Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial

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Summary

Background In patients with platinum-sensitive recurrent serous ovarian cancer, maintenance monotherapy with the PARP inhibitor olaparib significantly improves progression-free survival versus placebo. We assessed the effect of maintenance olaparib on overall survival in patients with platinum-sensitive recurrent serous ovarian cancer, including those with *BRCA1* and *BRCA2* mutations (*BRCA*m).

Methods In this randomised, placebo-controlled, double-blind, phase 2 trial involving 82 sites across 16 countries, patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more courses of platinum-based chemotherapy and had responded to their latest regimen were randomly assigned (1:1) using a computer-generated sequence to receive oral maintenance olaparib (as capsules; 400 mg twice a day) or a matching placebo by an interactive voice response system. Patients were stratified by ancestry, time to progression on penultimate platinum, and response to most recent platinum. Patients and investigators were masked to treatment assignment by the use of unique identifiers generated during randomisation. The primary endpoint of the trial was progression-free survival. In this updated analysis, we present data for overall survival, a secondary endpoint, from the third data analysis after more than 5 years' follow-up (intention-to-treat population). We did the updated overall survival analysis, described in this Article at 77% data maturity, using a two-sided α of 0·95%. As the study was not powered to assess overall survival, this analysis should be regarded as descriptive and the p values are nominal. We analysed randomly assigned patients for overall survival and all patients who received at least one dose of treatment for safety. This trial is ongoing and is registered with ClinicalTrials.gov, number NCT00753545.

Findings Between Aug 28, 2008, and Feb 9, 2010, 265 patients were randomly assigned to olaparib (n=136) or placebo (n=129). 136 patients had deleterious *BRCA*m. The data cutoff for this analysis was Sept 30, 2015. An overall survival advantage was seen with maintenance olaparib versus placebo in all patients (hazard ratio [HR] 0·73 [95% CI 0·55–0·96]; nominal p=0·025, which did not meet the required threshold for statistical significance [p<0·0095]; median overall survival was 29·8 months [95% CI 26·9–35·7] for those treated with olaparib *vs* 27·8 months [24·9–33·7] for those treated with placebo), and in patients with *BRCA*m (HR 0·62 [95% CI 0·41–0·94] nominal p=0·025; 34·9 months [95% CI 29·2–54·6] *vs* 30·2 months [23·1–40·7]). The overall survival data in patients with *BRCA* wild-type were HR 0·83 (95% CI 0·55–1·24, nominal p=0·37; 24·5 months [19·8–35·0] for those treated with olaparib *vs* 26·6 months [23·1–32·5] for those treated with placebo). 11 (15%) of 74 patients with *BRCA*m received maintenance olaparib for 5 years or more. Overall, common grade 3 or worse adverse events in the olaparib and placebo groups were fatigue (11 [8%] of 136 patients *vs* four [3%] of 128) and anaemia (eight [6%] *vs* one [1%]). 30 (22%) of 136 patients in the olaparib group and 11 (9%) of 128 patients in the placebo group reported serious adverse events. In patients treated for 2 years or more, adverse events in the olaparib and placebo groups included low-grade nausea (24 [75%] of 32 patients *vs* two [40%] of five), fatigue (18 [56%] of 32 *vs* two [40%] of five), vomiting (12 [38%] of 32 *vs* zero), and anaemia (eight [25%] of 32 *vs* one [20%] of five); generally, events were initially reported during the first 2 years of treatment.

Interpretation Despite not reaching statistical significance, patients with *BRCA*-mutated platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy after platinum-based chemotherapy appeared to have longer overall survival, supporting the reported progression-free survival benefit. Clinically useful long-term exposure to olaparib was seen with no new safety signals. Taken together, these data support both the long-term clinical benefit and tolerability of maintenance olaparib in patients with *BRCA*-mutated platinum-sensitive recurrent serous ovarian cancer.

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Research in context

Evidence before this study

We searched PubMed and the databases of the American Society of Clinical Oncology, European Society for Medical Oncology, Society of Gynecological Oncology, and the European Society of Gynaecological Oncology to identify journal publications and meeting abstracts published between March 1, 2015, and March 1, 2016, that included the search terms "poly(ADP-ribose) polymerase inhibitor" or "PARP inhibitor" and "ovarian cancer". We did not use any language restrictions in our search. Olaparib is an oral poly(ADP-ribose) polymerase inhibitor, which has shown significant clinical activity and tolerability in patients with recurrent ovarian cancer and is approved in the European Union and the USA for the treatment of *BRCA1/2*-mutated advanced ovarian cancer. Other PARP inhibitors in clinical development include rucaparib, veliparib, niraparib, and talazoparib. No studies have reported an advantage in overall survival for patients with ovarian cancer treated with maintenance treatment with a PARP inhibitor compared with placebo.

Added value of this study

This is the third overall survival analysis for a phase 2, randomised trial of olaparib maintenance monotherapy in patients with platinum-sensitive recurrent serous ovarian cancer and is, to our knowledge, the first analysis to report a survival advantage for patients with ovarian cancer given a PARP inhibitor. The survival analysis was done after more than 5 years of total follow-up, at high data maturity, with an additional 3 years of follow-up since the previous analysis. The observed survival advantage might have mainly been driven by a survival benefit in the subgroup of patients with *BRCA1/2* mutations (*BRCA*m). We believe this is also the first clinically useful report of long-term exposure to a PARP inhibitor in patients with recurrent ovarian cancer, with 18 (13%) of 136 patients receiving maintenance olaparib for 5 years or more. No new safety signals were reported and the long-term safety data were consistent with the known safety profile for olaparib monotherapy.

Implications of all of the available evidence

We have previously reported data from this phase 2 study that showed a significant improvement in progression-free survival with maintenance olaparib, with the greatest benefit seen in patients with *BRCA*m. Exploratory analyses have also shown a significant improvement in time to first and second subsequent therapy or death with olaparib compared with placebo. To our knowledge, this is the first analysis to show survival data in patients with recurrent *BRCA* mutated ovarian cancer that are consistent with previously reported benefits in progression-free survival and time to first and second subsequent therapy or death. Taken together, the available data support the long-term benefit and tolerability of maintenance olaparib in patients with *BRCA*m and platinum-sensitive recurrent serous ovarian cancer.

Introduction

Ovarian cancer is the fifth most common type of cancer for women in developed countries.[1,2] About 70% of patients relapse within 3 years of completing first-line chemotherapy and the mean 5 year survival rate in Europe is low when compared with other tumour types (about 38%).[3–5] Overall, ovarian cancer is the sixth highest cause of cancer-related deaths for women in high-income countries.[1,2]

Olaparib (Lynparza) is an oral poly(ADP-ribose) polymerase (PARP) inhibitor that has shown significant clinical activity in ovarian cancer, particularly in tumours that have mutations in *BRCA1* and *BRCA2* (*BRCA*m).[6–8] Olaparib traps PARP at sites of DNA damage, blocking base-excision repair and resulting in the collapse of DNA replication forks and the accumulation of DNA double-strand breaks.[9] Induced synthetic lethality is seen with olaparib in tumours that are deficient in homologous recombination repair pathways, such as those with *BRCA*m.[10,11]

Previously, we reported data from a randomised, double-blind, phase 2 trial (NCT00753545, D0810C00019 [Study 19]) that showed a significant improvement in progression-free survival for patients with platinum-sensitive, recurrent, serous ovarian cancer who received olaparib maintenance monotherapy, compared with placebo (hazard ratio [HR] 0·35 [95% CI 0·25–0·49]; p<0·0001).[6,7] A pre-planned analysis of the retrospectively identified *BRCA*-mutated subgroup showed that patients with *BRCA*m derived the greatest progression-free survival benefit from olaparib (HR 0·18 [0·10–0·31]; p<0·0001).[7] A significant improvement in time to first subsequent therapy or death and time to second subsequent therapy or death was also reported with maintenance olaparib compared with placebo.[7] On the basis of these data, olaparib (as capsules; 400 mg twice a day) was approved in the European Union as maintenance treatment for patients with platinum-sensitive, relapsed, *BRCA*-mutated ovarian cancer.[12] Olaparib is also approved in the USA as monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer.[13] This indication was based on data from another phase 2 study (NCT01078662, D0810C00042 [Study 42]).[8]

Two interim analyses of overall survival from Study 19 have previously been done, at 38% data maturity (HR 0·94 [95% CI 0·63–1·39]; p=0·75) and 58% data maturity (0·88 [0·64–1·21]; p=0·44) in the overall study population.[6,7] In this Article, we present an updated descriptive overall survival analysis following the deaths of 203 (77%) of 265 patients in this study, with an additional 3 years of overall survival follow-up since the previous analysis. We assessed the effect of maintenance olaparib on overall survival in women with platinum-sensitive recurrent serous ovarian cancer.

Methods

Study design and participants

Study 19 was a randomised, double-blind, placebo-controlled, multicentre, phase 2 trial, involving 82 sites across 16 countries (appendix p 10).

Eligible patients were aged 18 years or older, with recurrent ovarian, fallopian tube, or primary peritoneal cancer that had high-grade (grade 2 or 3) serous features or a serous component and was platinum-sensitive (no disease progression in the first 6 months after the last dose of the penultimate line of platinum-based chemotherapy). Patients must have received at least two previous courses of platinum-based chemotherapy and had to have shown a complete or partial response to their most recent regimen according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 or Gynecological Cancer InterGroup criteria. Additional eligibility criteria have been described previously.[6] Primary exclusion criteria included low-grade ovarian carcinoma (grade 1), second primary cancer, previous treatment with PARP inhibitors (including olaparib), receipt of any chemotherapy or radiotherapy within 2 weeks from the last dose before study entry, recent major surgery, and poor general health. Patients were recruited at centres globally in accordance with the eligibility criteria. Known *BRCA*m status was not required for eligibility, but was established via case report forms documenting previous local germline *BRCA* testing, or via retrospective germline *BRCA* testing (Integrated BRACAnalysis assay [Myriad Genetics, Salt Lake City, UT, USA]) or tumour *BRCA* testing (next-generation sequencing [Foundation Medicine, Cambridge, MA, USA]), as described previously.[7] Those patients whose *BRCA*m status was established during the study provided consent and samples at study entry.

All patients provided written informed consent. The institutional review boards or independent ethics committees of all investigational sites approved the protocol. The study was done in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics.[14]

Randomisation and masking

Patients were randomly assigned (1:1) to receive olaparib or placebo within 8 weeks following completion of their most recent platinum-based regimen. An interactive voice response system assigned patients to their treatment using a randomisation scheme generated by a computer program (AstraZeneca randomisation and unblinding system). The investigator who enrolled patients contacted an interactive voice response system centralised randomisation office by telephone for allocation of randomised treatment. Randomisation was stratified by ancestry (Jewish *vs* non-Jewish), time to progression from completion of penultimate platinum-based regimen (6–12 months *vs* >12 months), and response to most recent platinum-based regimen (complete *vs* partial response). Randomisation was stratified by ancestry to avoid imbalance caused by the substantially higher frequency of *BRCA*m in Jewish populations than in the general population.

Treatment assignment was masked from patients and from anyone administering interventions, assessing outcomes, or analysing data, by the use of unique identifiers generated during randomisation. Olaparib and placebo capsules were identical in appearance and packaging. Most patients in both treatment groups continued on treatment until disease progression as per protocol, indicating that investigators and patients were unaware of treatment allocation.

See Online for appendix

Procedures

Patients received oral olaparib maintenance monotherapy at 400 mg twice a day (capsules; manufactured by AstraZeneca, Macclesfield, UK, or Lonza, Visp, Switzerland) or matching placebo. Treatment continued until disease progression, provided that toxicities were manageable. After progression, patients could continue on study treatment if deemed appropriate by the investigator. Crossover between treatment groups within the study was not allowed. Dose modifications that were specified for toxicity management have been described previously.[6] Treatment was interrupted for any event of Common Terminology Criteria for Adverse Events grade 3 or 4 that was deemed to be related to treatment. If the toxicity resolved entirely or to a grade 1 level, treatment was restarted with a reduction in the dose to 200 mg or 100 mg twice a day. If the event did not resolve within 4 weeks after treatment, or if two previous treatment interruptions had occurred, the patient was withdrawn from the study.

We assessed tumours using CT scans or MRI every 12 weeks until week 60 and every 24 weeks thereafter until objective disease progression, unless patients withdrew consent. RECIST data were not collected after the primary data cutoff (June 30, 2010). We monitored patients for overall survival, with follow-up every 12 weeks after discontinuation of treatment. We monitored safety and tolerability of patients remaining on study treatment by recording adverse events, physical examination results, vital signs, and laboratory findings. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0.

For the **protocol** see http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_7111&studyid=242&filename=d0810c00019-revised-csp-8_Redacted.pdf

Outcomes

We have previously reported data for progression-free survival, which represented the primary endpoint for this study.[6] Overall survival was a secondary endpoint, but represents the main outcome for this descriptive analysis. We also assessed safety, tolerability, time to first subsequent therapy or death, and time to second subsequent therapy or death. Additional endpoints have been described previously or will be reported separately.[6,7]

Statistical analysis

Study 19 was powered to ensure a sufficient number of progression-free survival events in the overall study population.[7] The primary analysis was done when at least 137 progression-free survival events had occurred. Assuming that the true HR for progression or death with olaparib versus placebo was 0·75 (corresponding to a 33% increase in the median duration of progression-free survival, from 9 months to 12 months after randomisation), and that the overall type I error was 20% (one-sided test), the analysis would have 80% power to show a significant difference in favour of olaparib (one-sided p<0·20). We analysed overall survival on an intention-to-treat basis, but the study was not powered for overall survival analysis. The analysis set for overall survival included all patients randomly assigned to a group and the analysis sets for safety, time to first subsequent therapy or death, and time to second subsequent therapy or death included all patients who received at least one dose of treatment. Other than for overall survival, we made no adjustments for multiplicity introduced by analysis of multiple endpoints (time to first subsequent therapy or death and time to second subsequent therapy or death). We made no adjustments for analyses within the *BRCA*-mutated or *BRCA* wild-type (*BRCA*wt) subgroups. Two previous analyses of overall survival have been done, at 38% data maturity (data cutoff: Oct 31, 2011; two-sided α=0·1%) and 58% data maturity (data cutoff: Nov 26, 2012; two-sided α=3%).[6,7] We did the updated overall survival analysis after more than 5 years' total follow-up described in this Article at 77% data maturity, using a two-sided α of 0·95%. As the study was not powered to assess overall survival, this analysis should be regarded as descriptive and the p values are nominal. Exploratory analyses of time to first subsequent therapy or death (at 80% data maturity) and time to second subsequent therapy or death (at 74% data maturity) were previously done at the 2012 data cutoff.[7]

We analysed overall survival, time to first subsequent therapy or death, and time to second subsequent therapy or death using a Cox proportional hazards model, adjusted by stratification criteria. We did restricted means analyses for the overall survival data using the pseudovalues method, as previously described.[15] These analyses were done in the intention-to-treat population. All analyses used SAS version 8.2, except the restricted means analyses, which used the Comprehensive R Archive Network "pseudo" software. The study was overseen by a data monitoring committee. This study is registered with ClinicalTrials.gov, number NCT00753545.

Role of the funding source

The corresponding author (JAL) designed the study in collaboration with the sponsor, AstraZeneca. AstraZeneca authors (AF, SS, PR, EL, DH, and MAS) collected and analysed the data and had a role in data interpretation and manuscript writing. All authors had access to the raw data. The decision to submit the manuscript for publication was made by all authors. The corresponding

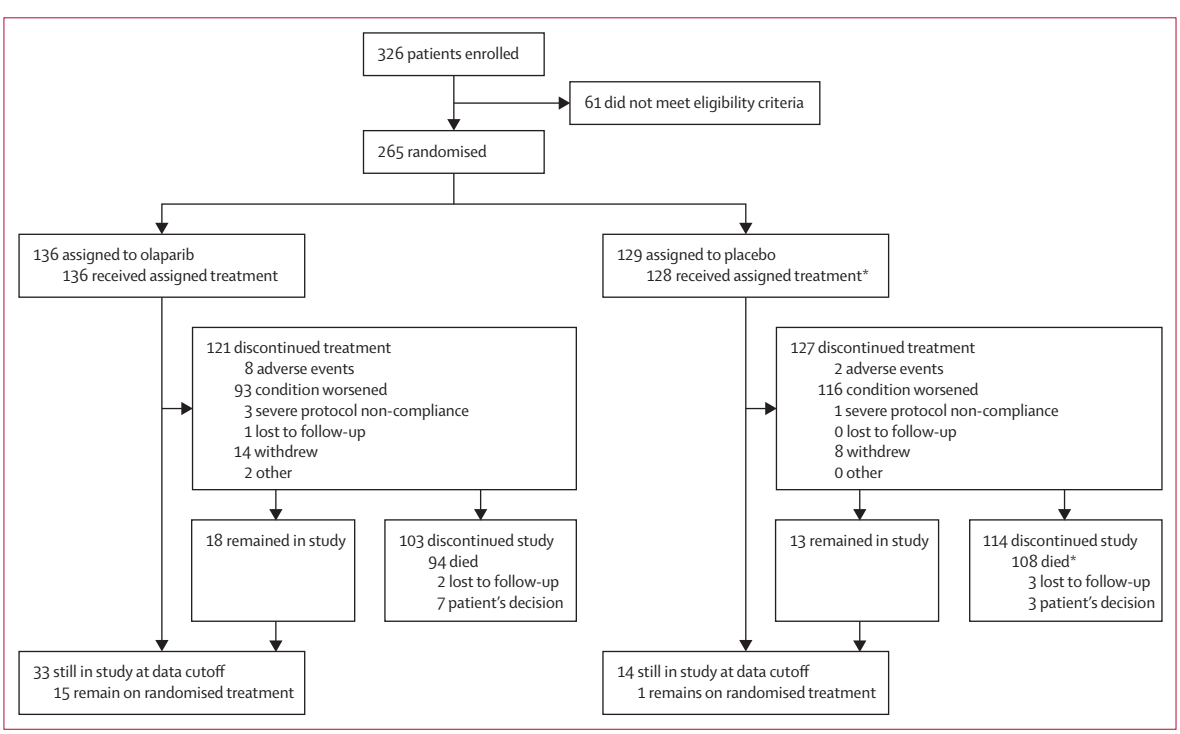

Figure 1: **Enrolment, randomisation, and treatment status at the third analysis of overall survival in Study 19**
Data cutoff was on Sept 30, 2015. *One patient was randomly assigned to the placebo group, but withdrew consent and withdrew from the study without receiving treatment, who subsequently died but is not included in the number of deaths for patients who discontinued the study after being treated with placebo.

author (JAL) had full access to all of the data and the final responsibility to submit for publication.

Results

Patient enrolment occurred between Aug 28, 2008, and Feb 9, 2010. Of the 326 patients who enrolled, 265 (81%) met the eligibility criteria; 136 of these patients were randomly assigned to olaparib and 129 were randomly assigned to placebo (figure 1). *BRCA*m status was established for 254 (96%) of 265 patients in the overall study population (olaparib [n=131]; placebo [n=123]), of whom 136 had a known or suspected deleterious *BRCA*m (olaparib [n=74]; placebo [n=62]).

Patient demographics and baseline characteristics were generally well balanced for the overall study population and *BRCA*-mutated and *BRCA*wt subgroups (table 1). The efficacy analysis set included all 265 patients randomly assigned to a group. One patient who was randomly assigned to placebo withdrew consent and withdrew from the study without receiving treatment; therefore, the analysis sets for safety, time to first subsequent therapy or death, and time to second subsequent therapy or death included the 264 patients who were treated.

The data cutoff for this updated overall survival analysis was Sept 30, 2015 (77% overall survival data maturity). At this data cutoff, the median follow-up for overall survival was 71·0 months (IQR 67·8–72·9) for the overall study population (olaparib: 71·0 months [IQR 68·5–72·7] *vs* placebo: 70·8 months [38·2–73·0]). This updated analysis represents an additional 3 years of follow-up since the previously reported overall survival.[7] The Cox proportional hazards analyses suggest an overall survival advantage for patients who received olaparib maintenance monotherapy compared with patients who received placebo (HR 0·73 [95% CI 0·55–0·96]; nominal p=0·025; figure 2), which did not meet the required threshold for statistical significance (p<0·0095). The *BRCA*-mutated subgroup data (70% overall survival data maturity) suggest an overall survival advantage for patients with *BRCA*m who were given maintenance olaparib (HR 0·62 [95% CI 0·41–0·94]; nominal p=0·025; figure 2). The overall survival data for the *BRCA*wt subgroup (84% overall survival data maturity) were HR 0·83 (95% CI 0·55–1·24; nominal p=0·37; figure 2).

Most patients in the *BRCA*-mutated subgroup had germline *BRCA*m (g*BRCA*m), but 20 (15%) of 136 (olaparib group [n=10], placebo group [n=10]) had somatic *BRCA*m (s*BRCA*m) only. We previously reported 18 patients with s*BRCA*m in Study 19, on the basis of data from tumour and blood testing, and 22 patients with tumour *BRCA*m for whom no blood testing data were available.[7] Subsequently, we used an algorithm to distinguish g*BRCA*m and s*BRCA*m based solely on tumour sequencing data and identified the 20 patients with s*BRCA*m; this group includes six of the 22 patients for whom blood testing data were unavailable and 14 of the original 18 patients with s*BRCA*m.[16] Four patients from the previously reported subgroup were therefore not included, three as a result of likely incomplete case report form-reported local blood-based g*BRCA*m tests and one as a result of discordant variant results, which revealed that the blood and tumour samples were from different individuals. We calculated the

	Overall study population (n=265)		Patients with *BRCA*m (n=136)†		Patients with *BRCA*wt‡ (n=118)†	
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=61)
Age (years)	58·0 (21–89)	59·0 (33–84)	57·5 (38–89)	55·0 (33–84)	62·0 (21–80)	63·0 (49–79)
Ancestry§						
Non-Jewish	115 (85%)	112 (87%)	60 (81%)	48 (77%)	51 (89%)	58 (95%)
Jewish	21 (15%)	17 (13%)	14 (19%)	14 (23%)	6 (11%)	3 (5%)
Number of previous lines of chemotherapy						
2	59 (43%)	63 (49%)	26 (35%)	28 (45%)	32 (56%)	35 (57%)
3	43 (32%)	34 (26%)	28 (38%)	18 (29%)	14 (25%)	14 (23%)
4	18 (13%)	19 (15%)	9 (12%)	10 (16%)	6 (11%)	9 (15%)
≥5	16 (12%)	13 (10%)	11 (15%)	6 (10%)	5 (9%)	3 (5%)
Primary tumour location						
Ovary	119 (88%)	109 (84%)	65 (88%)	54 (87%)	50 (88%)	49 (80%)
Fallopian tube or primary peritoneal	17 (13%)	20 (16%)	9 (12%)	8 (13%)	7 (12%)	12 (20%)
Time to progression after completion of penultimate platinum-based regimen						
>6 to ≤12 months	53 (39%)	54 (42%)	28 (38%)	26 (42%)	23 (40%)	24 (39%)
>12 months	83 (61%)	75 (58%)	46 (62%)	36 (58%)	34 (60%)	37 (61%)
Objective response to most recent platinum-based regimen						
Complete response	57 (42%)	63 (49%)	36 (49%)	34 (55%)	20 (35%)	25 (41%)
Partial response	79 (58%)	66 (51%)	38 (51%)	28 (45%)	37 (65%)	36 (59%)

Data are median (range) or n (%). *These baseline data have also been described previously.[6,7] †Data were not available for all randomised patients. ‡The *BRCA*wt subgroup included patients without detected *BRCA*m and patients with *BRCA*m of unknown significance. §Ancestry was self-reported.

Table 1: **Patient demographics and baseline characteristics***

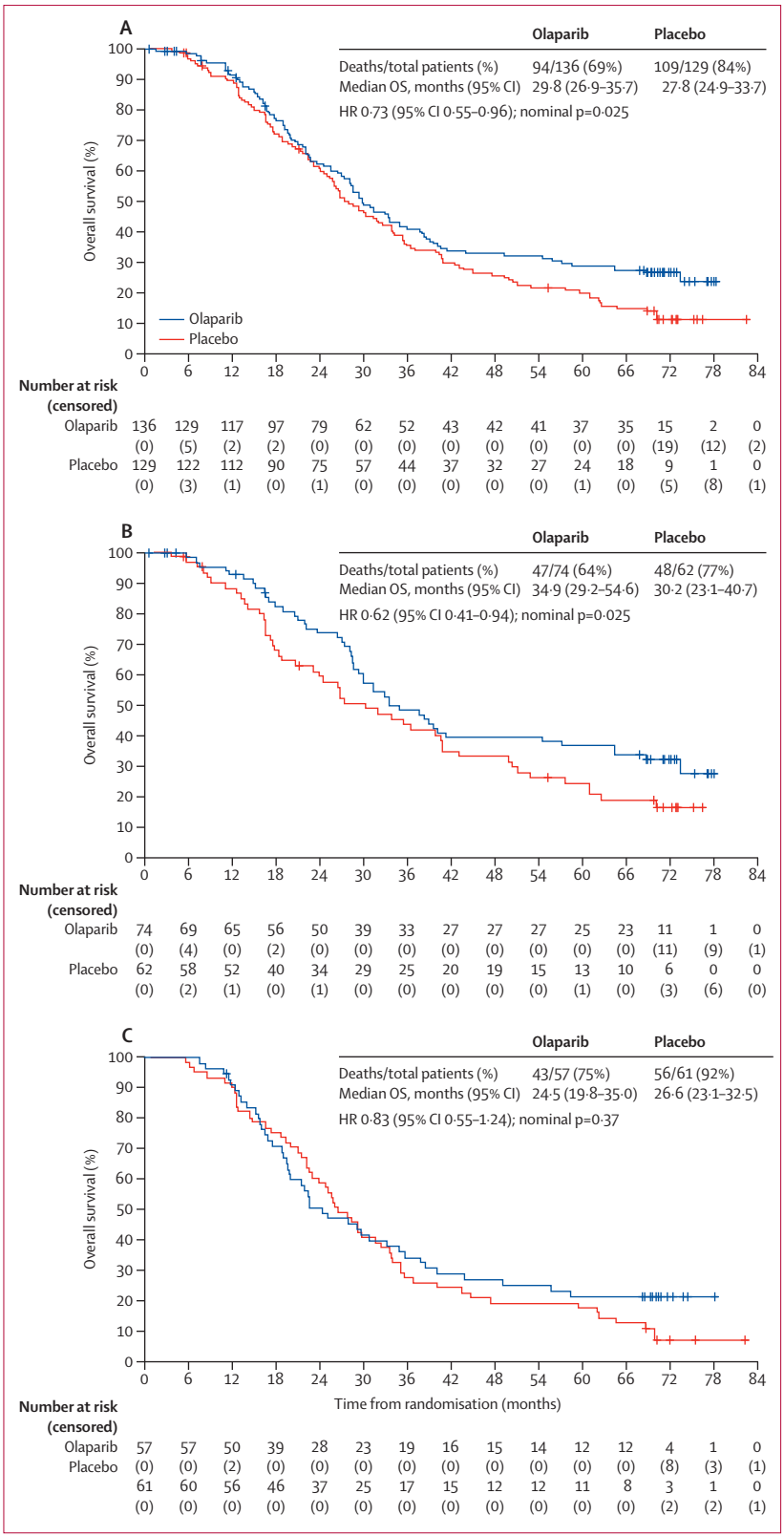

***Figure 2*: Overall survival in all patients and according to *BRCA*m status**
(A) All patients (n=265). (B) Patients with *BRCA*m (n=136). (C) Patients with *BRCA*wt (n=118). OS=overall survival.

overall survival for the overall, *BRCA*-mutated, g*BRCA*-mutated, and s*BRCA*-mutated populations (figure 3). The s*BRCA*-mutated subgroup data are not inconsistent with those from the other subgroups, but there are too few events in this group to draw conclusions. We also calculated the overall survival for patients with mutations in *BRCA1* and those with mutations in *BRCA2* (figure 3) and drew Kaplan-Meier survival curves (appendix p 2).

Formal tests of the proportionality of the hazards, using the methods of Grambsch and Therneau,[17] suggested that there was insufficient evidence to dismiss the proportional hazards assumption in either the overall population (p=0·19) or the *BRCA*-mutated subgroup (p=0·70). However, we also did restricted means analyses to enhance our understanding of average patient survival and the effect of study treatment (table 2). Results of the restricted means analysis are supportive of the overall survival advantage with olaparib. Additionally, we calculated the restricted means data using two alternative methods (appendix p 3), which gave similar estimates for the restricted mean overall survival. Log-rank test analyses were also consistent with the Cox proportional hazards analysis (table 2).

We did updated exploratory analyses for time to first subsequent therapy or death, and time to second subsequent therapy or death; since the previous analysis, the data maturity had increased from 80% to 86% for time to first subsequent therapy or death, and from 74% to 84% for time to second subsequent therapy or death.[7] The median follow-up for time to first subsequent therapy or death was 70·8 months (IQR 12·6–72·7) for the overall population (olaparib: 70·8 months [14·6–72·6] *vs* placebo: 39·0 months [4·1–74·7]); median follow-up for time to second subsequent therapy or death was 70·5 months (11·2–72·8) for the overall population (olaparib: 70·9 months [16·4–72·6] *vs* placebo: 7·8 months [5·2–72·8]). Median time to first subsequent therapy or death, and time to second subsequent therapy or death were both significantly prolonged with olaparib compared with placebo, in the overall study population and *BRCA*-mutated and *BRCA*wt subgroups (figure 4).

At the data cutoff for this updated overall survival analysis, 15 (11%) of the 136 patients assigned to olaparib were continuing to receive the drug, eight of whom had a *BRCA*m. Within this group, the initial dose (olaparib 400 mg twice a day) was being received by nine patients (five with *BRCA*m) and a reduced dose of 200 mg twice a day was being received by six patients (three with *BRCA*m), four of whom had a dose reduction owing to adverse events. One (1%) patient (with a *BRCA*m) of 129 patients in the overall population assigned to placebo group was still receiving placebo at the data cutoff in 2015. Overall, 18 (13%) of 136 patients had received olaparib for 5 years or more (table 3): 11 of these patients had *BRCA*m (15% of 74 patients with *BRCA*m) and seven were in the *BRCA*wt subgroup (12% of 57 patients with *BRCA*wt). We present baseline characteristics for the patients who received study treatment for 5 years or more (table 4).

Subsequent cancer treatments had been received by 89 (65%) of 136 patients from the olaparib group (45 [61%] of 74 patients with *BRCA*m) and 111 (86%) of 129 patients from the placebo group (55 [89%] of 62 patients with *BRCA*m). From the placebo group, 17 (13%) of 129 patients had received post-discontinuation PARP inhibitor treatment, of whom 14 (23%) of 62 patients had *BRCA*m. These data include one additional patient who had received subsequent PARP inhibitor treatment since the previous data cutoff (Nov 26, 2012). No patients from the olaparib group had received subsequent PARP inhibitor treatment.

There were no new safety findings in the overall study population when compared with those that have previously been reported.[6,7] Of the 32 patients who received olaparib for 2 years or more, 30 (94%) reported at least one adverse event, with 15 (47%) reporting adverse events of grade 3 or worse. For patients who received olaparib treatment for 2 years or more, the frequencies of previously reported common adverse events, such as low-grade nausea (olaparib: 24 [75%] of 32 patients *vs* placebo: two [40%] of five patients), fatigue (18 [56%] of 32 *vs* two [40%] of five), vomiting (12 [38%] of 32 *vs* no patients), and anaemia (eight [25%] of 32 *vs* one [20%] of five), were consistent with the frequencies that were previously reported in the overall population (appendix pp 4, 6–7). In general, these adverse events were initially reported during the first 2 years of treatment. 21 patients with *BRCA*-mutated ovarian cancer received olaparib for 2 years or more and this subgroup had a similar safety profile to the overall group of 32 patients. All five patients who received placebo for 2 years or more reported at least one adverse event; one (20%) of whom reported adverse events of grade 3 or worse. Of the 32 patients who received olaparib for 2 years or more, 23 (72%) reported adverse events after 2 years, with eight (25%), reporting adverse events of grade 3 or worse (appendix pp 5, 8–9). Four of the five patients who received placebo for 2 years or more reported adverse events after 2 years; none reported adverse events of grade 3 or worse. 15 (47%) of the 32 patients who received olaparib for 2 years or more had dose reductions (eight [25%] because of adverse events). One (20%) of the five patients in the placebo group who had received placebo for 2 years or more had dose reductions that were not related to adverse events. Three (9%) patients who had received olaparib for 2 years or more discontinued treatment because of adverse events, which were pharyngitis and pancytopenia (two adverse events in one patient), and squamous-cell carcinoma of the oral cavity and bronchiectasis (each in one patient). None of the patients who received placebo for 2 years or more discontinued because of adverse events.

In the overall study population, the most common grade 3 or worse adverse events in the olaparib and placebo groups were fatigue (11 [8%] of 136 patients *vs* four [3%] of 128) and anaemia (eight [6%] of 136 patients *vs* one [1%] of 128). Overall, 59 (43%) of 136 patients from the olaparib group and 29 (23%) of 128 patients from the placebo group had dose reductions. Dose reductions because of adverse events were reported in 34 (25%) of 136 patients in the olaparib group and five (4%) of 128 patients in the placebo group. Adverse events that led to discontinuation of treatment were reported for eight (6%) of 136 patients from the olaparib group and two (2%) of 128 patients from the placebo group; all of these adverse events were deemed to be related to treatment. For the olaparib group, in addition to the adverse events that led to late discontinuation after 2 years of treatment, the other adverse events resulting in discontinuation were palpitations and myalgia (two adverse events in one patient), and herpes zoster, nausea, erythematous rash, and haemorrhagic stroke (each in one patient). In the placebo group, the adverse events resulting in discontinuation of treatment were pruritic rash and nausea (each in one patient). 30 (22%) of 136 patients in the olaparib group and 11 (9%) of 128 patients in the placebo group reported serious adverse events. There were no additional reports of adverse events resulting in death at the 2015 data cutoff compared with the 2012 data cutoff, at which one patient had died solely from adverse events (haemorrhagic stroke and thrombocytopenia, deemed to be treatment related). Overall, 202 patients in the safety

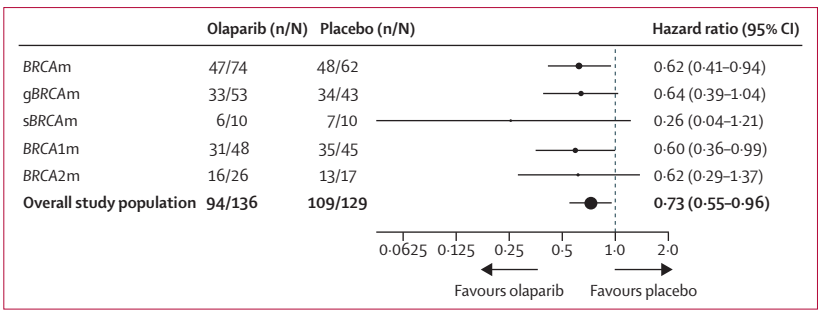

Figure 3: **Summary of the Cox proportional hazards analysis of overall survival in the overall study population and different *BRCA*m subgroups**
*BRCA1*m=mutation in *BRCA1* only. *BRCA2*m=mutation in *BRCA2* only. g*BRCA*m=germline *BRCA* mutation. s*BRCA*m=somatic *BRCA* mutation.

	Overall study population (n=265)	Patients with *BRCA*m (n=136)
Median OS (months)		
Olaparib	29·8 (26·9 to 35·7)*	34·9 (29·2 to 54·6)†
Placebo	27·8 (24·9 to 33·7)‡	30·2 (23·1 to 40·7)§
Difference in median OS (months)	2·0	4·7
Cox proportional hazards analysis (hazard ratio)	0·73 (0·55 to 0·96)	0·62 (0·41 to 0·94)
Log-rank test (hazard ratio)	0·72 (0·54 to 0·95)	0·61 (0·39 to 0·95)
Restricted mean OS (months)¶		
Olaparib	40·1*	44·3†
Placebo	34·9‡	36·9§
Difference in restricted mean OS (months)	5·2 (–0·8 to 11·2)	7·5 (–1·1 to 16·0)

Data in parentheses are 95% CI. OS=overall survival. *n=136. †n=74. ‡n=129. §n=62. ¶Differences were calculated before rounding.

Table 2: **Overall survival using a Cox proportional hazards analysis, a restricted-means analysis, and a log-rank test**

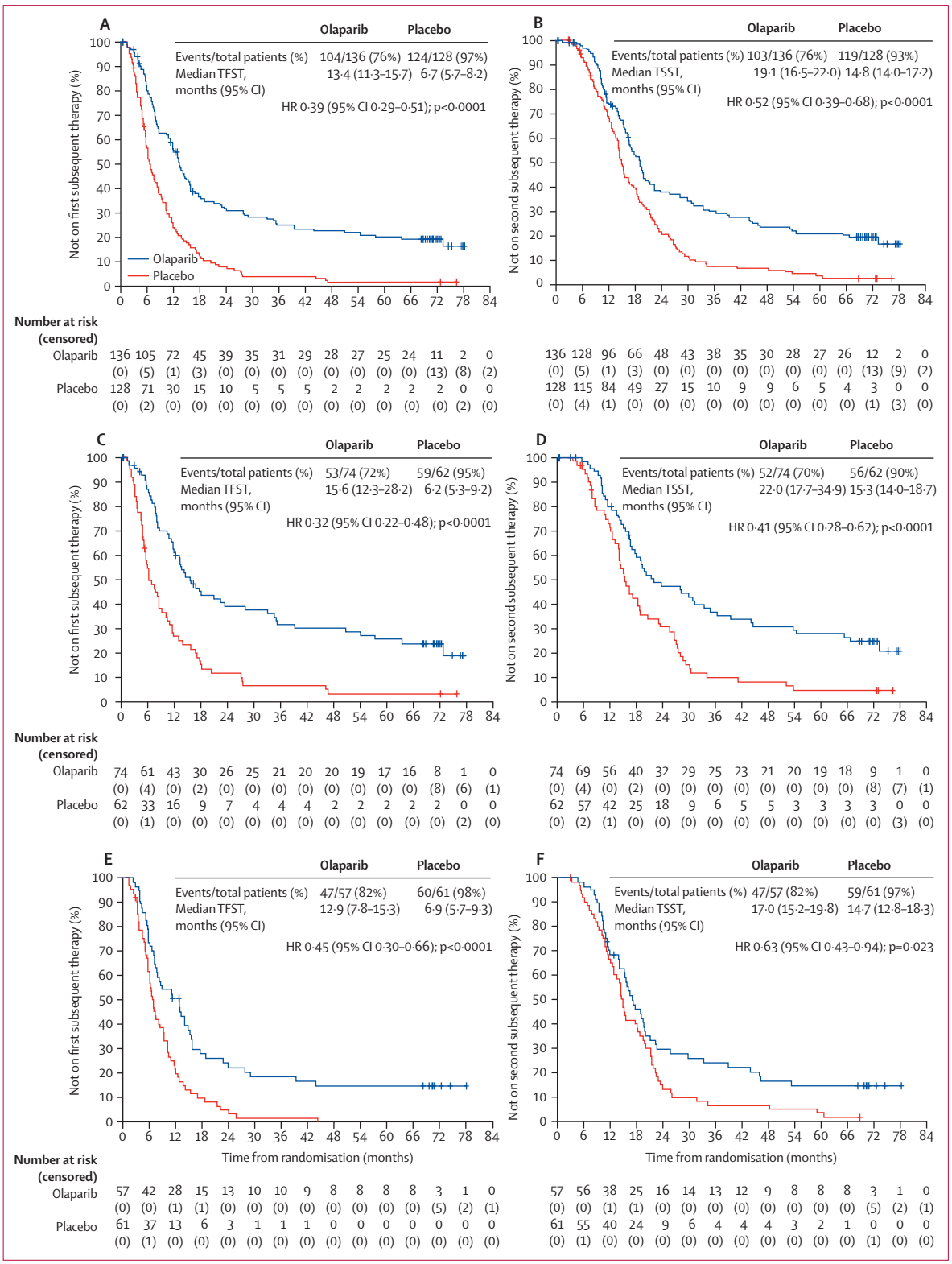

Figure 4: **Time to first subsequent treatment or death and time to second subsequent treatment or death in all patients and according to *BRCA*m status**
(A) TFST in all patients (n=264). (B) TSST in all patients (n=264). (C) TFST in patients with *BRCA*m (n=136). (D) TSST in patients with *BRCA*m (n=136). (E) TFST in patients with *BRCA*wt (n=118). (F) TSST in patients with *BRCA*wt (n=118). TFST=time to first subsequent treatment or death. HR=hazard ratio. TSST=time to second subsequent treatment or death. *BRCA*m=*BRCA1* and *BRCA2* mutations. *BRCA*wt=*BRCA* wild-type.

analysis set had died at the 2015 data cutoff (olaparib group [n=94] *vs* placebo group [n=108]). In the olaparib group, 83 patients died only from the disease under investigation; one patient had adverse events leading to death (haemorrhagic stroke and thrombocytopenia); one patient died from a combination of their underlying disease and an adverse event (myelodysplastic syndrome); and nine patients died from other causes (cardiac failure [n=1], euthanasia [n=1], septic shock [n=1], cerebrovascular disorder [n=1], cerebral haemorrhage [n=1], or unknown [n=4]). In the placebo group, 99 patients died only from the disease under investigation and nine patients died from other causes (acute renal failure and pneumonia [n=1], pulmonary embolism [n=1], cardiopulmonary failure [n=1], septic shock due to faecaloma [n=1], ovarian cancer [n=1], or unknown [n=4]). In total, three cases of myelodysplastic syndromes or acute myeloid leukaemia (two in the olaparib group and one in the placebo group) have been reported. All three of the patients who reported myelodysplastic syndromes or acute myeloid leukaemia had received two previous lines of chemotherapy. Two of these patients had received olaparib maintenance monotherapy for 57 months and 10 months, respectively, and one had received placebo for 44 months.

Discussion

These updated descriptive overall survival analyses suggest an overall survival advantage for patients with platinum-sensitive recurrent serous ovarian cancer who received olaparib maintenance monotherapy compared with placebo in Study 19. The overall survival data support the previously published results from Study 19, which showed that progression-free survival, time to first subsequent therapy or death, and time to second subsequent therapy or death are significantly prolonged with olaparib, particularly in patients with *BRCA*m.[6,7] Although a statistically significant improvement in overall survival was not shown, we observed that patients given olaparib seemed to gain a beneficial survival effect (HR 0·73). This beneficial effect was mainly driven by the treatment effect in the *BRCA*-mutated subgroup, who received the greatest overall survival benefit from olaparib (HR 0·62, [95% CI 0·41–0·94]; nominal p=0·025). The Kaplan-Meier survival curves for the two treatment groups in the overall study population begin to separate from about 42 months after randomisation (figure 2). This observation might be a result of the heterogeneous nature of the overall population and the different treatment effect in patients with *BRCA*m or *BRCA*wt. Patients with *BRCA*m receive the most benefit from olaparib and have a better prognosis than patients with *BRCA*wt, so the proportion of patients at risk with *BRCA*m to those with *BRCA*wt increases over time. At the tail end of the survival curve for the overall population, there are therefore fewer patients with *BRCA*wt at risk and as such the treatment effect in patients with *BRCA*m is less diluted, resulting in the observed separation. The separation of the survival curves at the tail end also suggests that the recorded overall survival advantage was affected by a group of patients who received long-term olaparib maintenance monotherapy. Biological factors that can predict these long-term responders are being investigated.[18]

	Overall study population (n=264)		Patients with *BRCA*m (n=136)	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)
≥1 year	54 (40%)	14 (11%)	34 (46%)	8 (13%)
≥2 years	32 (24%)	5 (4%)	21 (28%)	5 (8%)
≥3 years	24 (18%)	3 (2%)	16 (22%)	3 (5%)
≥4 years	20 (15%)	1 (1%)	12 (16%)	1 (2%)
≥5 years	18 (13%)	1 (1%)	11 (15%)	1 (2%)
≥6 years	7 (5%)	1 (1%)	4 (5%)	1 (2%)

Table 3: **Patients receiving long-term olaparib maintenance monotherapy, by number of years of treatment received**

	Overall study population (n=19)		Patients with *BRCA*m (n=12)		Patients with *BRCA*wt (n=7)	
	Olaparib (n=18)	Placebo (n=1)	Olaparib (n=11)	Placebo (n=1)	Olaparib (n=7)	Placebo (n=0)
Number of previous lines of chemotherapy						
2	7 (39%)	1 (100%)	4 (36%)	1 (100%)	3 (43%)	0
3	7 (39%)	0	4 (36%)	0	3 (43%)	0
4	2 (11%)	0	2 (18%)	0	0	0
≥5	2 (11%)	0	1 (9%)	0	1 (14%)	0
Platinum-free interval						
6–12 months	5 (28%)	0	2 (18%)	0	3 (43%)	0
>12 months	13 (72%)	1 (100%)	9 (82%)	1 (100%)	4 (57%)	0
Objective response to most recent platinum-based regimen						
Complete response	10 (56%)	1 (100%)	5 (45%)	1 (100%)	5 (71%)	0
Partial response	8 (44%)	0	6 (55%)	0	2 (29%)	0

Table 4: **Baseline characteristics for patients receiving study treatment for 5 years or more**

For the *BRCA*-mutated subgroup, early separation of the Kaplan-Meier survival curves is evident, with maximum separation from a timepoint of about 48 months (figure 2). Mutations in *BRCA1* and *BRCA2* are the best characterised predictors of homologous recombination repair deficiency in ovarian cancer. Our data support the proposed mechanism of action of olaparib as a synthetic lethality-inducing drug in the context of tumours with homologous recombination repair deficiencies, such as *BRCA*-mutated tumours. Ongoing translational analyses from Study 19 support the hypothesis that tumours with s*BRCA*m and tumours with g*BRCA*m are similar, both biologically and in sensitivity to olaparib.[16] The overall survival data for patients with s*BRCA*m were not inconsistent with those for patients with g*BRCA*m, but the small size of the s*BRCA*m subgroup (n=20) limits the interpretation of our findings.

An exploratory restricted means analysis, using a pseudovalues method, showed a difference in restricted mean overall survival with olaparib compared with placebo of 5·2 months (95% CI –0·8 to 11·2) in the

overall population and 7·5 months (–1·1 to 16·0) in the *BRCA*m subgroup. Two other methods were investigated for the restricted means analysis (appendix p 3) and all analyses gave similar results, suggesting an overall survival advantage with maintenance olaparib versus placebo, with a greater treatment effect in the *BRCA*m subgroup. The difference in median overall survival with maintenance olaparib compared with placebo was 2·0 months in the overall population and 4·7 months in the *BRCA*m subgroup. This is less than the difference in restricted mean overall survival; the mean offers an estimate of average life expectancy, which takes account of patients who do very well on treatment, whereas the median provides a more conservative estimate that is limited to the first half of the survival observations. For example, the median overall survival suggests that 50% of patients in the *BRCA*m subgroup who received olaparib lived for longer than 34·9 months, but the mean survival time was 44·3 months.

For the *BRCA*wt subgroup, some patients might have been homologous recombination repair-deficient as a result of alternative factors, such as mutations in genes that encode other proteins involved in the homologous recombination repair pathway, or epigenetic mechanisms, which do not yet have well defined clinical testing strategies.[19,20] Some separation is seen at the tail end of the *BRCA*wt survival curves for the two treatment groups (figure 2), suggesting that a further subset of patients might exist who receive benefit from olaparib treatment. Investigations into patients with *BRCA*wt but who are deficient in other homologous recombination repair genes are ongoing.[21]

Study 19 was designed and powered to show a statistically significant difference in progression-free survival in the patients who were randomly assigned to a group, from a population enriched for homologous recombination repair tumours as a result of high-grade serous histology and platinum sensitivity. No rules were prespecified to control the type 1 error rate for subgroups. The study was not designed to show a statistically significant difference in overall survival. However, a multiplicity strategy was prespecified to control the error rate at 5% (two-sided) for multiple analyses of overall survival. Two previous overall survival analyses have been done, which did not meet statistical significance, and only 0·95% two-sided α was available to test at this updated analysis. The p values did not meet this criterion for significance ($p<0·0095$) and therefore the favourable treatment effect reported for overall survival should only be regarded as descriptive and should be interpreted in the context of the clinically meaningful and statistically significant improvement in progression-free survival. All p values for overall survival are deemed nominal. The interpretation of the exploratory restricted means data is limited by the post-hoc nature of this analysis because it was not prespecified.

The updated analyses for time to first subsequent therapy or death, and time to second subsequent therapy or death show a significant improvement in these exploratory endpoints with olaparib in the overall study population and in the *BRCA*m and *BRCA*wt subgroups, consistent with the previous analysis.[7] Time to first subsequent therapy or death is an exploratory endpoint but is clinically meaningful because it represents the time that women are free from the next line of treatment. The updated time to first subsequent therapy or death data provide a long-term view on efficacy, with the time to first subsequent therapy or death Kaplan-Meier curves for the two treatment groups remaining clearly separated at a timepoint more than 5 years after randomisation. Patients remain blinded to study treatment beyond progression, and so these data support an extended benefit, beyond the progression-free survival, for patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy. Understanding the full therapeutic value of investigational treatments in ovarian cancer studies can be challenging because they often have a long follow-up for overall survival and analyses can be confounded by post-discontinuation treatment. Improvement in time to second subsequent therapy or death can show continued benefit, beyond the next line of treatment, and this intermediate endpoint can therefore support other efficacy endpoints when assessing the long-term effect of investigational treatments.[22]

We did not allow crossover in this study, but 17 patients from the placebo group (including 14 patients with *BRCA*m) had received post-discontinuation PARP inhibitor treatment by the 2015 data cutoff via other clinical studies. These additional treatments are deemed to have had the potential to confound the overall survival data; an exploratory analysis has previously been reported for the *BRCA*m subgroup, excluding all patients from sites where at least one patient from the placebo group received post-discontinuation PARP inhibitor treatment, and the analysis showed a greater treatment effect than the previously published overall survival analysis.[7,23]

Notably, at the data cutoff in 2015, 15 patients were continuing to receive olaparib and one was continuing to receive placebo. Long-term exposure to maintenance olaparib was reported, with 18 (13%) of 136 patients (11 [15%] of 74 of patients with *BRCA*m) receiving olaparib for 5 years or more. This observation supports the long-term benefit and tolerability of olaparib. Similar data for long-term treatment have not previously been seen in clinical trials in recurrent ovarian cancer. Baseline data show that most of the 19 patients who received study treatment for 5 years or more had two or three previous lines of chemotherapy and a platinum-free interval of more than 12 months.

Since the previous safety analysis, an additional 3 years of follow-up have been done, during which time no new safety signals were reported for the patients remaining on treatment and no change to the overall safety profile has been made. For patients who received olaparib for

2 years or more, the most frequent adverse events were not different to those in the overall population: specifically low-grade nausea, fatigue, anaemia, and vomiting, which are manageable and were generally reported in the first 2 years of treatment.[6–8] These long-term safety findings are consistent with previous data from Study 19 and other clinical olaparib monotherapy studies. As reported in 2012, a low proportion of patients had adverse events resulting in discontinuation of treatment.[7]

To conclude, in Study 19, an overall survival advantage with olaparib, given as maintenance treatment, is seen for patients with *BRCA*m and platinum-sensitive recurrent serous ovarian cancer. This observation is consistent with data showing a significant improvement with olaparib in progression-free survival and in the intermediate endpoints of time to first subsequent therapy or death and time to second subsequent therapy or death. Additionally, 11 (15%) of 74 patients with *BRCA*m continued on olaparib for 5 years or more, highlighting that this PARP inhibitor can significantly change the disease course. Ongoing analyses are investigating the potential benefit of olaparib for patients with wild-type *BRCA1* and *BRCA2* genes, but who have other homologous recombination repair deficiencies, some of whom could potentially continue on olaparib without disease progression for several years. The SOLO2 study (NCT01874353), a phase 3 clinical trial assessing maintenance treatment with olaparib (tablet formulation) in patients with *BRCA*m and platinum-sensitive recurrent serous ovarian cancer, who have received at least two previous lines of platinum-based chemotherapy, is ongoing.

Contributors

JAL was responsible for the study design. JAL, PH, CG, MF, IV, GR, CS, WM, RS-F, TS, DM, and UM obtained the data. AF, SS, PR, EL, DH, and MAS analysed the data. All authors interpreted the data and reviewed the draft and final versions of the manuscript.

Declaration of interests

JAL has participated in advisory boards and lecture symposia, and has received institutional and personal fees from AstraZeneca; personal fees from Roche and Pfizer; and institutional fees from Clovis Oncology and Merck. PH has participated in advisory boards for AstraZeneca and Roche. CG has received grants and personal fees from AstraZeneca and GlaxoSmithKline; personal fees from Roche, Nucana, and Clovis Oncology; grants from Aprea and Novartis; and has five patents broadly relevant to this work (issued: PCT/US2012/040805; pending: PCT/GB2013/053202, 1409479.1, 1409476.7, and 1409478.3). MF has participated in advisory boards for AstraZeneca and received personal fees from AstraZeneca, Roche, and Pfizer. IV has participated in advisory boards for AstraZeneca. GR has participated in advisory boards for Oxigene and Amgen. CS has received personal fees from AstraZeneca and travel support from AstraZeneca. DM has participated as a consultant for AstraZeneca and has received research support from AstraZeneca. AF, SS, EL, and DH are employees of AstraZeneca and own stock. PR and MAS are employees of AstraZeneca. UM has provided both paid and unpaid consulting to AstraZeneca. All other authors declare no competing interests.

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