5 (29%)	..	10 (21%)	10 (21%)	..	15 (23%)	15 (23%)	..	..	..	..	..	..	..	..	..	..
Dizziness	8 (47%)	8 (47%)	..	6 (13%)	6 (13%)	..	14 (22%)	14 (22%)	..	..	..	..	..	..	..	..	..	..
Abdominal pain	2 (12%)	1 (6%)	1 (6%)	11 (23%)	10 (21%)	1 (2%)	13 (20%)	11 (17%)	2 (3%)	..	..	..	..	..	..	..	..	..
Dyspnoea	..	..	..	..	..	..	..	..	..	2 (20%)	2 (20%)	..	4 (25%)	1 (6%)	3 (19%)	6 (23%)	3 (12%)	3 (12%)

Summary of adverse events occurring in ≥20% patients in the safety analysis set. Adverse events were classified according to Common Terminology Criteria for Adverse Events (version 3.0)[18]

Table 3: **Adverse events**

23 (89%) of 26 patients with breast cancer had an adverse event that was judged to be causally related to olaparib and eight (31%) had CTCAE events grade 3 or higher, of which five (19%) were judged to be causally related to olaparib (webappendix p 4). Only one (4%) patient had an adverse event (dyspnoea) that led to treatment discontinuation; this event was attributed to olaparib.

No unexpected clinically important changes from baseline in any haematological parameters were identified. Grade 3 or higher anaemia, commonly seen in patients with advanced malignancies, was reported in one (2%) of 64 patients with ovarian cancer, and in two (8%) of 26 patients with breast cancer.

Discussion

Olaparib is a well-tolerated oral PARP inhibitor, which has shown promising monotherapy activity in patients with *BRCA1* or *BRCA2* mutations who have breast and ovarian cancer.[7,8] To our knowledge, this study is the first to show that olaparib monotherapy has activity in women with pretreated high-grade serous ovarian cancer without germline *BRCA1* or *BRCA2* mutations (panel). The objective response rate of patients with *BRCA1* or *BRCA2* mutations in our study was similar to that reported in other studies.[7,8] Of note, objective responses were seen in patients with ovarian cancer without *BRCA1* or *BRCA2* mutations. Interpretation of the absence of objective responses in a few patients with non-serous ovarian cancer without *BRCA1 or BRCA2* mutations is difficult due to the small sample size. These objective response rates are similar to the response rates that have been reported with other treatments for ovarian cancer including pegylated liposomal doxorubicin and topotecan.[24,25] Our study suggests that olaparib is a promising treatment for women with these aggressive cancers and further assessment of the drug in clinical trials is needed.

Although responses were seen in both platinum-sensitive and platinum-resistant populations, our post-hoc analysis reported activity mostly in patients with platinum-sensitive disease. This analysis must be interpreted with some caution because of the small sample size, but it is consistent with other studies of *BRCA1* or *BRCA2* mutation carriers.[6] These studies suggested that earlier treatment with olaparib monotherapy or possibly in combination with a platinum-based drug in patients with high-grade serous ovarian cancer might be efficacious.

Unlike previous studies, no confirmed objective responses to olaparib in the breast-cancer cohorts were identified in our study. Although some patients with *BRCA1* or *BRCA2* mutations had more than 30% shrinkage in target lesions, these patients were not confirmed objective responders (assessed by RECIST). In a study by Fong and colleagues,[5] three *BRCA2*-mutation carriers were identified; one had a complete response and another had stable disease. The absence of objective responses could be due to chance because of the small sample size, or to the heavily pretreated characteristics of these patients. Analysis of tissue samples might provide further information.

Results from other studies of PARP inhibitors given in combination with cytotoxic chemotherapy reported efficacy with PARP inhibition in patients with triple-negative breast cancer; studies of additional combinations are in progress.[26] Despite encouraging phase 2 study results, a phase 3 study of iniparib in combination with gemcitabine and carboplatin for patients with triple-negative breast cancer did not show a difference in overall survival (median overall survival 11·1 months [gemcitabine and carboplatin) *vs* 11·8 months [gemcitabine and carboplatin plus iniparib]; p=0·284). Analyses of the hormonal status of the enrolled patients and of the true mechanism of iniparib might provide further information.[27,28]

Olaparib was well tolerated, which makes it an attractive option for use in early disease settings. Although theoretical concerns about long-term toxic effects have been associated with PARP inhibition,[29] especially secondary malignancies, these effects were not reported in our study; the duration of exposure to olaparib was up to 595 days. Long-term safety data from patients who have received olaparib in our study and other studies are

***Panel:* Research in context**

Systematic review

We searched Ovid Medline and American Society of Clinical Oncology databases to identify publications and international meeting abstracts about frequency of germline *BRCA* mutations in patients with advanced breast and ovarian cancer, without language restrictions with the search terms "BRCA mutation", "advanced ovarian cancer", and "advanced breast cancer". We also assessed the reported effects of treatments, especially PARP inhibitors, on these patient populations to understand the current therapeutic landscape.

Interpretation

To the best of our knowledge, this is the first study demonstrating activity of a PARP inhibitor in patients with high-grade serous ovarian cancer without germline *BRCA1* or *BRCA2* mutations. The objective response rates reported in our study were similar to those reported for other ovarian cancer treatments including pegylated liposomal doxorubicin and topotecan.[24,25] Thus, treatment with the generally well tolerated PARP inhibitor olaparib represents a promising therapeutic option for patients with this aggressive malignant disease for whom treatment options are limited to toxic chemotherapies. This study provides compelling evidence to warrant further clinical trials in this patient population.

being gathered to further assess this potential risk. Although measures of PARP inhibition were not assessed in this study, we are confident that inhibition occurred, because inhibition has been reported at similar doses of olaparib,[5] and because we saw responses suggesting an effective dose.

Cancer treatments have traditionally been investigated without fully understanding the mechanisms underlying response and resistance, nor being able to define effectively the target population for phase 3 studies. We can now identify a number of factors influencing sensitivity to PARP inhibitors, primarily dysfunction of the *BRCA1* and *BRCA2* pathway, or genetic changes other than *BRCA1* and *BRCA2* mutations that hinder homologous-recombination repair or other aspects of DNA repair.[30] Synthetic lethal small-interfering RNA screens of cancer cell lines have identified several kinase or putative DNA repair proteins associated with sensitivity to PARP inhibitors.[31] Conversely, resistance can also emerge during therapy, with acquired or secondary PARP-inhibitor resistance linked to secondary mutations that would restore homologous-recombination competency.[32,33]

We have shown that collection of repeat biopsies is possible, and we are now undertaking whole transcriptome sequencing to compare normal and tumour genome sets in responders and non-responders to define the genetic factors associated with response.

In summary, to our knowledge, we have shown for the first time that an oral PARP inhibitor, olaparib, resulted in responses in patients with high-grade serous ovarian carcinoma without germline *BRCA1* or *BRCA2* mutations. New treatments targeting DNA repair mechanisms seem to provide new hope for treatment of ovarian cancer. Subsequent reports of this study assessing tumour biopsies might identify which patients obtain most clinical benefit from olaparib.

Contributors

KAG and AO conceived and wrote the report. KAG, OA, DH, and JC designed the study. KAG, OA, DH, AR, MT, HM, KS, KT, HH, MC, BG, and RY gathered the data. JC and EM analysed the data. All authors contributed towards the interpretation of the data, critically reviewed and commented on the report, and approved the final version.

Conflicts of interest

KAG and AO have attended advisory boards for AstraZeneca. AR has attended the National Advisory Board for AstraZeneca Canada. KT and DH have received research funding from AstraZeneca. HH has received research funding from the Juravinski Cancer centre and consultancy fees from Alethia Biotherapeutics. BG has received consultancy fees from Roche Pharmaceuticals. MC has received consultancy fees and payment for lecturing at a speakers bureau for AstraZeneca. EM and JC are employees of and hold stock in AstraZeneca. All other authors declare no conflicts of interest.

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