Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial

Amit M Oza, David Cibula, Ana Oaknin Benzaquen, Christopher Poole, Ron H J Mathijssen, Gabe S Sonke , Nicoletta Colombo, Jiří Špaček, Peter Vuylsteke, Holger Hirte, Sven Mahner, Marie Plante, Barbara Schmalfeldt, Helen Mackay, Jacqui Rowbottom, Elizabeth S Lowe, Brian Dougherty, J Carl Barrett, Michael Friedlander

Summary

Background The poly(ADP-ribose) polymerase inhibitor olaparib has shown antitumour activity in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer with or without *BRCA1* or *BRCA2* mutations. The aim of this study was to assess the efficacy and tolerability of olaparib in combination with chemotherapy, followed by olaparib maintenance monotherapy, versus chemotherapy alone in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer.

Methods In this randomised, open-label, phase 2 study, adult patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer who had received up to three previous courses of platinum-based chemotherapy and who were progression free for at least 6 months before randomisation received either olaparib (200 mg capsules twice daily, administered orally on days 1–10 of each 21-day cycle) plus paclitaxel (175 mg/m², administered intravenously on day 1) and carboplatin (area under the curve [AUC] 4 mg/mL per min, according to the Calvert formula, administered intravenously on day 1), then olaparib monotherapy (400 mg capsules twice daily, given continuously) until progression (the olaparib plus chemotherapy group), or paclitaxel (175 mg/m² on day 1) and carboplatin (AUC 6 mg/mL per min on day 1) then no further treatment (the chemotherapy alone group). Randomisation was done by an interactive voice response system, stratified by number of previous platinum-containing regimens received and time to disease progression after the previous platinum regimen. The primary endpoint was progression-free survival according to Response Evaluation Criteria in Solid Tumors version 1.1, analysed by intention to treat. Prespecified exploratory analyses included efficacy by *BRCA* mutation status, assessed retrospectively. This study is registered with ClinicalTrials.gov, number NCT01081951, and has been completed.

Findings Between Feb 12 and July 30, 2010, 173 patients at 43 investigational sites in 12 countries were enrolled into the study, of whom 162 were eligible and were randomly assigned to the two treatment groups (81 to the olaparib plus chemotherapy group and 81 to the chemotherapy alone group). Of these randomised patients, 156 were treated in the combination phase (81 in the olaparib plus chemotherapy group and 75 in the chemotherapy alone group) and 121 continued to the maintenance or no further treatment phase (66 in the olaparib plus chemotherapy group and 55 in the chemotherapy alone group). *BRCA* mutation status was known for 107 patients (either at baseline or determined retrospectively): 41 (38%) of 107 had a *BRCA* mutation (20 in the olaparib plus chemotherapy group and 21 in the chemotherapy alone group). Progression-free survival was significantly longer in the olaparib plus chemotherapy group (median 12·2 months [95% CI 9·7–15·0]) than in the chemotherapy alone group (median 9·6 months [95% CI 9·1–9·7]) (HR 0·51 [95% CI 0·34–0·77]; p=0·0012), especially in patients with *BRCA* mutations (HR 0·21 [0·08–0·55]; p=0·0015). In the combination phase, adverse events that were reported at least 10% more frequently with olaparib plus chemotherapy than with chemotherapy alone were alopecia (60 [74%] of 81 *vs* 44 [59%] of 75), nausea (56 [69%] *vs* 43 [57%]), neutropenia (40 [49%] *vs* 29 [39%]), diarrhoea (34 [42%] *vs* 20 [27%]), headache (27 [33%] *vs* seven [9%]), peripheral neuropathy (25 [31%] *vs* 14 [19%]), and dyspepsia (21 [26%] *vs* 9 [12%]); most were of mild-to-moderate intensity. The most common grade 3 or higher adverse events during the combination phase were neutropenia (in 35 [43%] of 81 patients in the olaparib plus chemotherapy group *vs* 26 [35%] of 75 in the chemotherapy alone group) and anaemia (seven [9%] *vs* five [7%]). Serious adverse events were reported in 12 (15%) of 81 patients in the olaparib plus chemotherapy group and 16 of 75 (21%) patients in the chemotherapy alone group.

Interpretation Olaparib plus paclitaxel and carboplatin followed by maintenance monotherapy significantly improved progression-free survival versus paclitaxel plus carboplatin alone, with the greatest clinical benefit in *BRCA*-mutated patients, and had an acceptable and manageable tolerability profile.

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(Prof M Friedlander FRACP)

Correspondence to:
Prof Amit Oza, University of
Toronto, Princess Margaret
Cancer Centre, 610 University
Avenue, Toronto, ON, M5G 2M9,
Canada
amit.oza@uhn.ca

For the **protocol** see http://www.
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oci/documents/D0810C00041_
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Introduction

Ovarian cancer is the fifth most common cancer in women in developed countries worldwide.[1,2] Despite significant initial response to platinum-based chemotherapies, many patients with ovarian cancer undergo relapse followed by disease progression within 1 year of treatment,[3–8] which emphasises the need for treatments that improve clinical outcomes. In roughly half of patients with high-grade serous ovarian carcinoma, deficiencies in homologous recombination repair in tumour cells prevent efficient repair of double-stranded DNA breaks.[9,10] Homologous recombination repair deficiencies are often caused by mutations in the tumour suppressor genes *BRCA1* and *BRCA2*. The inhibition of poly(ADP-ribose) polymerase enzymes, which repair single-stranded DNA breaks mainly through the base-excision repair pathway, leads to the formation of double-stranded breaks that in tumours with homologous recombination repair deficiencies are then subject to low-fidelity repair by non-homologous end-joining; this absence of an accurate repair mechanism results in cell death.[11,12]

Olaparib is a potent oral poly(ADP-ribose) polymerase inhibitor that causes synthetic lethality in *BRCA1*-deficient or *BRCA2*-deficient tumour cells.[13,14] In phase 1–2 monotherapy studies, olaparib treatment had demonstrable antitumour activity in patients with ovarian cancer with or without a *BRCA* mutation.[15–20] In patients with platinum-sensitive relapsed serous ovarian cancer, olaparib maintenance treatment significantly improved the duration of progression-free survival compared with placebo (hazard ratio [HR] 0·35 [95% CI 0·25–0·49]; p<0·0001), with the greatest clinical benefit recorded in patients with *BRCA* mutations (HR 0·18 [95% CI 0·10–0·31]; p<0·0001).[21,22]

Preclinical data suggest that olaparib might potentiate the efficacy of DNA-damaging chemotherapies, including platinum-containing drugs such as carboplatin.[13,14] The combination of carboplatin with paclitaxel, a mitotic inhibitor, is widely used to treat patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer.[4] Recent trials assessing olaparib in combination with chemotherapy in patients with advanced ovarian, breast, and other solid tumours have shown encouraging efficacy.[23–25]

In this trial, we compared the efficacy and tolerability of olaparib capsules plus carboplatin and paclitaxel, followed by olaparib monotherapy as a maintenance treatment, versus carboplatin and paclitaxel chemotherapy alone (with no further treatment) in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer.

Methods

Study design and participants

For this multicentre, multinational phase 2, open-label study, we enrolled patients from 43 investigational sites in 12 countries (see appendix for list of countries and centres). Eligible participants were aged 18 years or older and had histologically or cytologically diagnosed ovarian

cancer, including primary peritoneal and fallopian tube cancer, with serous histology or a serous component. Patients had received a maximum of three previous courses of platinum-based chemotherapy and, in the investigator's opinion, were progression free for at least 6 months before randomisation. Other key eligibility criteria included: at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and adequate bone marrow, hepatic, and renal function. The full eligibility criteria and exclusion criteria are available in the protocol. Knowledge of *BRCA* mutation status was not necessary for study entry, but if it was known at enrolment it was recorded. The study was done in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics.[26] All patients provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio, with use of an interactive voice response system, to the two treatment groups: olaparib plus paclitaxel and carboplatin chemotherapy or paclitaxel and carboplatin chemotherapy alone. Randomisation was stratified by number of previous platinum-containing regimens received (1 or >1) and time to disease progression following the previous platinum regimen (>6 to ≤12 months or >12 months). Following confirmation of a patient's eligibility, the investigator (or their nominated assistant) contacted the interactive voice response system by telephone for allocation of randomised treatment. After four to six cycles of combination treatment (six cycles were intended for all patients, but some individuals received four or five if they discontinued the combination treatment prematurely), patients in the olaparib plus chemotherapy group continued to receive olaparib maintenance monotherapy until objective disease progression, defined by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), or another discontinuation criterion (adverse event, severe non-compliance to the study protocol, or patient decision) was met. Meanwhile, patients in the chemotherapy alone group received no further treatment in the maintenance phase of the study.

Procedures

In the olaparib plus chemotherapy group, patients received olaparib (200 mg capsules twice daily, administered orally on days 1–10 of each 21-day cycle) plus paclitaxel (175 mg/m², administered intravenously on day 1 of each 21-day treatment cycle) and carboplatin (area under the curve [AUC] 4 mg/mL per min, according to the Calvert formula, administered intravenously on day 1 of each 21-day cycle) in the combination phase, then olaparib monotherapy (400 mg capsules twice daily, given continuously) until progression in the maintenance phase. In the chemotherapy alone group, patients received paclitaxel

(175 mg/m² on day 1 of each 21-day treatment cycle) and carboplatin (AUC 6 mg/mL per min on day 1 of each 21-day cycle) in the combination phase, then no further treatment in the maintenance phase.

During the combination phase, toxicities that occurred in the chemotherapy alone group were managed according to standard clinical practice. In the olaparib plus chemotherapy group, two olaparib dose reductions were allowed, first to 100 mg twice daily and then by reducing the dosing period (for 100 mg twice daily) to days 1–5 of each treatment cycle. Dose adjustments of paclitaxel, carboplatin, or both could be considered after olaparib dose reduction. The management of toxicities resulting from olaparib maintenance monotherapy involved dose interruption and, if necessary, dose reduction.

Outcomes

The primary endpoint of progression-free survival was defined as the time from randomisation until objective disease progression, according to RECIST version 1.1 guidelines, or death, whichever occurred first. Progression-free survival was analysed by masked independent central review of tumour assessments (on CT or MRI scans), which was done by an external panel of experts who were masked to treatment allocation and adverse events experienced. Before the primary data cutoff on Oct 10, 2011, tumour assessments were done at baseline, week 9, week 18, and every 12 weeks thereafter until disease progression. We did a progression-free survival sensitivity analysis using tumour assessments from the site investigators.

Secondary efficacy endpoints were: overall survival; percentage change in tumour size; the proportion of patients with an objective response according to RECIST;[27] cancer antigen 125 (CA-125) response, assessed using Gynecological Cancer InterGroup criteria;[28] and the proportion of patients with a RECIST or CA-125 response (ovarian cancer response).

Post-hoc exploratory analyses were time to first subsequent therapy or death and time to second subsequent therapy or death, which was used as an estimation of the time to the second disease progression or death. Time to first subsequent therapy or death and time to second subsequent therapy or death were measured as the time from randomisation to the start of the respective therapy subsequent to discontinuation of randomised treatment.

A prespecified exploratory objective was the collection of archival tumour samples for retrospective biomarker analyses. For consenting patients, archival tumour samples were analysed for deleterious, or suspected deleterious, mutations in *BRCA* with use of next-generation sequencing (performed by Foundation Medicine, Cambridge, MA, USA); the sequence variants were classified in accordance with the American College of Medical Genetics and Genomics' recommendations using
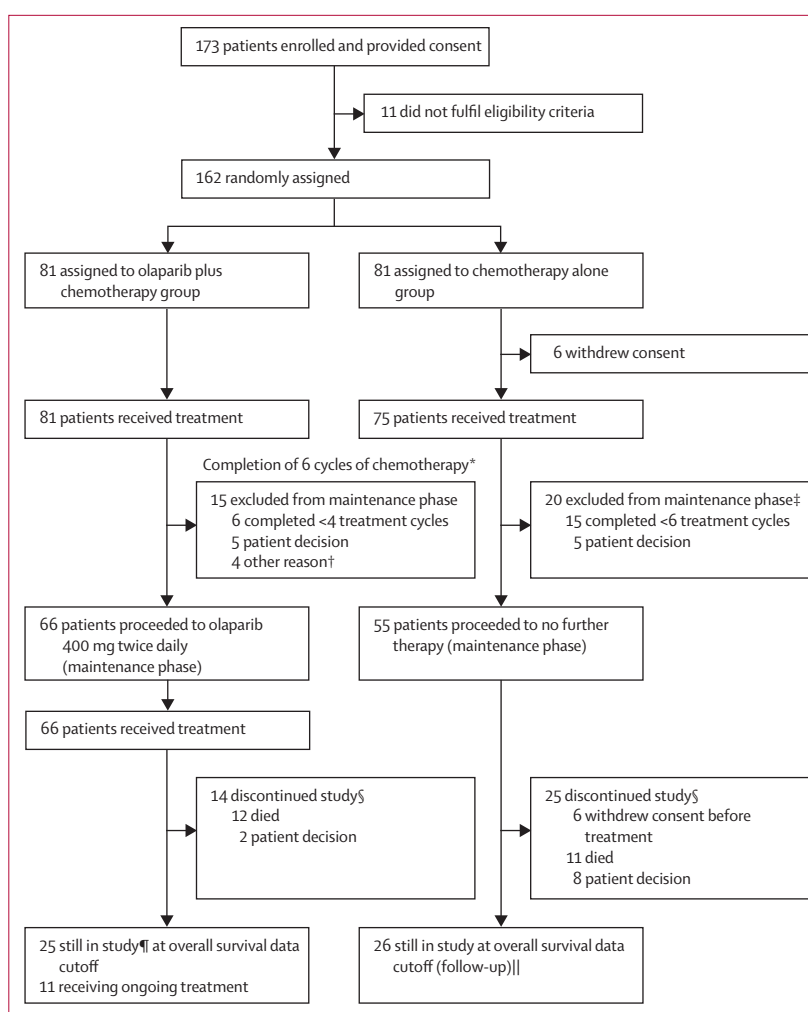

Figure 1: Trial profile
AUC=area under the curve. *Patients in the olaparib plus chemotherapy group who discontinued treatment prematurely during the combination phase were allowed to participate in the olaparib maintenance phase, as long as they had completed at least four cycles of study treatment and had not received any other anticancer therapy since discontinuation. †Other reasons: death before start of monotherapy (n=1); progression at chemotherapy discontinuation visit (n=1); adverse event (n=1); adverse event and hypersensitivity to carboplatin (n=1). ‡Does not include the six patients who entered the combination phase but withdrew consent before receiving chemotherapy. §Includes patients who discontinued during the combination and maintenance phase (ie, patients who discontinued the study at any time). ¶Includes patients receiving ongoing olaparib monotherapy and those in follow-up. ||Includes patients who did not enter the maintenance phase but remained in follow-up.

the Breast Cancer Information Core database.[29,30] The scientists who established tumour *BRCA* mutation status of both *BRCA1* and *BRCA2* for each sample were masked to all individual patient clinical data, including treatment and baseline germline *BRCA* mutation status.

Safety was assessed throughout the study by monitoring of adverse events (assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE], version 3.0), biochemical laboratory tests, vital signs, and physical examinations. Safety data were summarised separately for the combination and maintenance phases (see appendix p 4 for details about management of toxicities).

	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=81)
Age (years)	59 (27–78)	62 (31–79)
Ethnic origin		
White	70 (86%)	69 (85%)
Asian	8 (10%)	8 (10%)
Black	0	2 (2%)
Other	3 (4%)	2 (2%)
ECOG performance status		
0	58 (72%)	63 (78%)
1	21 (26%)	15 (19%)
2	2 (2%)	1 (1%)
Unknown	0	2 (2%)
Germline *BRCA* mutation status at study entry*		
Germline *BRCA1* mutation	7 (9%)	10 (12%)
Germline *BRCA2* mutation	5 (6%)	2 (2%)
Wild type	3 (4%)	8 (10%)
Missing	66 (81%)	61 (75%)
Previous platinum-containing chemotherapy regimens†		
1	58 (72%)	53 (65%)
>1	23 (28%)	28 (35%)
Time to disease progression after previous platinum therapy†		
>6 to ≤12 months	39 (48%)	40 (49%)
>12 months	42 (52%)	41 (51%)
Primary tumour location		
Ovary	69 (85%)	72 (89%)
Peritoneum	7 (9%)	4 (5%)
Fallopian tube	4 (5%)	2 (2%)
Other‡	1 (1%)	2 (2%)
Unknown	0	1 (1%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. *Germline *BRCA* mutation status at baseline was recorded on case report forms; germline *BRCA* testing procedures can vary, so patients defined as wild type at study entry might not have undergone comprehensive *BRCA* testing. †Stratification factor for patient randomisation. ‡Other primary tumour locations were as follows: olaparib plus chemotherapy group: pelvis (n=1); chemotherapy alone group: bilateral ovary (n=1), and synchronous ovarian and fallopian tube (n=1).

Table 1: Patient demographics and baseline characteristics

Statistical analysis

We planned to enrol 150 patients to provide 70 events (at 47% maturity) for the primary analysis. With the assumption of a HR of 0·6, with a one-sided type I error rate of 10%, the analysis would have 80% power to show a significant difference between groups. Additional preplanned analyses included an interim analysis at 38 events and a post-primary analysis at 90 events (at 60% maturity). Following the interim analysis (which was done after 60 events rather than the planned 38 events; data not shown), the primary analysis (70 events) was not done because of the insufficient increase in maturity; therefore, the post-primary analysis (90 events) became the primary analysis.

The final overall survival analysis was planned at 90 events (at 60% maturity); the median survival from randomisation was estimated to be 38 months in the olaparib plus chemotherapy group and 24 months in the chemotherapy alone group.

We analysed progression-free and overall survival on an intention-to-treat basis by a stratified log-rank test that used the same stratification factors as those used at randomisation. We explored predictive and prognostic factors for progression-free survival using pre-planned subgroup analyses, including number of previous platinum-based treatments, time to disease progression following the previous platinum-containing therapy, and *BRCA* mutation status. Objective response, and CA-125 and ovarian cancer responses were analysed by logistic regression, with adjustment for the same stratification factors as for progression-free survival. We assessed the least-squares mean percentage change in tumour size using an analysis of covariance, which included covariates for baseline tumour size, previous platinum treatments, and time to disease progression after the previous platinum-containing therapy. SAS version 8.1 was used for all analyses.

This trial is registered with ClinicalTrials.gov, number NCT01081951.

Role of the funding source

The corresponding author designed the trial in collaboration with the study funder. The funder provided funding and organisational support, collected data, did the analyses, and had a role in data interpretation and writing of the report. All authors had access to all the study data. The corresponding author had unrestricted access to all the raw study data and had final responsibility for the decision to submit for publication.

Results

Between Feb 12 and July 30, 2010, 173 patients were enrolled. 162 patients were randomly assigned to the two treatment groups (81 to olaparib plus chemotherapy and 81 to chemotherapy alone; figure 1). At the primary data cutoff (Oct 10, 2011), 123 patients (67 in the olaparib plus chemotherapy group and 56 in the chemotherapy group) were still in the trial; of these, 23 were still receiving olaparib maintenance monotherapy at primary data cutoff. At the overall survival cutoff (Jan 31, 2014), 26 patients in the chemotherapy group and 25 patients in the olaparib plus chemotherapy group were still in the trial, 11 of whom were still receiving maintenance olaparib monotherapy. Baseline characteristics were generally well balanced between the treatment groups (table 1).

The efficacy analysis set included all 162 randomised patients. Six patients in the chemotherapy alone group withdrew consent before treatment and therefore did not receive any chemotherapy; therefore, the safety analysis set included 156 patients (81 in the olaparib plus chemotherapy group and 75 in the chemotherapy alone group).

Based on germline *BRCA* mutation status at baseline and retrospective tumour BRCA testing, *BRCA* mutation status was known for 107 (66%) of 162 patients, of whom

41 (38%) had *BRCA* mutations (appendix p 6). The proportion of *BRCA* mutation-positive patients was well balanced between treatment groups (20 [25%] of 81 in the olaparib plus chemotherapy group, and 21 [26%] of 81 in the chemotherapy alone group).

At the primary data cutoff, the median duration of follow-up was 9·8 months (IQR 7·1–13·9) in the olaparib plus chemotherapy group and 7·5 months (4·3–9·8) in the chemotherapy alone group. The primary analysis, which was done after central review of 102 of 162 progression events (63% of patients), showed a significant improvement in progression-free survival in the olaparib plus chemotherapy group compared with the chemotherapy alone group (median 12·2 months [95% CI 9·7–15·0] *vs* 9·6 months [9·1–9·7]; HR 0·51 [95% CI 0·34–0·77]; p=0·0012; figure 2A). A sensitivity analysis of tumour assessments undertaken by site investigators was consistent with the primary analysis (HR 0·61 [95% CI 0·41–0·90]; p=0·012; appendix p 9). For all subgroup analyses, patients in the olaparib plus chemotherapy group had a lower risk of disease progression than did those in the chemotherapy alone group (appendix p 9). In patients with *BRCA* mutations, a significant improvement in progression-free survival was recorded in the olaparib plus chemotherapy group compared with the chemotherapy alone group (HR 0·21 [95% CI 0·08–0·55]; p=0·0015; figure 2B).

At the final analysis of overall survival (Jan 31, 2014), 101 (62%) of 162 patients had died (54 [67%] of 81 in the olaparib plus chemotherapy group, and 47 [58%] of 81 in the chemotherapy-alone group), including 20 (49%) of 41 *BRCA* mutation-positive patients (10 [50%] of 20 in the olaparib plus chemotherapy group, and 10 [48%] of 21 in the chemotherapy alone group). The median duration of follow-up was 33·4 months (IQR 20·4–42·9) in the olaparib plus chemotherapy group and 32·2 months (19·5–43·6) in the chemotherapy alone group. Overall survival did not differ significantly between the treatment groups in the overall patient population (figure 3A) or in patients with *BRCA* mutations (figure 3B).

Percentage change in tumour size did not differ significantly between the olaparib plus chemotherapy group (least-squares mean −38·4% [SE 4·0]) and the chemotherapy alone group (−39·1% [4·0]) after 9 weeks (p=0·90), or after 18 weeks (−53·7% [4·3%] *vs* −52·5% [4·4%]; p=0·85; appendix p 10). The proportion of patients with an objective response by central review was similar between treatment groups (p=0·42; table 2). The two treatment groups had a similar proportion of patients having a CA-125 response (p=0·12; table 2) and ovarian cancer response (p=0·16; table 2). Ten patients in the chemotherapy alone group who withdrew by the second treatment cycle with no follow-up assessment were classed as non-responders by RECIST and Gynecological Cancer Intergroup criteria; therefore, to avoid potential bias, we did unplanned exploratory analyses that excluded these patients. These analyses showed that objective response,
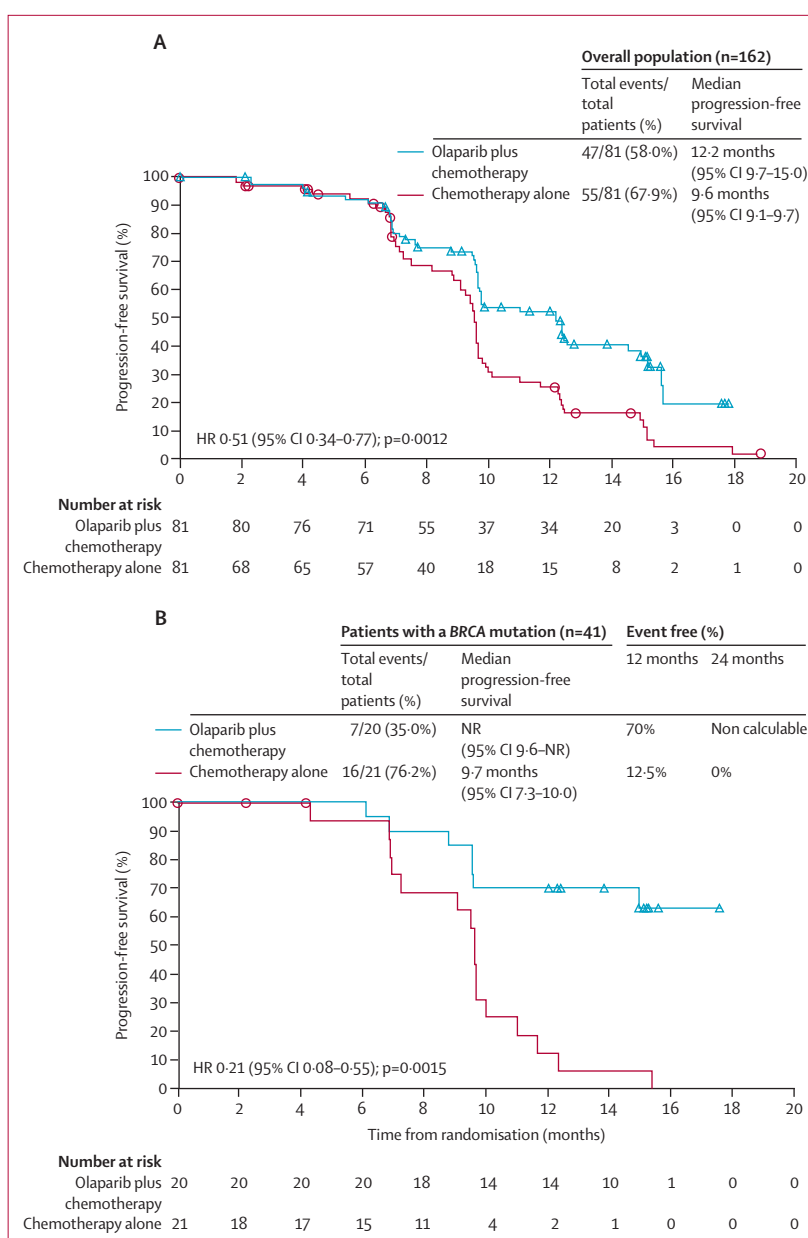

Figure 2: **Progression-free survival results**
(A) Progression-free survival in all patients. (B) Progression-free survival in patients with a *BRCA* mutation. HR=hazard ratio. NR=not reported.

CA-125, and ovarian cancer response were similar for both groups (table 2).

At the overall survival data cutoff, the exploratory analyses of time to first subsequent therapy or death and time to second subsequent therapy or death showed a significant benefit in time to first subsequent therapy or death in favour of the olaparib plus chemotherapy group (HR 0·60 [95% CI 0·42–0·86]; p=0·0053), but no significant difference in time to second subsequent therapy or death between the groups (0·83 [0·57–1·20]; p=0·32; appendix pp 11–12). In patients with *BRCA*
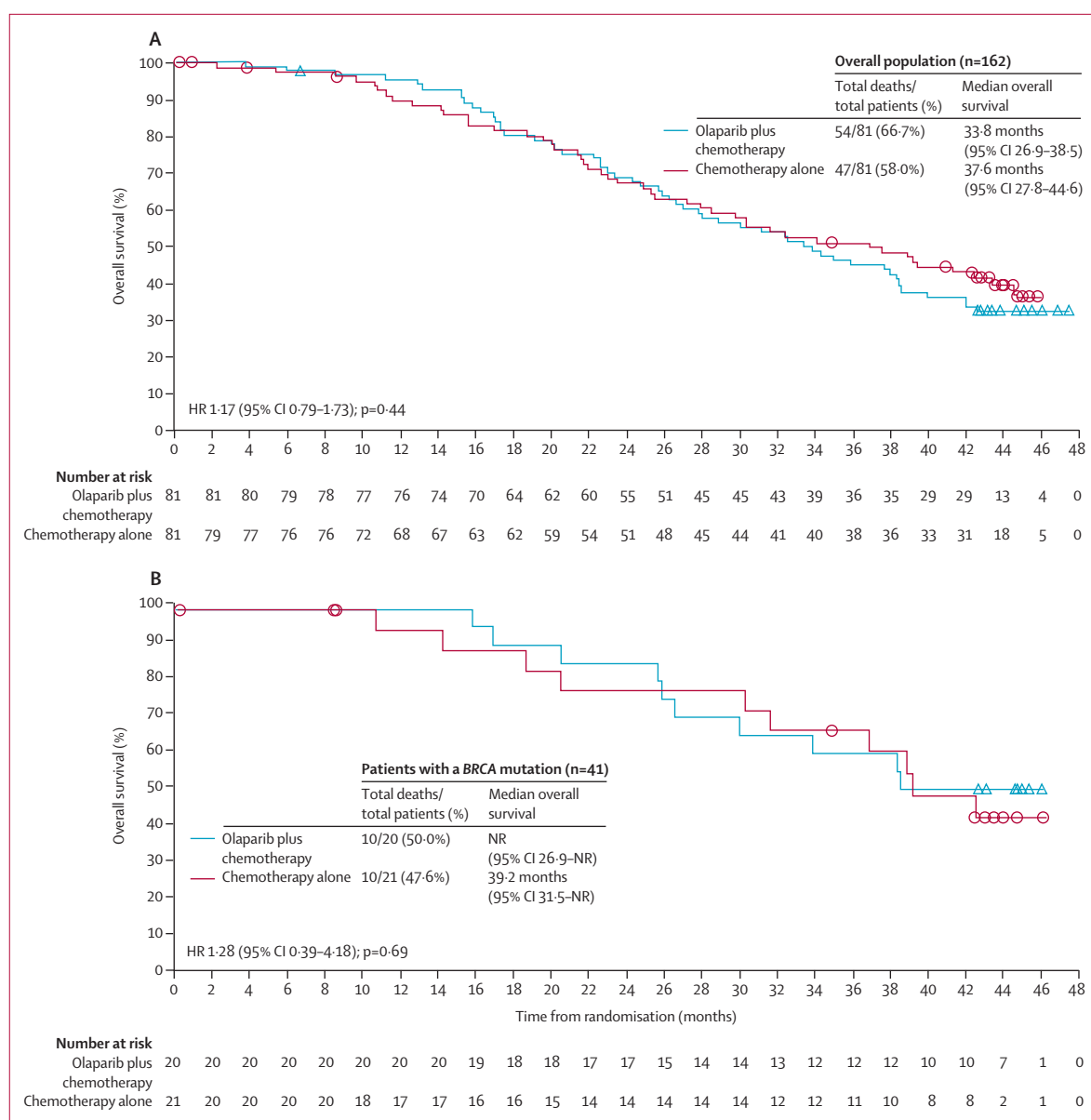
Figure 3: **Overall survival results**
(A) Overall survival in all patients. (B) Overall survival in patients with a *BRCA* mutation. HR=hazard ratio. NR=not reported.

mutations, significant improvements in both time to first subsequent therapy or death (HR 0·12 [95% CI 0·04–0·31]; p<0·0001) and time to second subsequent therapy or death (0·26 [0·11–0·59]; p=0·0013) were recorded in the olaparib plus chemotherapy group compared with the chemotherapy alone group (appendix pp 11–12).

During the combination phase, based on 21-day treatment cycles, the mean duration of olaparib exposure during this phase was 112 days (SD 26·6). The mean total duration of exposure to carboplatin and paclitaxel was similar in both groups (123 days [SD 27·3] in the olaparib plus chemotherapy group, and

116 days [SD 41·4] in the chemotherapy alone group); although, owing to the different carboplatin doses, patients in the chemotherapy alone group received greater carboplatin exposure. In both groups, most patients (75%) received six treatment cycles, and in the olaparib plus chemotherapy group, most patients (80%) received the intended 10 days of olaparib treatment per cycle. 30 (37%) of 81 patients had an olaparib dose modification (interruption and/or reduction) because of an adverse event.

Table 3 shows the most common adverse events that occurred in this study. Adverse events with an incidence

that was at least 10% higher in the olaparib plus chemotherapy group than in the chemotherapy alone group were alopecia, nausea, neutropenia (including cases of febrile neutropenia), diarrhoea, headache, peripheral neuropathy, and dyspepsia (table 3). With the exception of neutropenia, most adverse events (about 90%) were mild to moderate in intensity. In the olaparib plus chemotherapy group, 53 (65%) of 81 patients had grade 3 or higher adverse events (compared with 43 [57%] of 75 patients in the chemotherapy alone group), 12 (15%) of 81 patients had serious adverse events (compared with 16 [21%] of 75 patients), and 15 (19%) of 81 patients had adverse events leading to treatment discontinuation (compared with 12 [16%] of 75 patients). During the combination phase (including the 30-day follow-up period), one death occurred in each group, both of which were due to disease progression. No fatal adverse events were reported. Changes in haematological parameters were generally similar between groups. Changes in haemoglobin (two or more CTCAE grades from baseline) were more common in the olaparib plus chemotherapy group than in the chemotherapy alone group (40 [49%] of 81 patients vs 26 [36%] of 72 patients), although similar numbers of patients in both groups had CTCAE grade 3–4 changes (four [5%] of 81 patients vs five [7%] of 72 patients). Changes in neutrophil count (two or more CTCAE grades from baseline) were recorded in 74 (91%) of 81 patients in the olaparib plus chemotherapy group and in 61 (86%) of 71 patients in the chemotherapy alone group.

At data cutoff for the primary analysis, the mean total duration of olaparib exposure during the maintenance phase was 235 days (SD 127·6). 32 (49%) of 66 patients needed olaparib dose modifications (interruption and/or reduction) during the maintenance phase because of an adverse event. In the olaparib plus chemotherapy group, during the maintenance phase 19 (29%) of 66 patients had grade 3 or higher adverse events and six (9%) had serious adverse events, compared with nine (16%) and four (7%) of 55, respectively, in the chemotherapy alone (no-further-treatment) group. Five (8%) of 66 patients in the olaparib plus chemotherapy group had adverse events that led to discontinuation of olaparib (anaemia, ascites, dysphagia, haemoptysis, and erythropoiesis abnormal). During the maintenance phase (and 30-day follow-up period), no deaths occurred in the olaparib plus chemotherapy group, and six deaths, all caused by disease progression, occurred in the no-further-treatment group. Changes in laboratory parameters were similar between groups; few haematological changes of CTCAE grade 3–4 were recorded.

The appendix provides information about exposure and tolerability at the Jan 31, 2014 data cutoff and by BRCA mutation status.

Discussion

In this open-label, randomised, phase 2 trial of patients with recurrent platinum-sensitive serous ovarian cancer,

	Full analysis set		Post-hoc exploratory analysis set†	
	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=81)	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=71)
Best objective RECIST response				
Complete response	8 (10%)	6 (7%)	8 (10%)	6 (8%)
Partial response	44 (54%)	41 (51%)	44 (54%)	41 (58%)
Overall response	52 (64%)	47 (58%)	52 (64%)	47 (66%)
Non-response				
Stable disease ≥9 weeks	26 (32%)	20 (25%)	26 (32%)	20 (28%)
Progression	2 (2%)	2 (2%)	2 (2%)	2 (3%)
RECIST progression	1 (1%)	2 (2%)	1 (1%)	2 (3%)
Progression, >2 non-evaluable tumour assessments	1 (1%)	0	1 (1%)	0
Not evaluable	1 (1%)	12 (15%)	1 (1%)	2 (3%)
Total	29 (36%)	34 (42%)	29 (36%)	24 (34%)
Other responses				
CA-125 response rate (GCIG criteria)‡	51/59 (86%)	37/50 (74%)	51/59 (86%)	37/46 (80%)
Ovarian cancer response§	64 (79%)	56 (69%)	64 (79%)	56 (79%)

RECIST=Response Evaluation Criteria in Solid Tumors. CA-125=cancer antigen 125. GCIG=Gynecological Cancer InterGroup. *Based on the best patient response before data cutoff. †The exploratory analysis set excluded a group of ten patients from the chemotherapy alone group who withdrew after little or no treatment and had no RECIST follow-up data. ‡Baseline CA-125 data were available for 59 patients in the olaparib plus chemotherapy group and 50 patients in the chemotherapy alone group. §Ovarian cancer response is defined as the proportion of patients with a response based on either RECIST or GCIG criteria.

Table 2: Responses* according to independent central review of full analysis set and exploratory analysis set

the addition of olaparib to paclitaxel and carboplatin chemotherapy, followed by olaparib maintenance monotherapy, provided a significant improvement in progression-free survival versus paclitaxel and carboplatin alone. An exploratory analysis showed that the greatest progression-free survival benefit was recorded in patients with BRCA mutations (panel).

The progression-free survival benefits occurred despite a longer median follow-up in the olaparib plus chemotherapy group, which might have introduced bias in favour of the chemotherapy group because of early censoring in this group. The progression-free survival benefits also occurred despite the lower carboplatin dose in the olaparib plus chemotherapy group (AUC 4 mg/mL per min, compared with AUC 6 mg/mL per min in the chemotherapy alone group) during the chemotherapy phase; the decision to use the lower AUC 4 mg/mL per min dose was based on tolerability data from a phase 1 study assessing olaparib (capsule and tablet formulations) with carboplatin and paclitaxel to establish optimum dosing regimens.[32] Carboplatin AUC 4 mg/mL per min is also used frequently in clinical practice, in combination with gemcitabine, in patients with relapsed ovarian cancer.[7] Based on preclinical data,[13,14] one aim of our trial was to establish the extent by which the addition of olaparib to carboplatin and paclitaxel potentiates the cytotoxic effect of these agents. Our results suggest that olaparib might provide an additive effect or potentiate

	Combination phase				Maintenance phase			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=75)	Olaparib plus chemotherapy (n=81)	Chemotherapy alone (n=75)	Olaparib (n=66)	No treatment (n=55)	Olaparib (n=66)	No treatment (n=55)
Patients with any adverse event	81 (100%)	73 (97%)	53 (65%)	43 (57%)	64 (97%)	41 (75%)	19 (29%)	9 (16%)
Non-haematological adverse events								
Alopecia	60 (74%)	44 (59%)	0	0	0	0	0	0
Nausea	56 (69%)	43 (57%)	1 (1%)	1 (1%)	33 (50%)	3 (6%)	1 (2%)	0
Fatigue	52 (64%)	43 (57%)	6 (7%)	3 (4%)	13 (20%)	5 (9%)	0	0
Diarrhoea*	34 (42%)	20 (27%)	0	1 (1%)	10 (15%)	4 (7%)	0	0
Headache	27 (33%)	7 (9%)	1 (1%)	0	8 (12%)	1 (2%)	0	0
Myalgia	27 (33%)	18 (24%)	0	0	0	1 (2%)	0	0
Peripheral neuropathy	25 (31%)	14 (19%)	0	0	1 (2%)	4 (7%)	0	0
Constipation	24 (30%)	24 (32%)	0	0	7 (11%)	0	1 (2%)	0
Arthralgia	22 (27%)	20 (27%)	0	0	5 (8%)	1 (2%)	0	0
Decreased appetite	21 (26%)	19 (25%)	1 (1%)	0	11 (17%)	1 (2%)	0	0
Dyspepsia	21 (26%)	9 (12%)	0	0	5 (8%)	1 (2%)	0	0
Vomiting	21 (26%)	18 (24%)	0	0	19 (29%)	4 (7%)	0	0
Dysgeusia	20 (25%)	12 (16%)	0	0	5 (8%)	0	0	0
Abdominal pain	19 (24%)	11 (15%)	0	2 (3%)	9 (14%)	8 (15%)	0	0
Peripheral sensory neuropathy	16 (20%)	21 (28%)	0	1 (1%)	2 (3%)	0	1 (2%)	0
Drug hypersensitivity	15 (19%)	13 (17%)	4 (5%)	5 (7%)	0	0	0	0
Insomnia	14 (17%)	12 (16%)	0	0	6 (9%)	2 (4%)	0	0
Stomatitis	14 (17%)	8 (11%)	0	0	4 (6%)	0	0	0
Dizziness	13 (16%)	6 (8%)	0	0	6 (9%)	2 (4%)	0	0
Pain in extremity	13 (16%)	11 (15%)	0	1 (1%)	2 (3%)	3 (6%)	0	0
Abdominal pain upper	12 (15%)	5 (7%)	0	0	8 (12%)	4 (7%)	0	0
Cough	12 (15%)	7 (9%)	0	0	11 (17%)	6 (11%)	0	1 (2%)
Hypomagnesaemia	8 (10%)	6 (8%)	0	3 (4%)	1 (2%)	1 (2%)	0	0
Nasopharyngitis	5 (6%)	3 (4%)	0	0	11 (17%)	3 (6%)	0	0
Haematological adverse events								
Neutropenia*†	40 (49%)	29 (39%)	35 (43%)	26 (35%)	7 (11%)	4 (7%)	3 (5%)	0
Anaemia*	21 (26%)	16 (21%)	7 (9%)	5 (7%)	8 (12%)	5 (9%)	5 (8%)	1 (2%)
Thrombocytopenia*	18 (22%)	13 (17%)	5 (6%)	6 (8%)	5 (8%)	1 (2%)	0	0
Leucopenia*	11 (14%)	8 (11%)	4 (5%)	4 (5%)	5 (8%)	2 (4%)	1 (2%)	0
White blood cell count decreased	2 (3%)	5 (7%)	2 (3%)	3 (4%)	1 (2%)	0	0	0
Neutrophil count decreased	2 (3%)	3 (4%)	2 (3%)	3 (4%)	1 (2%)	0	0	0

Adverse events are listed by Medical Dictionary for Regulatory Activities (MedDRA)-preferred term. Individual investigators might have used different MedDRA-preferred terms to report particular adverse events (eg, "peripheral neuropathy" and "peripheral sensory neuropathy"); these events are reported separately because of separate system organ class coding. CTCAE=Common Terminology Criteria for Adverse Events. *Grade 4 events reported by the primary data cutoff were: anaemia (two in the olaparib plus chemotherapy group [combination phase] and three in the olaparib plus chemotherapy group [maintenance phase]), febrile neutropenia (two in the olaparib plus chemotherapy group [combination phase]), leucopenia (one in the olaparib plus chemotherapy group [combination phase]), neutropenia (13 in the olaparib plus chemotherapy group and 13 in the chemotherapy alone group [combination phase]; and one in the olaparib plus chemotherapy group [maintenance phase]), thrombocytopenia (one in the olaparib plus chemotherapy group and two in the chemotherapy alone group [combination phase]), diarrhoea (one in the chemotherapy alone group [combination phase]), acute hepatitis (one in the chemotherapy alone group [maintenance phase]), anaphylactic reaction (one in the chemotherapy alone group [combination phase]), drug hypersensitivity (one in the olaparib plus chemotherapy group and one in the chemotherapy alone group [combination phase]), and hyponatraemia (one in the chemotherapy alone group [combination phase]). No grade 5 events were reported by the primary data cutoff. †Includes patients with febrile neutropenia events (three in the olaparib plus chemotherapy group, and one in the chemotherapy alone group; all occurred during the combination phase and were grade ≥3).

Table 3: Adverse events (any grade) experienced by 15% or more of patients in either treatment group, and CTCAE grade 3 or higher events occurring in 3% or more of patients in either group

the cytotoxic effect of the lower carboplatin dose; however, the extent of any contribution to overall treatment outcomes is unknown and needs further investigation.

Although our study was not designed to measure the contribution of each treatment phase, the late separation of the progression-free survival curves and improvement in objective response during the combination phase suggest that the maintenance phase was probably the key contributor to the improvement in progression-free survival. On the basis of these findings, the combination of olaparib plus chemotherapy with the current schedule is not believed to provide an advantage over olaparib maintenance therapy alone. Previously, Ledermann and colleagues[21] reported results from a randomised phase 2 trial in which olaparib maintenance monotherapy led to a significant improvement in progression-free survival versus placebo in patients who had platinum-sensitive recurrent ovarian cancer who had responded to chemotherapy. By contrast, our study investigated olaparib plus chemotherapy, followed by maintenance olaparib treatment in a population not restricted to patients with an objective response to chemotherapy. Furthermore, patients in Ledermann and colleagues' trial were required to have received, and responded to, at least two previous platinum-containing regimens.[21] Thus, the two trials are complementary, but their outcomes cannot be compared directly.

The progression-free survival improvement in our trial did not translate into an overall survival benefit in either the overall population or in patients with *BRCA* mutations. Our overall survival analysis might have been compromised by an imbalance in early censoring, with nine patients censored before the overall survival data cutoff (one in the olaparib plus chemotherapy group [who withdrew consent], whose follow-up for survival was 6·5 months; and eight in the chemotherapy alone group [five withdrew consent, and three for other reasons], for whom median follow-up for survival was 8·5 months [IQR 2·2–37·9]). All eight patients in the chemotherapy alone group had one or more poor prognostic factor at baseline and were therefore at increased risk of early death, which therefore potentially introduces a bias in favour of the chemotherapy alone group. In the subset of patients with *BRCA* mutations, imbalances in prognostic baseline stratification factors (previous platinum therapies received and time to progression following the previous platinum regimen) were identified in both the number of patients and death events between treatment groups. Since the primary overall survival analysis used a stratified log-rank test, we did an exploratory post-hoc analysis of overall survival using a Cox proportional hazards model that adjusted for these imbalances. This analysis also showed no significant difference between treatment groups in the subgroup of patients with *BRCA* mutations (HR 0·98 [95% CI 0·37–2·61]; p=0·97) or the overall population (1·17 [0·79–1·74]; p=0·43). Finally, in patients with *BRCA*

mutations, a lower proportion of patients in the olaparib plus chemotherapy group received subsequent therapies (nine [45%] of 20, compared with 16 [76%] of 21 in the chemotherapy alone group), with five (24%) of 21 patients in the chemotherapy alone group receiving a subsequent poly(ADP-ribose) polymerase inhibitor compared with no patients in the olaparib plus chemotherapy group.

Although we did not record progression data beyond the primary analysis, preventing an assessment of time from randomisation to second objective disease progression or death, subsequent therapies were recorded, allowing time to first subsequent therapy or death and time to second subsequent therapy or death to be assessed. A significant improvement in time to first subsequent therapy or death in the olaparib plus chemotherapy group indicated that the progression-free survival benefit was maintained after

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Panel: Research in context

Systematic review

On Aug 1, 2014, we searched PubMed and the American Society of Clinical Oncology and European Society for Medical Oncology database to identify publications between September, 2000, and Aug 1, 2014, describing the use of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with ovarian cancer. We used the search terms "PARP inhibitor" and "ovarian cancer" without restrictions on language or article type. Olaparib monotherapy has previously shown clinical activity in patients with relapsed ovarian cancer.[15,18,19,21] Recently, patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer with a *BRCA* mutation have been shown to benefit most from olaparib maintenance monotherapy.[22] Other PARP inhibitors are at various stages of development for ovarian cancer;[31] ongoing trials include studies of niraparib and rucaparib as maintenance treatments in women with platinum-sensitive ovarian cancer.

Interpretation

To our knowledge, our phase 2 trial is the first to show that, compared with chemotherapy alone, patients with relapsed ovarian cancer respond preferentially to a PARP inhibitor in combination with platinum-based chemotherapy, followed by maintenance monotherapy with the PARP inhibitor. In this study, patients in the olaparib plus chemotherapy group had a significant improvement in progression-free survival compared with those in the chemotherapy alone group, with the greatest benefit reported in patients with *BRCA* mutations. Exploratory analyses of time to first subsequent therapy or death and time to second subsequent therapy or death, which are indicators of post-progression efficacy, showed that the progression-free survival treatment benefit was maintained when patients in the olaparib plus chemotherapy group received subsequent therapy. Our results show that, following combination treatment with platinum-based chemotherapy, olaparib is suitable for long-term maintenance treatment in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer.

the primary analysis; however, no significant improvement in time to second subsequent therapy or death (a proxy for time from randomisation to second objective disease progression or death) was recorded in the overall population.

Patients with *BRCA* mutations had the greatest benefits in progression-free survival, time to first subsequent therapy or death, and time to second subsequent therapy or death from olaparib plus chemotherapy; the significant improvement in time to second subsequent therapy or death suggests that the treatment benefit is maintained beyond the first progression. These results are consistent with those reported by Ledermann and colleagues[22] and support the hypothesis that poly(ADP-ribose) polymerase inhibitors provide the greatest antitumour benefit in patients with homologous recombination repair deficiencies.

Our results were based on quite a small patient population and, to accommodate the use of different carboplatin doses, the study had an open-label design, which could have introduced bias in the time to first subsequent treatment or death analyses in favour of the olaparib plus chemotherapy group because patients in the chemotherapy alone group (in which no maintenance treatment was given) are considered more likely to advance to a subsequent therapy. To reduce potential bias, RECIST data were assessed by external investigators who were masked to treatment assignment. Furthermore, because our trial was open label and since olaparib maintenance therapy was compared with no further treatment, quality of life—which is important for assessments of maintenance therapies—was not assessed.

Olaparib combined with carboplatin AUC 4 mg/mL per min and paclitaxel had a similar tolerability profile to carboplatin AUC 6 mg/mL per min plus paclitaxel, with higher incidences (>10%) of only a few adverse events (alopecia, nausea, neutropenia, diarrhoea, headache, peripheral neuropathy, and dyspepsia). Most events were mild to moderate in intensity; the exception was neutropenia, which was also more common with olaparib plus chemotherapy than with chemotherapy alone, suggesting that concurrent administration of a poly(ADP-ribose) polymerase inhibitor with platinum-based chemotherapy might intensify or prolong platinum-induced neutropenia. In the maintenance phase, the tolerability profile of olaparib monotherapy was consistent with that reported previously,[15,16,21,33] which confirms that olaparib monotherapy is generally well tolerated and is suitable for long-term use after combination with chemotherapy.

In summary, in patients with recurrent platinum-sensitive serous ovarian cancer, olaparib plus paclitaxel and carboplatin, followed by olaparib maintenance therapy, was associated with a significant improvement in progression-free survival compared with paclitaxel and carboplatin alone, and had an acceptable and manageable tolerability profile. The treatment benefit seemed to derive mostly from the maintenance olaparib monotherapy phase, and the most compelling progression-free survival benefit was recorded in patients with *BRCA* mutations. Phase 3 confirmatory trials of olaparib as a maintenance treatment for patients with *BRCA* mutations are in progress (SOLO 1 [NCT01844986]) or who have platinum-sensitive recurrent disease following at least two lines of platinum-based chemotherapy (SOLO 2 [NCT01874353]).[34]

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