Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial

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Summary

Background Maintenance monotherapy with the PARP inhibitor olaparib significantly prolonged progression-free survival (PFS) versus placebo in patients with platinum-sensitive recurrent serous ovarian cancer. We aimed to explore the hypothesis that olaparib is most likely to benefit patients with a *BRCA* mutation.

Methods We present data from the second interim analysis of overall survival and a retrospective, preplanned analysis of data by *BRCA* mutation status from our randomised, double-blind, phase 2 study that assessed maintenance treatment with olaparib 400 mg twice daily (capsules) versus placebo in patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen. Randomisation was by an interactive voice response system, stratified by time to progression on penultimate platinum-based regimen, response to the most recent platinum-based regimen before randomisation, and ethnic descent. The primary endpoint was PFS, analysed for the overall population and by *BRCA* status. This study is registered with ClinicalTrials.gov, number NCT00753545.

Findings Between Aug 28, 2008, and Feb 9, 2010, 136 patients were assigned to olaparib and 129 to placebo. *BRCA* status was known for 131 (96%) patients in the olaparib group versus 123 (95%) in the placebo group, of whom 74 (56%) versus 62 (50%) had a deleterious or suspected deleterious germline or tumour *BRCA* mutation. Of patients with a *BRCA* mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11·2 months [95% CI 8·3–not calculable] *vs* 4·3 months [3·0–5·4]; HR 0·18 [0·10–0·31]; p<0·0001); similar findings were noted for patients with wild-type *BRCA*, although the difference between groups was lower (7·4 months [5·5–10·3] *vs* 5·5 months [3·7–5·6]; HR 0·54 [0·34–0·85]; p=0·0075). At the second interim analysis of overall survival (58% maturity), overall survival did not significantly differ between the groups (HR 0·88 [95% CI 0·64–1·21]; p=0·44); similar findings were noted for patients with mutated *BRCA* (HR 0·73 [0·45–1·17]; p=0·19) and wild-type *BRCA* (HR 0·99 [0·63–1·55]; p=0·96). The most common grade 3 or worse adverse events in the olaparib group were fatigue (in ten [7%] patients in the olaparib group *vs* four [3%] in the placebo group) and anaemia (seven [5%] *vs* one [<1%]). Serious adverse events were reported in 25 (18%) patients who received olaparib and 11 (9%) who received placebo. Tolerability was similar in patients with mutated *BRCA* and the overall population.

Interpretation These results support the hypothesis that patients with platinum-sensitive recurrent serous ovarian cancer with a *BRCA* mutation have the greatest likelihood of benefiting from olaparib treatment.

Funding AstraZeneca.

Introduction

In developed countries, ovarian cancer is the fifth highest cause of cancer deaths in women.[1,2] Patients with platinum-sensitive recurrent cancer (defined as relapse ≥6 months after platinum-based chemotherapy) are thought to be likely to respond to further platinum treatment, and re-treatment with platinum-based chemotherapy is common. However, cumulative toxicities and the emergence of resistance limit the use of these drugs.[3] An alternative and preferable approach is to consolidate and prolong tumour responses to platinum-based chemotherapy using maintenance therapy with an effective and well tolerated oral antitumour agent; this approach could delay disease progression and defer initiation of subsequent chemotherapy.

Up to 50% of patients with high-grade serous ovarian cancer are deficient in homologous recombination—a key pathway for repair of DNA damage—due to germline or somatically acquired *BRCA1* or *BRCA2* mutations, epigenetic inactivation of *BRCA1*, or *BRCA*-independent defects in the homologous recombination pathway.[4,5] The proportion of patients with germline *BRCA* mutations is

greater in those with high-grade serous ovarian cancer[6] than in the overall ovarian cancer population (22·6% *vs* ≤15%).[7,8] Furthermore, *BRCA* mutations occur more frequently in patients with platinum-sensitive epithelial ovarian cancer than in patients with platinum-resistant disease (38% *vs* 17%).[9] Additionally, a higher frequency of women without a germline *BRCA* mutation who responded to platinum-based treatment had a somatic *BRCA* mutation than did women with unselected high-grade serous ovarian cancer.[6]

PARP inhibitors induce synthetic lethality in tumours with homologous recombination deficiency due to, for example, loss-of-function *BRCA* mutations.[10–12] Olaparib is a potent oral PARP inhibitor that has shown antitumour activity in phase 1/2 trials in patients with *BRCA*-mutated or sporadic high-grade serous ovarian cancer.[13–17] Irrespective of whether the origin of the *BRCA* mutation is germline or somatic, tumours in patients with a *BRCA* mutation are postulated to be sensitive to PARP inhibition because of the loss of function of the gene within the tumour.[18]

Previously, we reported the results of a randomised, double-blind phase 2 study,[19] in which maintenance treatment with olaparib 400 mg (capsule formation) twice daily led to a significant improvement in median progression-free survival (PFS) compared with placebo in patients with platinum-sensitive recurrent serous ovarian cancer (8·4 months with olaparib *vs* 4·8 months with placebo; HR 0·35 [95% CI 0·25–0·49]; p<0·001). An interim analysis of overall survival (when 38% of patients had died) did not detect a benefit for olaparib compared with placebo (HR 0·94 [95% CI 0·63–1·39]; p=0·75).[19] Although *BRCA* mutation status was known for only 98 (37%) of 265 patients at study entry, a preplanned subgroup analysis suggested that olaparib might lead to longer PFS in patients with a known *BRCA* mutation than those with an unknown mutation status.[19]

We aimed to update the efficacy and safety results (data cutoff Nov 26, 2012) from this phase 2 trial in a greatly expanded subset of patients who underwent retrospective germline and somatic *BRCA* mutation testing. More complete patient-reported outcomes will be presented separately.

Methods

Study design and patients

This study was a preplanned retrospective analysis of data from our phase 2, randomised, double-blind, multicentre trial, undertaken at 82 sites in 16 countries. The institutional review boards or independent ethics committees of all investigational sites approved the protocol and informed consent details. The study was done in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics.[20]

Eligible patients were aged 18 years or older and had recurrent ovarian or fallopian tube cancer, or primary peritoneal cancer, with high-grade (grade 2 or 3) serous features or a serous component, which was

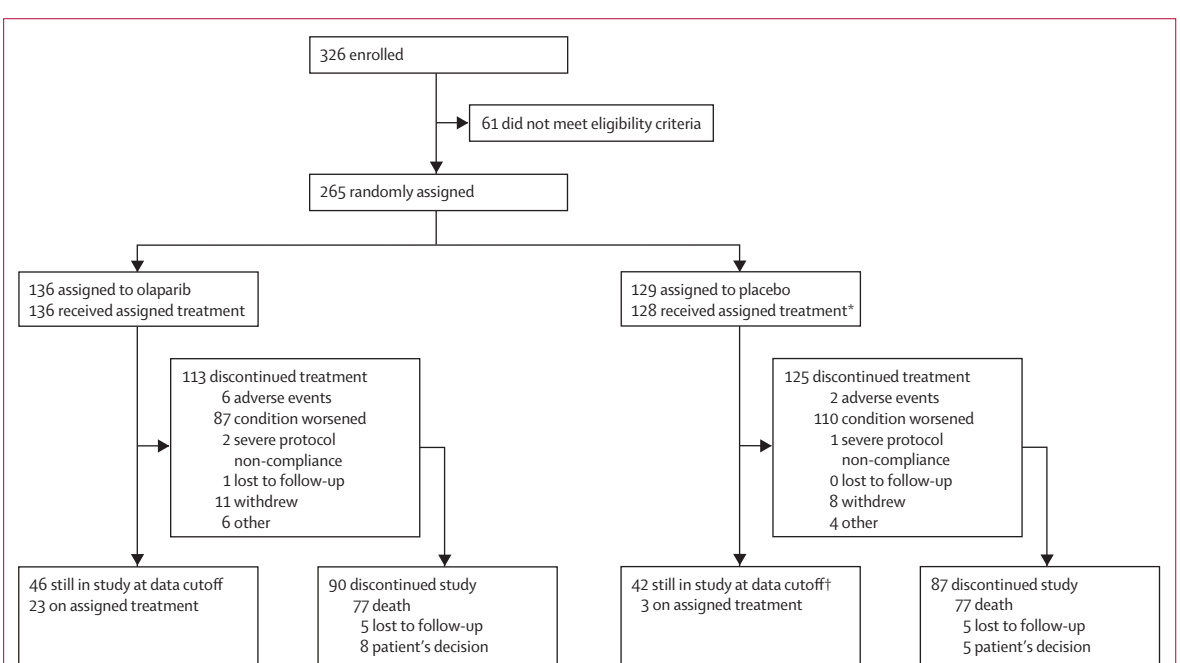

***Figure 1*: Enrolment, randomisation, and treatment status at the second interim analysis of overall survival**
Data cutoff was on Nov 26, 2012. *One patient was randomly assigned to the placebo group but voluntarily withdrew consent (and completely withdrew from the study) without receiving treatment. †One patient withdrew from the study on Aug 25, 2010, but, at the time of database lock (Nov 26, 2012), the necessary case report form pages were not available; therefore, this patient appears incorrectly as still in the study.

	Mutated tumour *BRCA*	Wild-type tumour *BRCA*		Tumour *BRCA* status not available	All patients
		No known mutation	*BRCA* variant of unknown significance		
Mutated germline *BRCA*	71 (27%)	3 (1%)	0	22 (8%)	96 (36%)
Wild-type germline *BRCA**					
No known/reported mutation†	18 (7%)	65 (25%)	4 (2%)	23 (9%)	110 (42%)
BRCA variant of unknown significance	0	0	4 (2%)	0	4 (2%)
Germline *BRCA* status not available	22 (8%)	18 (7%)	4 (2%)	11 (4%)	55 (21%)‡
All patients	111 (42%)	86 (32%)	12 (5%)	56 (21%)§	265

Data are number (%). *BRCA* mutation status was not available from both germline *BRCA* and tumour *BRCA* testing for 11 (4%) of 265 patients. Both germline *BRCA* and tumour *BRCA* mutation status was available for 165 (62%) of 265 patients. Four patients were classified as wild-type *BRCA* on the basis of case report form data alone (neither tumour *BRCA* nor retrospective germline *BRCA* mutation status was available for these patients). *19 (16%) of the 114 patients classified as having wild-type germline *BRCA* were classified on the basis of case report form data alone (ie, samples from these 19 patients were not tested by the Myriad Integrated BRCA*analysis* assay). †Includes patients who underwent *BRCA* testing (by Myriad Integrated BRCA*analysis* assay or by local testing [reported in the case report form], or both) and that have no recorded deleterious or suspected deleterious mutation, and no genetic variant of unknown significance. ‡Of the 55 patients for whom germline *BRCA* mutation status was not available, 44 had a known tumour *BRCA* mutation status. §Of the 56 patients for whom tumour *BRCA* mutation status was not available, 45 had a known germline *BRCA* mutation status.

***Table 1*: Germline *BRCA* mutation status according to tumour *BRCA* mutation status**

	Patients with *BRCA* mutation		Patients with wild-type *BRCA*	
	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=61)
Age, years	57·5 (38–89)	55·0 (33–84)	62·0 (21–80)	63·0 (49–79)
Age group				
<50 years	19 (26%)	16 (26%)	10 (18%)	1 (2%)
≥50 to <65 years	38 (51%)	35 (56%)	20 (35%)	37 (61%)
≥65 years	17 (23%)	11 (18%)	27 (47%)	23 (38%)
Ancestry*				
Non-Jewish	60 (81%)	48 (77%)	51 (89%)	58 (95%)
Jewish	14 (19%)	14 (23%)	6 (11%)	3 (5%)
ECOG performance status				
0	62 (84%)	45 (73%)	45 (79%)	45 (74%)
1	11 (15%)	15 (24%)	10 (18%)	14 (23%)
2	0	1 (2%)	1 (2%)	1 (2%)
Unknown	1 (1%)	1 (2%)	1 (2%)	1 (2%)
Primary tumour location				
Ovary	65 (88%)	54 (87%)	50 (88%)	49 (80%)
Fallopian tube or primary peritoneal	9 (12%)	8 (13%)	7 (12%)	12 (20%)
Time to progression after completion of penultimate platinum-based regimen				
>6 to ≤12 months	28 (38%)	26 (42%)	23 (40%)	24 (39%)
>12 months	46 (62%)	36 (58%)	34 (60%)	37 (61%)
Objective response to most recent platinum-based regimen				
Complete response	36 (49%)	34 (55%)	20 (35%)	25 (41%)
Partial response	38 (51%)	28 (45%)	37 (65%)	36 (59%)

Data are median (range) or number (%). ECOG=Eastern Cooperative Oncology Group. *Ancestry was self-reported.

***Table 2*: Patient demographics and baseline characteristics according to *BRCA* mutation status**

platinum-sensitive (defined as no disease progression in the first 6 months after the last dose of the penultimate line of platinum-based chemotherapy). Patients entering the study had received two or more previous courses of platinum-based chemotherapy and were required to have shown an objective response (complete or partial response) according to Response Evaluation Criteria In Solid Tumors (RECIST) or Gynecologic Cancer Intergroup criteria. Key inclusion criteria have been described previously.[19] All patients provided written informed consent. Consent to further follow-up and *BRCA* mutation analysis was provided by patients continuing in the study.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio by an interactive voice response system (IVRS) to receive olaparib or matching placebo. The investigator contacted the IVRS centralised randomisation centre by telephone for allocation of randomised therapy. Randomisation was stratified according to time from completion of penultimate platinum-based regimen to disease progression (6–12 months *vs* >12 months), objective response to platinum therapy before randomisation (complete response *vs* partial response), and ethnic descent (Jewish *vs* non-Jewish). Participants, those administering the interventions, and those assessing the outcomes were masked to treatment assignment. Masking was achieved with the use of unique identifiers generated during randomisation, and the olaparib and placebo capsules were identical in appearance and presented in the same packaging.

Procedures

Patients assigned to olaparib received 400 mg twice daily (capsules), as described previously.[19] Study treatment was continued until progression in the absence of unacceptable toxicity. As described previously, treatment interruptions and dose reductions were permitted for toxicity management.[19]

A prespecified exploratory analysis of all efficacy endpoints was done according to *BRCA* status. Germline *BRCA* mutation status was either reported on case report forms after local testing or it was established retrospectively using the Integrated BRCA*analysis* assay (Myriad Genetics Laboratories, Salt Lake City, UT, USA), with DNA extracted from blood samples obtained before randomisation.[21] *BRCA* genes were sequenced and examined for mutations and rearrangements (deletions and duplications) in the coding regions and 10–20 base pairs of flanking intronic sequence. Tumour *BRCA* status was established retrospectively using DNA extracted from formalin-fixed, paraffin-embedded archival tumour samples using a previously validated next-generation sequencing protocol (Foundation Medicine, Cambridge, MA, USA).[22] This process involved enrichment of coding regions for 287 genes and deep resequencing with Illumina HiSeq

technology to more than 250 times the median coverage for about 5% sensitivity to detect mutations.[22] Classification of *BRCA* variants was based on the American College of Medical Genetics recommendations for standards of interpretation and reporting of sequence variants.[23] Patients were included in the *BRCA*-mutation group if they harboured a deleterious, or suspected deleterious, *BRCA* mutation in their germline or tumour DNA. Patients with no known or reported *BRCA* mutation and patients with *BRCA* variants of unknown significance were included in the wild-type *BRCA* group.

Tumour assessments were done every 12 weeks until week 60 and every 24 weeks thereafter, until objective disease progression or withdrawal of patient consent. Adverse events and laboratory parameters were recorded throughout the trial and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. RECIST progression data were not obtained after the primary PFS analysis (data cutoff June 30, 2010), for which data were reported previously.[19]

To assess PFS with additional maturity, we did a retrospective exploratory analysis of time to first subsequent therapy or death (TFST) in all patients who had received at least one dose of treatment. To provide information about the treatment benefit beyond progression, and in line with recently updated European Medicines Agency guidelines,[24] we did a retrospective exploratory analysis of time to second subsequent therapy or death (TSST) in all patients who had received at least one dose of treatment. We measured TFST and TSST as the time from randomisation to the start of the respective subsequent therapy. Additionally, a supportive analysis of PFS was done by blinded independent central review of tumour scans. Patients and investigators remained masked to treatment allocation to avoid bias in future analyses.

Outcomes

The primary endpoint was PFS, as determined by RECIST version 1.0. Secondary endpoints included overall survival, best overall response, health-related quality of life (trial outcome index [TOI], functional assessment of cancer therapy for ovarian cancer [FACT-O], FACT-O symptom index [FOSI]), and safety and tolerability.

Statistical analysis

We planned to enrol 250 patients to ensure that a sufficient number of PFS events occurred in the full analysis set and that the subgroup of patients with homologous recombination deficiency had 80% power to show a benefit in favour of olaparib. The primary analysis was to be done when at least 137 PFS events had occurred. Assuming that the true hazard ratio (HR) for progression or death with olaparib versus placebo was 0·75 (corresponding to a 33% increase in the median duration of PFS, from 9 to 12 months after randomisation) and that the overall type I error was 20% (one-sided test), we calculated that the analysis would have 80% power to show a significant difference in favour of olaparib (one-sided p<0·20). We did an interim

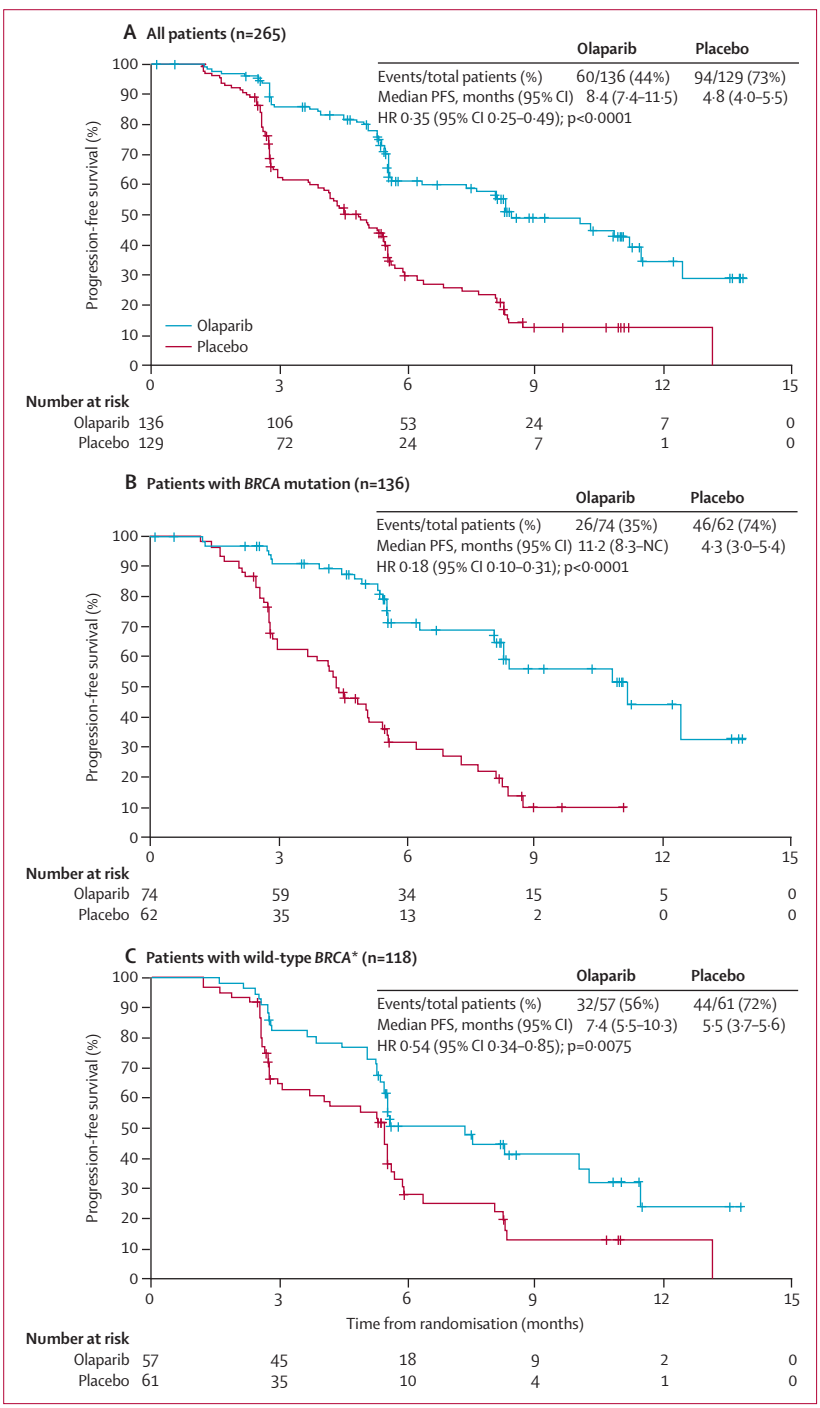

***Figure 2*: Progression-free survival in all patients and according to *BRCA* mutation status**
NC=not calculable. PFS=progression-free survival. *Wild-type *BRCA* includes patients with no known *BRCA* mutation and those with a *BRCA* mutation of unknown significance.

analysis of overall survival when 58% of patients had died (data cutoff Nov 26, 2012). At this data cutoff, 154 progression events had been recorded. We will undertake the final survival analysis at about 85% maturity (roughly 222 deaths).

We analysed PFS and overall survival with a Cox proportional hazards model adjusted for treatment, ethnic descent (Jewish *vs* non-Jewish), time to progression on penultimate platinum therapy (6–12 months *vs* >12 months), and response to platinum therapy before randomisation (complete response *vs* partial response), as described previously.[19]

This trial is registered with ClinicalTrials.gov, number NCT00753545.

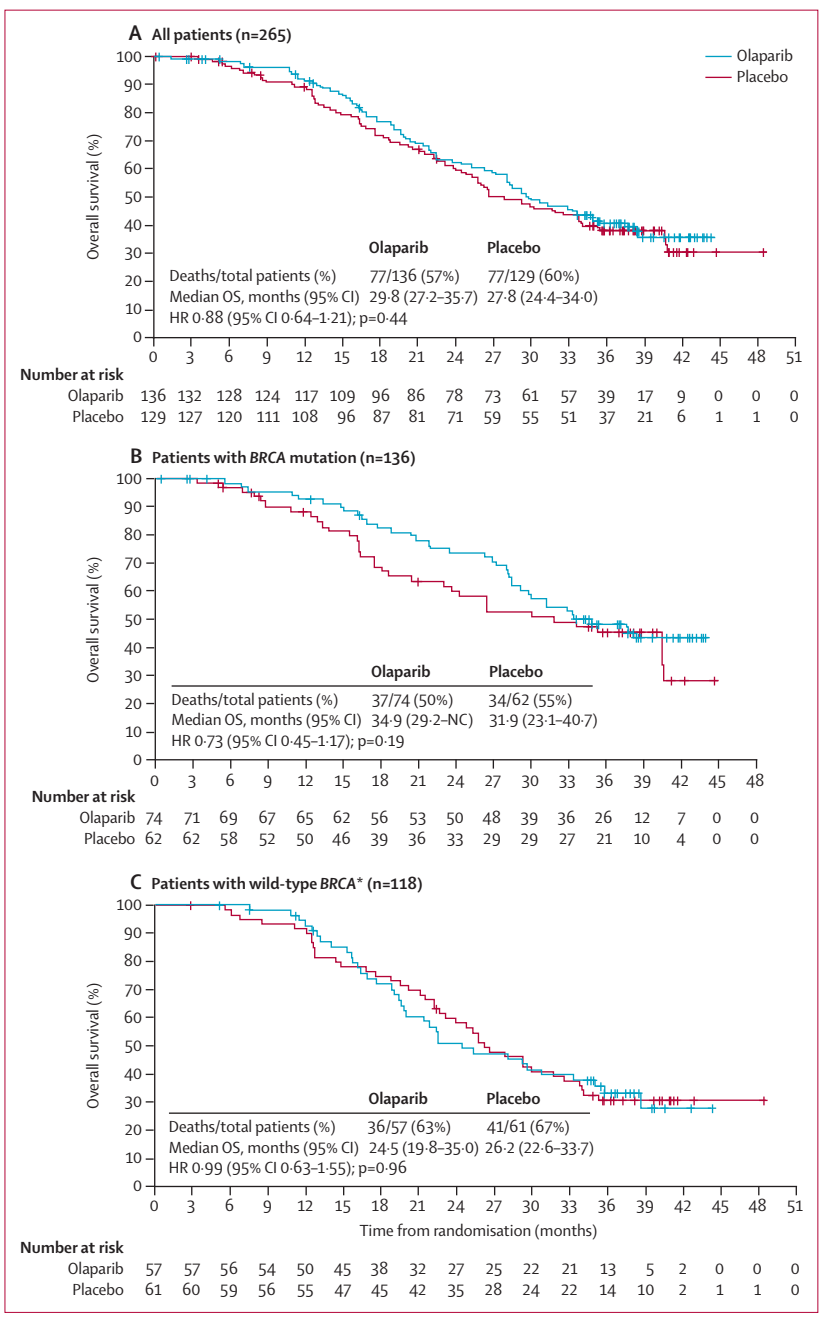

***Figure 3*: Overall survival in all patients and according to *BRCA* mutation status**
NC=not calculable. OS=overall survival. *Wild-type *BRCA* includes patients with no known *BRCA* mutation and those with a *BRCA* mutation of unknown significance.

Role of the funding source

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

Results

Between Aug 28, 2008, and Feb 9, 2010, 326 patients were enrolled. 136 of the 265 patients who met eligibility criteria were randomly assigned to receive olaparib and 129 were randomly assigned to placebo (figure 1). On the basis of local germline *BRCA* mutation testing reported on case report forms, germline *BRCA* mutation status was known for 98 (37%) of 265 patients (49 [36%] of 136 in the olaparib group *vs* 48 [37%] of 129 in the placebo group). Further germline *BRCA* or tumour *BRCA* testing (or both) was done in patients who had provided consent and samples at study entry, with germline *BRCA* status being established retrospectively for 160 (60%) patients (78 [57%] of 136 *vs* 82 [64%] of 129) and tumour *BRCA* status being established for 209 (79%) patients (108 [79%] *vs* 101 [78%]). Combining data from the case report forms and retrospective germline *BRCA* testing, germline *BRCA* mutation status was known for 210 (79%) of 265 patients (data were available from both the case report form and retrospective germline *BRCA* testing for 48 patients). Both germline *BRCA* and tumour *BRCA* mutation statuses were known for 165 (62%) of 265 patients (80 [59%] in the olaparib group *vs* 85 [66%] in the placebo group). Overall, these assessments provided *BRCA* mutation status data for 254 (96%) of 265 patients (131 [96%] in the olaparib group *vs* 123 [95%] in the placebo group), of whom 136 (54%; 74 [56%] of 131 *vs* 62 [50%] of 123) had a known deleterious or suspected deleterious *BRCA* mutation, corresponding to 51% of the overall study population (table 1). Of the 136 patients with a *BRCA* mutation, 92 (68%; 48 [65%] of 74 patients in the olaparib group *vs* 44 [71%] of 62 patients in the placebo group) had a mutation in the *BRCA1* gene only, 43 (32%; 26 [35%] *vs* 17 [27%]) had a mutation in the *BRCA2* gene only, and one patient (<1%; none *vs* one [2%]) had a mutation in both the *BRCA1* and *BRCA2* genes. Demographic and baseline characteristics were generally well balanced between patients with a *BRCA* mutation and those with wild-type *BRCA* (table 2), and between patients with a known *BRCA* status and the overall population (data not shown).

At the data cutoff for the primary PFS analysis (June 30, 2010), the median follow-up was 5·6 months (IQR 4·5–8·7). Our exploratory analysis of PFS at this cutoff point showed that in patients with a *BRCA* mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11·2 months [95% CI 8·3–not calculable] *vs* 4·3 months [3·0–5·4]; HR 0·18 [95% CI 0·10–0·31]; p<0·0001; figure 2); this benefit was greater than that previously reported in the overall population[19] (figure 2) and in the wild-type *BRCA* subgroup (7·4 months [95% CI 5·5–10·3] *vs* 5·5 months [3·7–5·6]; HR 0·54 [95% CI 0·34–0·85]; p=0·0075; figure 2). Supportive analyses of PFS in patients with *BRCA* mutations by blinded independent central review and use of the log-rank test (stratified by randomisation factors) were consistent with the investigator-assessed benefit (HR 0·22 [95% CI 0·12–0·40]; p<0·0001 for independent central review, and HR 0·18 [0·13–0·25]; p<0·0001 for log-rank test). The number of PFS and overall survival events recorded for patients with *BRCA* mutations according to *BRCA1* and *BRCA2* mutation status are shown in the appendix.

At the data cutoff for the interim overall survival analysis (Nov 26, 2012), the median follow-up was 37·3 months (IQR 34·7–40·2): 37·1 months (34·4–39·7) in the olaparib group versus 37·6 months (34·9–40·3) in the placebo group. The interim analysis of median overall survival (at 58% maturity) in the overall population did not show a significant difference between the two groups (figure 3). In patients with a *BRCA* mutation, the overall survival analysis was done at 52% maturity (71 events) and also did not show a significant difference between the two groups (figure 3). No overall survival advantage was noted in patients with wild-type *BRCA* either (figure 3).

In the overall population, median TFST was significantly longer in the olaparib group than in the placebo group, and in both the mutated *BRCA* and wild-type *BRCA* subgroups (figure 4). Significant improvements in TSST were also reported in the olaparib group versus placebo, irrespective of *BRCA* mutation status (figure 5).

Improvements in TOI, FOSI, and total FACT-O scores did not significantly differ according to treatment group in the overall population or when analysed by *BRCA* mutation status (appendix). No differences in time to worsening of TOI, FOSI, and Total FACT-O were reported (data not shown).

At the data cutoff for the interim overall survival analysis, 41 (55%) of 74 patients with a *BRCA* mutation in the olaparib group had received subsequent cancer therapy after completing randomised study treatment compared with 52 (84%) of 62 patients with a *BRCA* mutation in the placebo group. About a quarter of patients with mutated *BRCA* in the placebo group (14 [23%] of 62) went on to receive a PARP inhibitor.

As of Jan 31, 2014, 20 patients remained on study treatment (19 in the olaparib group and one in the placebo group). 24 (18%) of 136 patients had received olaparib for more than 3 years (16 [67%] patients with mutated *BRCA*; two [8%] with *BRCA* variants of unknown significance; six [25%] with no known or reported *BRCA* mutation).

The most common adverse events at the data cutoff for interim overall survival are shown in table 3, and exposure-adjusted adverse events are shown in the appendix. Nine patients (seven patients in the olaparib

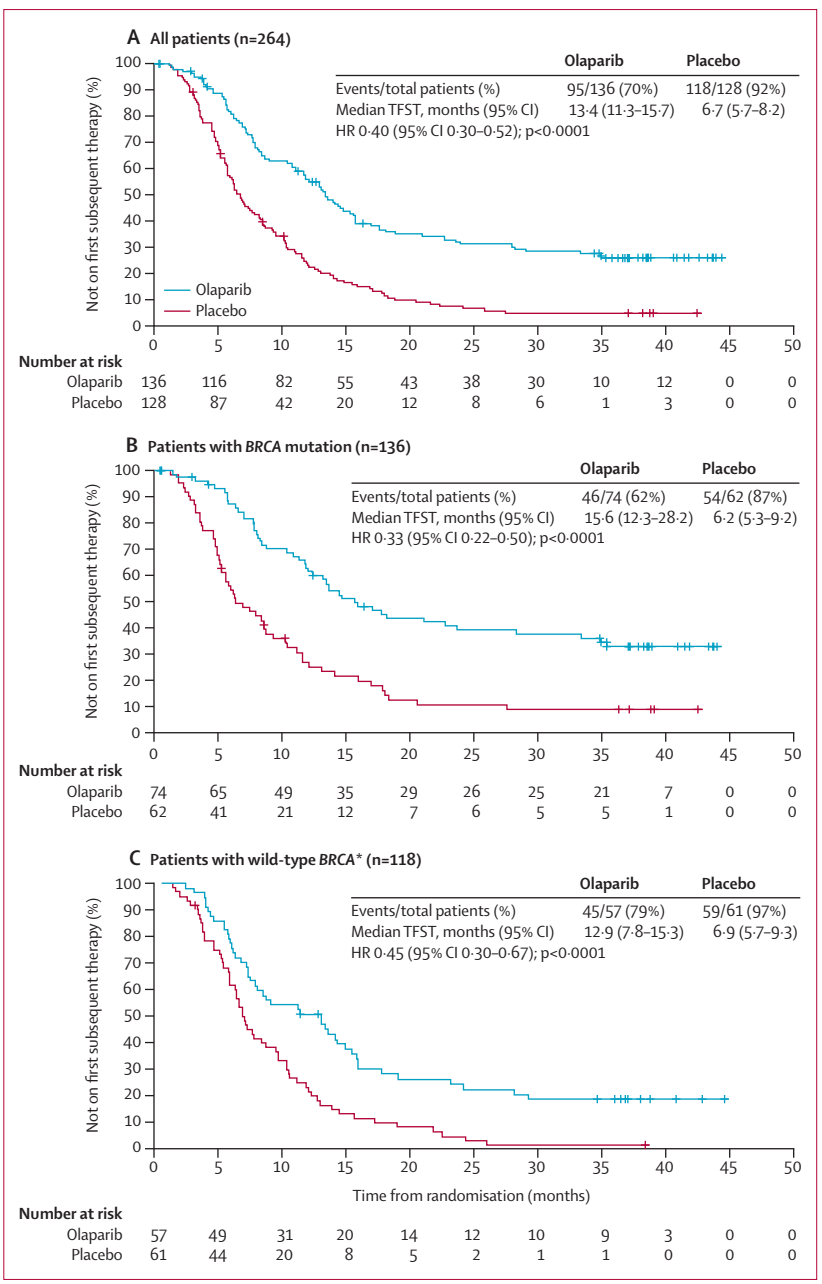

***Figure 4*: Time to first subsequent therapy or death in all patients and according to *BRCA* mutation status**
TFST=time to first subsequent therapy or death. *Wild-type *BRCA* includes patients with no known *BRCA* mutation and those with a *BRCA* mutation of unknown significance.

See Online for appendix

group and two patients in the placebo group) discontinued study treatment due to adverse events. More patients in the olaparib group than in the placebo group had dose interruptions (49 [36%] of 136 *vs* 21 [16%] of 128) or dose reductions 57 [42%] *vs* 28 [22%]): vomiting, nausea, and fatigue were the most common causes of dose interruptions or reductions in the olaparib group. Serious adverse events were reported in 25 (18%) of 136 patients in the olaparib group and 11 (9%) of 128 patients in the placebo group; the most common serious adverse event was small intestinal obstruction (two [1%] patients in the olaparib group and three [2%] in the placebo group). For both the olaparib and placebo groups, the tolerability profile reported in patients with a *BRCA* mutation was similar to the overall population (table 3). Nausea and vomiting tended to occur earlier in the olaparib group, with nausea having a longer duration in patients in the olaparib group than in those in the placebo group (median time to first occurrence 4 days [IQR 2–16] *vs* 13 days [5–30] for nausea, 46 days [11–107] *vs* 65 days [26–107] for vomiting; median duration: 2·7 months [0·5–14·9] *vs* 0·8 months [0·1–2·9] for nausea and 2 days [1–6] *vs* 2 days [1–4] for vomiting). Adverse events that were regarded as causally related to treatment by the investigator were reported in 121 (89%) of patients in the olarparib group compared with 93 (73%) of patients in the placebo group.

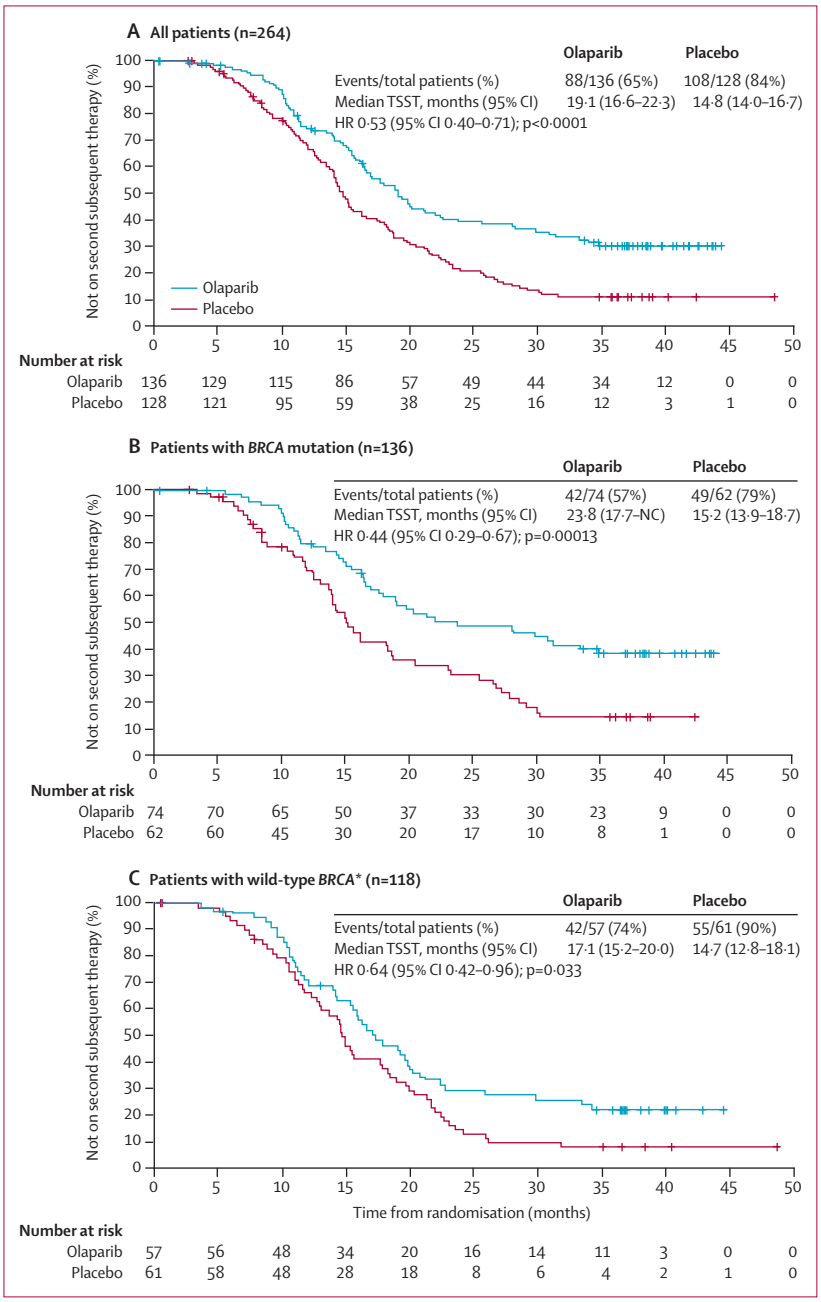

***Figure 5*: Time to second subsequent therapy or death, in all patients and according to *BRCA* mutation status**
NC=not calculable. TSST=time to second subsequent therapy or death. *Wild-type *BRCA* includes patients with no known *BRCA* mutation and those with a *BRCA* mutation of unknown significance.

Discussion

In this retrospective analysis, we postulated that the subgroup of patients with platinum-sensitive relapsed serous ovarian cancer with *BRCA*-mutated disease would be most likely to benefit from treatment with a PARP inhibitor. Initial subgroup analyses of PFS suggested promising results in patients with a germline *BRCA* mutation. To improve confidence in these results, *BRCA* mutation testing was done retrospectively in all patients who provided appropriate consent and samples: the results suggested that 51% of the overall population had a *BRCA* mutation in their germline or tumour DNA (or both), confirming that the study population was enriched for patients with *BRCA* mutations (ie, the proportion of patients with mutated *BRCA* was higher than would be expected in an unselected population of patients with high-grade ovarian cancer). Patients with a *BRCA* mutation had the greatest PFS benefit from treatment with olaparib maintenance therapy compared with placebo, with a significant reduction in risk of disease progression; this result translated into a statistically significant and clinically meaningful improvement in median PFS of 6·9 months compared with placebo. An interim overall survival analysis at 58% maturity showed no statistically significant benefit for either treatment group in the overall population. In patients with a *BRCA* mutation, the risk of death after olaparib treatment was reduced compared with placebo, but not significantly so. We cannot conclude that olaparib had a survival benefit in patients with mutated *BRCA*, but we found no evidence of a survival detriment in these patients (one-sided 90% upper CI 0·99). The final overall survival analysis will be done after 226 deaths (85% maturity).

A significant PFS benefit in favour of olaparib was also reported in patients with wild-type *BRCA* using a log-rank analysis. Although the best-described predictors of homologous recombination deficiency are mutations or rearrangements in the *BRCA* genes, other *BRCA*-related

	Overall patient population				Patients with BRCA mutation			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=74)	Placebo (n=62)
Patients with any AE	132 (97%)	119 (93%)	55 (40%)	28 (22%)	72 (97%)	58 (94%)	28 (38%)	11 (18%)
Nausea	96 (71%)	46 (36%)	3 (2%)	0	54 (73%)	20 (32%)	1 (1%)	0
Fatigue	71 (52%)	50 (39%)	10 (7%)*	4 (3%)	40 (54%)	23 (37%)	5 (7%)	1 (2%)
Vomiting	46 (34%)	18 (14%)	3 (2%)	1 (<1%)	27 (36%)	5 (8%)	2 (3%)	0
Diarrhoea	37 (27%)	31 (24%)	3 (2%)	3 (2%)	22 (30%)	12 (19%)	2 (3%)	1 (2%)
Abdominal pain	34 (25%)	34 (27%)	3 (2%)	4 (3%)*	17 (23%)	18 (29%)	0	2 (3%)
Anaemia	29 (21%)	7 (5%)	7 (5%)*	1 (<1%)	19 (26%)	3 (5%)	4 (5%)	1 (2%)
Headache	28 (21%)	16 (13%)	0	1 (<1%)	13 (18%)	10 (16%)	0	1 (2%)
Constipation	28 (21%)	14 (11%)	0	0	14 (19%)	7 (11%)	0	0
Decreased appetite	28 (21%)	17 (13%)	0	0	14 (19%)	6 (10%)	0	0
Dyspepsia	24 (18%)	11 (9%)	0	0	13 (18%)	4 (6%)	0	0
Cough	24 (18%)	13 (10%)	0	0	11 (15%)	7 (11%)	0	0
Upper abdominal pain	24 (18%)	10 (8%)	0	1 (<1%)	14 (19%)	4 (6%)	0	0
Arthralgia	23 (17%)	18 (14%)	1 (<1%)	0	11 (15%)	10 (16%)	1 (1%)	0
Back pain	22 (16%)	14 (11%)	3 (2%)	0	14 (19%)	9 (15%)	2 (3%)	0
Dysgeusia	22 (16%)	8 (6%)	0	0	14 (19%)	4 (6%)	0	0
Nasopharyngitis	20 (15%)	14 (11%)	0	0	10 (14%)	4 (6%)	0	0
Asthenia	19 (14%)	12 (9%)	1 (<1%)	0	12 (16%)	8 (13%)	1 (1%)	0
Dizziness	18 (13%)	9 (7%)	0	0	11 (15%)	3 (5%)	0	0
Abdominal distension	17 (13%)	11 (9%)	0	0	9 (12%)	6 (10%)	0	0
Neutropenia	7 (5%)	5 (4%)	5 (4%)†	1 (<1%)	5 (7%)	3 (5%)	3 (4%)*	1 (2%)

Data are number of patients (%). Grade 4 events not listed in table 3 are: increased blood amylase (n=1, olaparib group), increased blood creatine phosphokinase (n=2, olaparib group), leucopenia (n=1, olaparib group [*BRCA* mutation subgroup]), pulmonary embolism (n=1, olaparib group [*BRCA* mutation subgroup]), small intestinal obstruction (n=2, olaparib group; n=1, placebo group [*BRCA* mutation subgroup]), thrombocytopenia (n=1, olaparib group [*BRCA* mutation subgroup]). Grade 5 events not listed in table 3 are: cholestatic jaundice (n=1, olaparib group [*BRCA* mutation subgroup]), haemorrhagic stroke (n=1, olaparib group [*BRCA* mutation subgroup]). AE=adverse event. *Includes one patient with a grade 4 AE. †Includes three patients with a grade 4 AE.

***Table 3*: Adverse events (any grade) in ≥10% of patients overall and grade ≥3 events in ≥3% of patients in either treatment group**

and non-*BRCA* mechanisms exist that lead to homologous recombination deficiency, including mutations in other genes that are important in the homologous recombination deficiency pathway, or in other mechanisms including epigenetic silencing,[4,25] which cannot currently be readily identified clinically and which might explain some of the benefit identified in patients with wild-type *BRCA*. Additionally, 18 (14%) of 136 of patients with a *BRCA* mutation in this study had tumour *BRCA* mutations of somatic origin, without a reported germline *BRCA* mutation (eight in the olaparib group and ten in the placebo group). Although we could not undertake formal analyses in this small patient group, efficacy data from these patients seem to be consistent with the predicted biology that olaparib is most effective in tumours with a *BRCA* mutation, irrespective of whether the mutation originates in the germline or tumour DNA,[18,26] with fewer patients in the olaparib group reporting progression events (three [38%] of eight in the olaparib group *vs* six [60%] of ten in the placebo group) or deaths (four [50%] of eight *vs* six [60%] of ten).

No statistically significant or clinically relevant differences in health-related quality-of-life endpoints were noted between treatment groups in the overall or mutated *BRCA* populations. However, we did no formal hypothesis testing because assessment of quality of life was exploratory and not powered to detect significant differences. Additionally, patients enrolled in this study had good ECOG performance status, and quality-of-life scores were obtained up to progression when patients were still in good health. Olaparib, therefore, seemed to have no detrimental effect on patient-reported quality of life.

Because no RECIST data were obtained after the primary PFS analysis, the exploratory endpoints of TFST and TSST were analysed retrospectively. In ovarian cancer trials, the long follow-up needed to obtain sufficient overall survival data increases the

Panel: Research in context

Systematic context

We searched PubMed, and the American Society of Clinical Oncology and European Society for Medical Oncology databases, to identify publications and international meeting abstracts describing the use of PARP inhibitors in patients with ovarian cancer. We used the search terms "PARP inhibitor" and "ovarian cancer", and did not apply any language restrictions. Monotherapy with olaparib, an oral PARP inhibitor, has been shown to have clinical activity in patients with relapsed ovarian cancer.[13,16,17,19] Other PARP inhibitors, including veliparib, rucaparib, niraparib, and BMN 673, are at various stages of development for ovarian cancer.[27]

Interpretation

To our knowledge, our study is the first phase 2 trial in ovarian cancer to show that patients with *BRCA1* or *BRCA2* mutations respond preferentially to a PARP inhibitor. In this study of patients with platinum-sensitive relapsed serous ovarian cancer, maintenance treatment with olaparib 400 mg twice daily led to a significant improvement in progression-free survival when compared with placebo, with the greatest benefit reported in patients with a *BRCA* mutation. At the data cutoff for interim overall survival (52% maturity in patients with a *BRCA* mutation), we did not find a significant difference in overall survival, partly because 14 (23%) of 62 patients with mutated *BRCA* in the placebo group who were eligible for subsequent cancer therapy received a PARP inhibitor post-progression. Furthermore, the overall survival data were insufficiently mature to allow for a properly powered comparison between the treatment groups. Exploratory analyses of time to subsequent treatment or death and time to second subsequent treatment or death, indicators of the post-progression efficacy of olaparib, showed significant advantages in favour of olaparib over placebo in the overall and *BRCA*-mutation populations. These results support the hypothesis that, in patients with platinum-sensitive relapsed serous ovarian cancer, a personalised therapeutic approach based on *BRCA* mutation status could be used to maximise clinical benefit.

chance that data can be affected by post-progression therapy and patient crossover. TSST can provide supportive evidence that the reported PFS benefit is maintained after subsequent therapy. In this study, exploratory analyses of TFST showed that the PFS benefit remains with additional maturity of data. In patients with a *BRCA* mutation, the difference in median TFST between treatment groups was numerically greater than the difference in median PFS, in favour of olaparib, suggesting that the clinical pattern of relapse was different. Exploratory analyses of TSST showed that olaparib conferred a significant advantage compared with placebo, in the overall and *BRCA*-mutation populations, suggesting that the benefit provided by olaparib maintenance treatment in extending PFS persists beyond the first subsequent treatment.

A lower proportion of patients received subsequent therapies after receiving olaparib than after placebo. However, the olaparib group had less opportunity to receive a subsequent therapy up to data cutoff (Nov 26, 2012) because of generally longer PFS times. Crossover to olaparib was not permitted within the study design, but some patients were able to access PARP inhibitors in other clinical studies, after specific requests for unblinding after progression. In the *BRCA*-mutation subgroup, 23% of placebo patients received a subsequent PARP inhibitor compared with no patients in the olaparib group. This imbalance might have led to confounding of the overall survival results.

The most frequently reported adverse events in patients with a *BRCA* mutation who received olaparib were nausea, fatigue, vomiting, diarrhoea, and anaemia, which are consistent with adverse events reported in the overall population and with those reported in the initial PFS analysis. Low numbers of patients discontinued therapy due to adverse events. Overall, olaparib seems to have a tolerability profile suitable for long-term maintenance treatment.

In summary, in patients with platinum-sensitive relapsed serous ovarian cancer, maintenance therapy with olaparib 400 mg twice daily (capsule formulation) led to a greater clinical benefit in patients with a *BRCA* mutation compared with those with wild-type *BRCA*. These results support the hypothesis that tumours harbouring a homologous recombination deficiency, including *BRCA* mutations, respond preferentially to a PARP inhibitor (panel). The safety and tolerability of olaparib are appropriate for long-term maintenance therapy. These data have led to phase 3 trials assessing olaparib in patients with *BRCA* mutations and advanced ovarian cancer after first-line platinum-based chemotherapy (SOLO 1 [NCT01844986]) and in patients with *BRCA* mutations and platinum-sensitive relapsed serous ovarian cancer after two or more lines of platinum-based chemotherapy (SOLO 2 [NCT01874353]).

Contributors

JL, GR, TS, WM, and DH were responsible for the study design. JL and IV undertook the scientific literature searches. JL, PH, MF, CG, RS-F, IV, GR, TS, CLS, DM, UM, and MO obtained the data. JL, IV, WM, DH, DM, AF, SS, BD, and MO analysed the data. JL, PH, MF, CG, IV, GR, TS, CLS, WM, DH, RS-F, DM, AF, SS, BD, MO, and UM interpreted the data. All authors were responsible for writing the manuscript. JL created the figures. JCB designed and interpreted the analysis of the *BRCA* mutations in tumour tissues. All authors reviewed draft and final versions of the manuscript.

Declaration of interests

JL has received travel grants from AstraZeneca. PH has received a grant from AstraZeneca. CG has served on advisory boards for, and received travel grants from AstraZeneca. GR has served on advisory boards for AstraZeneca, Oxigene, Roche, Amgen, Boehringer Ingelheim and Clovis. CLS has received travel grants from AstraZeneca. DM has received fees from AstraZeneca for a consultant role. AF, SS, BD, MO, DH, and JCB are employees of, and own stock in AstraZeneca. All other authors declare no competing interests.

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