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

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

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Summary

Background: In patients with platinum-sensitive recurrent serous ovarian cancer (PSR SOC), maintenance monotherapy with the PARP inhibitor olaparib (Lynparza™) significantly improves progression-free survival (PFS) versus placebo. We assessed the effect of maintenance olaparib on overall survival (OS) in patients with PSR SOC, including those with *BRCA1/2* mutations (*BRCA*m).

Methods: In this Phase II trial, patients had PSR SOC, had received ≥2 courses of platinum-based chemotherapy and responded to their latest regimen. Patients were randomised, using a computer-generated sequence, to oral maintenance olaparib (400 mg twice daily; capsules) or placebo by an interactive voice response system, stratified by ancestry, time to progression on penultimate platinum and response to most recent platinum. The primary endpoint was PFS. Here, we present data for OS, a secondary endpoint, from the third data analysis after >5 years' follow-up (intention-to-treat population). Randomised patients were analysed for OS; treated patients were analysed for safety. This trial is ongoing and is registered with ClinicalTrials.gov (NCT00753545).

Findings: Between 28 August 2008 and 9 February 2010, 136 patients were randomised to olaparib and 129 to placebo. 136 patients had deleterious *BRCA*m. The data cut-off for this analysis was 30 September 2015. An OS advantage was observed with maintenance olaparib versus placebo in all patients (HR 0·73 [95% CI 0·55–0·96]; median OS 29·8 vs 27·8 months) and *BRCA*m patients (HR 0·62 [0·41–0·94]; 34·9 vs 30·2 months). 11 (15%) of 74 *BRCA*m patients received maintenance olaparib for ≥5 years. Overall, common grade ≥3 adverse events (AEs) were fatigue (olaparib: 11/136 patients [8%]; placebo: 4/128 [3%]) and anaemia (olaparib: 8/136 patients [6%]; placebo: 1/128 [1%]). Serious AEs were reported in 30/136 patients (22%) on olaparib and 11/128 patients (9%) on placebo. In patients treated for ≥2 years, AEs included low-grade nausea (olaparib: 24/32 patients [75%]; placebo: 2/5 patients [40%]), fatigue (18/32 [56%]; 2/5 [40%]), vomiting (12/32 [38%]; 0) and anaemia (8/32 [25%]; 1/5 [20%]); generally, events were initially reported during the first 2 years of treatment.

Interpretation: An OS advantage was seen for patients with *BRCA*m PSR SOC receiving olaparib maintenance monotherapy after platinum-based chemotherapy, supporting the reported PFS benefit. Significant long-term exposure to olaparib was observed. There were no new safety signals. Taken together, these data support both the long-term clinical benefit and tolerability of maintenance olaparib in *BRCA*m patients with PSR SOC.

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Introduction

Ovarian cancer is the fifth most common type of cancer for women in developed countries.[1,2] Approximately 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 (approximately 38%).[3–5] Overall, ovarian cancer is the sixth highest cause of cancer-related deaths for women in developed countries.[1,2]

Olaparib (Lynparza™) is an oral poly(ADP-ribose) polymerase (PARP) inhibitor that has demonstrated significant clinical activity in ovarian cancer, particularly in tumours that have mutations in *BRCA1/2* (*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 observed with olaparib in tumours that are deficient in homologous recombination repair (HRR) pathways, such as those with *BRCA*m.[10,11]

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

Two interim analyses of overall survival (OS) from Study 19 have previously been conducted, at 38% data maturity (HR 0·94, 95% CI 0·63–1·39, *P*=0·75) and 58% data maturity (HR 0·88, 95% CI 0·64–1·21, *P*=0·44) in the overall study population.[6,7] Here, we present an updated descriptive OS analysis following the deaths of 203 (77%) of 265 patients in this study, with an additional 3 years of OS follow-up since the previous analysis. We assessed the impact of maintenance olaparib on OS in women with PSR SOC.

Methods

Study design and participants

Study 19 was a Phase II, randomised, double-blind, placebo-controlled, multicentre trial, involving 82 sites across 16 countries. The institutional review boards or independent ethics committees of all investigational sites approved the protocol. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on bioethics.[14]

Eligible patients were aged ≥18 years, 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 prior 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) v1·0 or Gynecological Cancer InterGroup criteria. Additional eligibility criteria have been described.[6] All patients provided written informed consent.

Known *BRCA*m status was not required for eligibility, but was established via case report forms (CRF) documenting previous local germline *BRCA* testing, or via retrospective germline *BRCA* testing (Integrated BRAC*Analysis* 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.

Randomisation and masking

Patients were randomised (1:1) to receive olaparib or placebo within 8 weeks following completion of their most recent platinum-based regimen. An interactive voice response system (IVRS) assigned patients to their treatment, using a randomisation scheme generated by a computer program (GRand). The investigator who enrolled patients contacted an IVRS 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).

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.

Procedures

Patients received oral olaparib maintenance monotherapy, at 400 mg bid (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 arms within the study was not allowed. Dose modifications that were specified for toxicity management have been described previously.[6]

Tumours were assessed by computed tomography scans or magnetic resonance imaging 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 cut-off (DCO) of 30 June 2010. Patients were monitored for OS, with follow-up every 12 weeks after discontinuation of treatment. Safety and tolerability were monitored for patients remaining on study treatment by record of adverse events (AEs), physical examination, vital signs and laboratory findings. AEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events v3·0.

Outcomes

We have previously reported data for PFS, which represented the primary endpoint for this study.[6] OS was a secondary endpoint, but represents the main outcome for

this descriptive analysis. Safety, tolerability, TFST and TSST were also assessed. Additional endpoints have been described previously.[6,7]

Statistical analysis

Study 19 was sized to ensure a sufficient number of PFS events in the overall study population.[7] OS was analysed on an intention-to-treat basis. The analysis set for OS included all randomised patients and the analysis sets for safety, TFST and TSST included all patients who received at least one dose of treatment. Other than for OS, no adjustments were made for multiplicity introduced by analysing multiple endpoints (TFST and TSST). No adjustments were made for analyses within the *BRCA*m or *BRCA* wild-type (*BRCA*wt) subgroups. Two previous analyses of OS have been conducted, at 38% data maturity (DCO: 31 October 2011; alpha [two-sided] = 0·1%) and 58% data maturity (DCO: 26 November 2012; alpha [two-sided] = 3%).[6,7] The updated OS analysis described here was conducted at 77% data maturity, using an alpha (two-sided) of 0·95%. This OS analysis is considered to be descriptive and the *P*-values are nominal. Exploratory analyses of TFST and TSST were previously performed at the 2012 DCO, when these endpoints had 80% and 74% data maturity, respectively.[7]

OS, TFST and TSST were analysed using a Cox proportional hazards model, which was adjusted for treatment, ancestry (Jewish vs non-Jewish), time to progression from completion of penultimate platinum-based regimen (6–12 vs >12 months) and response to most recent platinum-based regimen (complete vs partial response). Restricted means analyses were performed for the OS data using the pseudovalues method, as previously described.[15] All analyses used SAS v8.2 except the restricted means analyses, which used the Comprehensive R Archive Network “pseudo” software. 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 author (JAL) had full access to all of the data and the final responsibility to submit for publication.

Results

Patient enrolment occurred between 28 August 2008 and 9 February 2010. Of the 326 patients who enrolled, 265 met the eligibility criteria; 136 of these patients were randomised to olaparib and 129 were randomised to placebo (Figure 1). *BRCA*m status was established for 254/265 patients (96%), of whom 136 (51% of 265 patients in the overall study population) had a known or suspected deleterious *BRCA*m. Patient demographics and baseline characteristics were generally well balanced for the overall study population, *BRCA*m and *BRCA*wt subgroups (Table 1). The efficacy analysis set included all 265 randomised patients. One patient who was randomised to placebo withdrew consent and withdrew from the study without receiving treatment; therefore, the analysis sets for safety, TFST and TSST included the 264 patients who were treated.

The DCO for this updated OS analysis was 30 September 2015 (OS data maturity: 77%). At this DCO, the median follow-up for OS was 71·0 months (inter-quartile range [IQR] 67·8–72·9 months) for the overall study population (olaparib: 71·0 months [68·5–72·7] vs placebo: 70·8 months [38·2–73·0]). This represents an additional 3 years of follow-up since the previously reported OS.[7] The Cox proportional hazards analyses indicate an OS 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 2a), although this did not meet the required threshold for statistical significance (*P*<0.0095). The *BRCA*m subgroup data (70% OS data maturity) indicate an OS advantage for *BRCA*m patients who were treated with maintenance olaparib (HR 0.62, 95% CI 0.41–0.94, nominal *P*=0.025; Figure 2b). The OS data for the *BRCA*wt subgroup (84% OS data maturity) were: HR 0.83, 95% CI 0.55–1.24, nominal *P*=0.37 (Figure 2c).

Most patients in the *BRCA*m subgroup had germline *BRCA*m (g*BRCA*m), but 20 (15%) of 136 (olaparib: n=10, placebo: n=10) had somatic *BRCA*m (s*BRCA*m) only. We previously reported 18 s*BRCA*m patients in Study 19, based on 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 s*BRCA*m patients who are discussed here: this group includes six of the 22 patients for whom blood testing data were unavailable and 14 of the original 18 s*BRCA*m patients.[16] Four patients from the previously reported subgroup were therefore not included, three as a result of likely incomplete CRF-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. Figure 3 shows the OS data for the overall, *BRCA*m, g*BRCA*m and s*BRCA*m populations. The s*BRCA*m subgroup data are not inconsistent with those from the other subgroups, but there are too few events in this group to draw conclusions. Figure 3 also shows the *BRCA1*m and *BRCA2*m OS data, and Kaplan-Meier survival curves for these two subgroups are presented in the Supplementary Material (page 2).

Formal tests of the proportionality of the hazards, using the methods of Grambsch and Therneau, indicated that there was insufficient evidence to dismiss the proportional hazards assumption in either the overall population (*P*=0.19) or the *BRCA*m subgroup (*P*=0.70).[17] However, restricted means analyses were also performed, in order to enhance our understanding of average patient survival and the effect of study treatment. Table 2 shows the results from these restricted means analyses for the overall population and the *BRCA*m subgroup. These data are supportive of the OS advantage with olaparib indicated by the Cox proportional hazards analysis. In addition, the Supplementary Material (page 3) shows the restricted means data using two alternative methodologies, which gave similar estimates for the restricted mean OS. Log-rank test analyses were also consistent with the Cox proportional hazards analysis (Table 2).

Updated exploratory analyses were conducted for TFST and TSST; since the previous analysis, the data maturity had increased from 80% to 86% for TFST and from 74% to 84% for TSST.[7] The median follow-up for TFST was 70.8 months (IQR 12.6–72·7 months) 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 TSST was 70.5 months (IQR 11.2–72.8 months) for the overall population (olaparib: 70.9 months [16.4–72.6) vs placebo: 7.8 months [5.2–72.8 months). Median TFST and TSST were significantly prolonged with olaparib compared with placebo, in the overall study population, *BRCA*m and *BRCA*wt subgroups (Figure 4).

At the DCO for this updated OS analysis, 15 (11%) of 136 patients were continuing to receive olaparib, eight of whom had a *BRCA*m. Within this group, the initial dose (olaparib 400 mg bid) was being received by nine patients (five *BRCA*m) and a reduced dose of 200 mg bid was being received by six patients (three *BRCA*m), four of whom had a dose reduction owing to AEs. One patient, with a *BRCA*m, was still receiving placebo (<1% of 129). Overall, 18 (13%) of 136 patients had received olaparib for ≥5 years (Table 3): 11 of these patients had a *BRCA*m (15% of 74) and seven were in the *BRCA*wt subgroup (12% of 57). Baseline characteristics for the patients who received study treatment for ≥5 years are listed in Table 4.

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

There were no new safety findings in the overall study population when compared to those that have previously been reported.[6,7] Figure 5a shows the most common AEs reported between the start of treatment and the 2015 DCO by patients in the overall population who received treatment for ≥2 years. For the 32 patients who received olaparib for ≥2 years, 30 (94%) of 32 reported at least one AE, with 15 (47%) of 32 reporting AEs of grade ≥3. For patients who received olaparib treatment for ≥2 years, the frequencies of previously reported common AEs, such as low-grade nausea, fatigue, vomiting and anaemia, were consistent with the frequencies that were previously reported in the overall population. In general, these AEs were initially reported during the first 2 years of treatment. Twenty-one *BRCA*m patients received olaparib for ≥2 years and this subgroup had a similar safety profile to the overall group of 32 patients. All five patients who received placebo for ≥2 years reported at least one AE; one (20%) of five reported AEs of grade ≥3. Figure 5b shows the common AEs reported after 2 years by patients who received treatment for ≥2 years.

Twenty-three of the 32 patients who received olaparib for ≥2 years reported AEs after 2 years (72%), with 8 (25%) of 32 reporting AEs of grade ≥3. Four of the five patients who received placebo for ≥2 years reported AEs after 2 years; none reported AEs of grade ≥3. Fifteen of the 32 patients who received olaparib for ≥2 years had dose reductions (47%), eight of whom (25%) had dose reductions owing to AEs. One patient from the placebo arm (20% of five) had dose reductions, which were not related to AEs. Three of the patients who received olaparib for ≥2 years discontinued treatment owing to AEs, which were: pharyngitis and pancytopenia (two AEs in one patient); squamous cell carcinoma of the oral cavity and bronchiectasis (each in one patient). None of the patients who received placebo for ≥2 years discontinued owing to AEs.

In the overall study population, the most common grade ≥3 AEs were fatigue (olaparib: 11/136 patients [8%]; placebo: 4/128 [3%]) and anaemia (olaparib: 8/136 patients [6%]; placebo: 1/128 [1%]). Overall, 59 (43%) of 136 patients from the olaparib arm and 29 (23%) of 128 from the placebo arm had dose reductions. Dose reductions owing to AEs were reported in 34/136 (25%) and 5/128 (4%) patients from the olaparib and placebo arms, respectively. AEs that led to discontinuation of treatment were reported for eight (6%) of 136 patients from the olaparib arm and two (2%) of 128 patients from the placebo arm; all of these AEs were considered to be related to treatment. For the olaparib arm, in addition to the AEs that led to late discontinuation after 2 years of treatment, the other AEs resulting in discontinuation were: palpitations and myalgia (two AEs in one patient); herpes zoster, nausea, erythematous rash and haemorrhagic stroke (each in one patient). In the placebo arm, the AEs resulting in discontinuation of treatment were pruritic rash and nausea (each in one patient). Thirty (22%) of 136 patients and 11 (9%) of 128 patients reported serious AEs in the olaparib and placebo arms, respectively. There were no additional reports of AEs resulting in death at the 2015 DCO compared with the 2012 DCO, at which one patient had died solely from AEs (haemorrhagic stroke and thrombocytopenia, considered to be treatment-related). Overall, 202 patients in the safety analysis set had died at the 2015 DCO (olaparib arm: n=94; placebo arm: n=108). In the olaparib arm, 83 patients died only from the disease under investigation; one patient had AEs leading to death (haemorrhagic stroke and

thrombocytopenia); one patient died from a combination of their underlying disease and an AE (myelodysplastic syndrome); and nine patients died from other reasons (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 arm, 99 patients died only from the disease under investigation and nine patients died from other reasons (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/acute myeloid leukaemia (MDS/AML; two in the olaparib arm and one in the placebo arm) have been reported. All three of the patients who reported MDS/AML had received two prior lines of chemotherapy. Two of these patients had received olaparib maintenance monotherapy for 57 and 10 months, respectively, and one had received placebo for 44 months.

Discussion

These updated descriptive OS analyses indicate an OS advantage for patients with PSR SOC who received olaparib maintenance monotherapy compared with placebo in Study 19. The OS data support the previously published results from Study 19, which showed that PFS, TFST and TSST are significantly prolonged with olaparib, particularly in *BRCA*m patients.[6,7] Although a statistically significant improvement in OS was not demonstrated, we observed that olaparib had a beneficial treatment effect on OS in the overall population (HR=0.73). This was primarily driven by the treatment effect in the *BRCA*m subgroup, who received the greatest OS benefit from olaparib (HR=0.62). The Kaplan-Meier survival curves for the two treatment arms begin to separate from approximately 42 months after randomisation for the overall study population (Figure 2a). This observation may be a consequence of the heterogeneous nature of the overall population and the different treatment effect in *BRCA*m and *BRCA*wt patients. As *BRCA*m patients receive the most benefit from olaparib and have a better prognosis than *BRCA*wt patients, the proportion of *BRCA*m to *BRCA*wt patients at risk increases over time. At the tail end of the survival curve for the overall population, there are therefore relatively fewer *BRCA*wt patients at risk and so the treatment effect in *BRCA*m patients is less diluted, resulting in the observed separation. The separation of the survival curves at the tail end also suggests the observed OS advantage was influenced by a group of patients who received long-term olaparib maintenance monotherapy. Biological factors that may predict these long-term responders are being investigated.[18]

For the *BRCA*m subgroup, early separation of the Kaplan-Meier survival curves is evident, with maximal separation from a time point of approximately 48 months (Figure 2b). Mutations in *BRCA1* and *BRCA2* are the best characterised predictors of HRR deficiency in ovarian cancer. Our data support the proposed mechanism of action of olaparib as a synthetic lethality-inducing agent in the context of tumours with HRR deficiencies, such as *BRCA*m tumours. Ongoing translational analyses from Study 19 support the hypothesis that tumours with s*BRCA*m and g*BRCA*m are similar, both biologically and in sensitivity to olaparib.[16] The OS data for s*BRCA*m patients were not inconsistent with those for g*BRCA*m patients, 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 methodology, showed a difference in restricted mean OS with olaparib compared with placebo of 5·2 months in the overall population and 7·5 months in the *BRCA*m subgroup. Two other methodologies were investigated for the restricted means analysis (Supplementary Material, page 3) and all analyses gave comparable results, indicating an OS advantage with maintenance olaparib versus placebo, with a greater treatment effect in the *BRCA*m subgroup. The difference in median OS 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 OS; 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, in the *BRCA*m subgroup who received olaparib, the median OS indicates that 50% of patients lived for longer than 34.9 months, but the mean survival time was 44.3 months.

For the *BRCA*wt subgroup, some patients may have been HRR-deficient as a result of alternative factors, such as mutations in genes that encode other proteins involved in the HRR 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 2c), suggesting that there may be a further subset of patients who receive benefit from olaparib treatment. Investigations into patients who were *BRCA*wt but deficient in other HRR genes are ongoing.[21]

Study 19 was designed to demonstrate a statistically significant difference in PFS in the patients who were randomised: a population enriched for HRR tumours as a result of high-grade serous histology and platinum sensitivity. No rules were pre-specified to control the Type 1 error rate for subgroups. The study was not designed to show a statistically significant difference in OS. However, a multiplicity strategy was pre-specified to control the error rate at 5% (two-sided) for multiple analyses of OS. Two previous OS analyses have been conducted, which did not meet statistical significance, and only 0·95% alpha (two-sided) was available to test at this updated analysis. The *P*-values did not meet this criterion for statistical significance

(*P*<0.0095) and therefore the favourable treatment effect observed for OS should only be considered descriptive and should be interpreted in the context of the clinically meaningful and statistically significant improvement in PFS. All *P*-values for OS are deemed nominal. The interpretation of the exploratory restricted means data is limited by the *post-hoc* nature of this analysis, as it was not pre-specified.

The updated analyses for TFST and TSST show a significant improvement in these exploratory endpoints with olaparib in the overall study population, *BRCA*m and *BRCA*wt subgroups, consistent with the previous analysis.[7] TFST is an exploratory endpoint but is clinically meaningful, as it represents the time that women are free from the next line of treatment. The updated TFST data provide a long-term view on efficacy, with the TFST Kaplan-Meier curves for the two treatment arms remaining clearly separated at a time point over 5 years from randomisation. As patients remain blinded to study treatment beyond progression, these data support an extended benefit, beyond PFS, for patients with PSR SOC receiving olaparib maintenance monotherapy. It can be challenging to understand the full therapeutic value of investigational treatments in ovarian cancer studies, as there is often a long follow-up for OS and analyses can be confounded by post-discontinuation therapy. Improvement in TSST can demonstrate continued benefit, beyond the next line of therapy, and this intermediate endpoint can therefore support other efficacy endpoints when evaluating the long-term impact of investigational treatments.[22]

Crossover was not allowed in this study, but 17 patients from the placebo arm (14 *BRCA*m patients) had received post-discontinuation PARPi treatment by the 2015 DCO, via other clinical studies. This is considered to have had the potential to confound the OS 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 arm received post-discontinuation PARPi therapy, and this showed a greater treatment effect than the previously published OS analysis.[7,23]

Notably, at the DCO in 2015, there were 15 patients continuing on olaparib and one on placebo. Significant long-term exposure to maintenance olaparib was observed, with 18/136 (13%) of all patients (11/74 [15%] of *BRCA*m patients) receiving olaparib for ≥5 years. 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 the majority of the 19 patients who received study treatment for ≥5 years had two or three prior lines of chemotherapy and a platinum-free interval >12 months.

Since the previous safety analysis, there has been an additional 3 years of follow-up, during which time no new safety signals were reported for the patients remaining on treatment and there was no change to the overall safety profile. For patients who received olaparib for ≥2 years, the most frequent AEs were not different to those in the overall population, specifically low-grade nausea, fatigue, constipation and vomiting, which are manageable and were generally reported prior to 2 years on 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 experienced AEs resulting in discontinuation of treatment.[7]

To conclude, an OS advantage is seen for patients with *BRCA*m PSR SOC treated with olaparib as maintenance therapy in Study 19. This observation is consistent with data showing a significant improvement in PFS and in the intermediate endpoints TFST and TSST with olaparib. Additionally, 11 (15%) of 74 patients with *BRCA*m continued on olaparib for ≥5 years, highlighting that this PARPi can significantly alter the disease course. Ongoing analyses are investigating the potential benefit of olaparib for patients who are *BRCA*wt but have other HRR deficiencies, some of whom may continue on olaparib without progression for several years. There is an extensive Phase III clinical programme for olaparib, with the SOLO2 study (NCT01874353) assessing maintenance olaparib treatment (tablets) in *BRCA*m patients with PSR SOC who have received at least two prior lines of platinum-based chemotherapy.

Research in context

Evidence before this study

We conducted searches of PubMed and the databases of the American Society of Clinical Oncology, European Society for Medical Oncology, Society of Gynecological Oncology and European Society of Gynaecological Oncology between 1 March 2015 and 1 March 2016 to identify journal publications and meeting abstracts that included the search terms “poly(ADP-ribose) polymerase inhibitor” or “PARP inhibitor” and “ovarian cancer”. No language restrictions were used. Olaparib is an oral PARP inhibitor (PARPi) that has shown significant clinical activity and tolerability in patients with recurrent ovarian cancer and is approved in the EU and the US for the treatment of *BRCA1/2*-mutated advanced ovarian cancer. Other PARPis in clinical development include rucaparib, veliparib, niraparib and talazoparib. There have been no reports of an advantage in overall survival for ovarian cancer patients treated with maintenance therapy with a PARPi compared with placebo.

Added value of this study

This is the third overall survival analysis for a Phase II, randomised trial of olaparib maintenance monotherapy in patients with platinum-sensitive recurrent serous ovarian cancer (PSR SOC) and is, to our knowledge, the first analysis to indicate a survival advantage for patients with ovarian cancer treated with a PARPi. The survival analysis was conducted after more than 5 years total follow-up, at high data maturity, with an additional 3 years of follow-up since the previous analysis. The observed survival advantage may have primarily been driven by a survival benefit in the subgroup of patients with *BRCA1/2* mutations (*BRCA*m). We believe this is also the first report of significant long-term exposure to a PARPi in recurrent ovarian cancer, with 18 (13%) of 136 patients receiving maintenance olaparib for ≥5 years. No new safety signals were observed 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 II study that showed a significant improvement in progression-free survival (PFS) with maintenance olaparib, with the

greatest benefit seen in patients with a *BRCA*m. Exploratory analyses have also shown a significant improvement in time to first and second subsequent therapy or death (TFST and TSST) with olaparib compared with placebo. To our knowledge, this is the first analysis to show survival data in recurrent *BRCA*m ovarian cancer that are consistent with previously reported benefits in PFS, TFST and TSST. Taken together, the available data support the long-term benefit and tolerability of maintenance olaparib in *BRCA*m patients with PSR SOC.

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 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 have no disclosures.

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Figure legends

Figure 1. Enrolment, randomisation and treatment status at the third analysis of OS in Study 19.

Footnote: DCO was on 30 September 2015. *One patient was randomly assigned to the placebo arm, but withdrew consent and withdrew from the study without receiving treatment

Figure 2. OS in all patients and according to *BRCA*m status. **a)** All patients (n=265); **b)** *BRCA*m patients (n=136); **c)** *BRCA*wt patients (n=118).

Figure 3. Summary of the Cox proportional hazards analysis of OS in the overall study population and different *BRCA*m subgroups.

Figure 4. TFST and TSST in all patients and according to *BRCA*m status. **a)** TFST in all patients (n=264); **b)** TFST in *BRCA*m patients (n=136); **c)** TFST in *BRCA*wt patients (n=118); **d)** TSST in all patients (n=264); **e)** TSST in *BRCA*m patients (n=136); **f)** TSST in *BRCA*wt patients (n=118).

Figure 5. Common AEs of all grades and grade ≥3 in patients who received study treatment for ≥2 years (olaparib n=32; placebo n=5).
a) AEs reported from the start of treatment to the 2015 DCO*

Footnote: *AEs that were reported in ≥8 patients are presented. Additional data for AEs in patients who received study treatment for ≥2 years are listed in the Supplementary Material (page 4–5)

b) AEs reported after 2 years*

Footnote: *AEs that were reported in ≥4 patients are presented. Additional data for AEs reported after 2 years by patients who received study treatment for ≥2 years are listed in the Supplementary Material (page 6–7)