SOLO2/ENGOT-Ov21: A phase 3, randomised, double-blind, placebo-controlled trial of olaparib tablets as maintenance therapy in platinum-sensitive, relapsed ovarian cancer

Eric Pujade-Lauraine MD,[1] Jonathan A Ledermann MD,[2] Frédéric Selle MD,[3] Val Gebski FRANZCR,[4] Richard T Penson MD,[5] Amit M Oza MD,[6] Jacob Korach MD,[7] Tomasz Huzarski PhD,[8] Andrés Poveda MD,[9] Sandro Pignata MD,[10] Michael Friedlander MBChB,[11] Nicoletta Colombo MD,[12] Philipp Harter MD,[13] Keiichi Fujiwara MD,[14] Isabelle Ray-Coquard MD,[15] Susana Banerjee MRCP,[16] Joyce Liu MD,[17] Elizabeth S Lowe MD,[18] Ralph Bloomfield MSc,[19] Patricia Pautier MD[20]

[1]Université Paris Descartes, AP-HP, Paris, France and GINECO; [2]University College London, London, UK and MRC/NCRI; [3]Hôpital Tenon, Paris, France and GINECO; [4]University of Sydney, Sydney, Australia; [5]Massachusetts General Hospital, Boston, MA and US Consortium; [6]Princess Margaret Cancer Centre, Toronto, Canada and PHMC; [7]Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel and ISGO; [8]Pomeranian Medical University, Szczecin, Poland; [9]Instituto Valenciano de Oncología, Valencia, Spain and GEICO; [10]Istituto Tumori Pascale di Napoli, Naples, Italy and MITO; [11]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia and ANZGOG; [12]University of Milan-Bicocca and Istituto Europeo Oncología (IEO), Milan, Italy and MANGO; [13]Kliniken Essen Mitte, Essen, Germany and AGO; [14]Saitama Medical University International Medical Center, Saitama, Japan; [15]Centre Léon Bérard and University Claude Bernard, Lyon, France and GINECO; [16]The Royal Marsden NHS Foundation Trust, London, UK and MRC/NCRI; [17]Dana-Farber Cancer Institute, Boston, MA and US Consortium; [18]AstraZeneca, Gaithersburg, MD; [19]AstraZeneca, Cambridge, UK; [20]Gustave Roussy Cancer Campus, Villejuif, France and GINECO

Article type: Original research article

Running title: Olaparib in platinum-sensitive, relapsed ovarian cancer

Word count: 3195/4500

References: 21/30

Corresponding author: Professor Eric Pujade-Lauraine, Hôpital Hôtel-Dieu, Place Jean-Paul II, 75004, Paris, France. Tel: +33 1 42 34 83 25. Fax: +33 1 42 34 81 10. Email: epujade@arcagy.org

Summary

Background: Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study (capsule formulation) in patients with platinum-sensitive, relapsed high-grade serous ovarian cancer.

Methods: This randomised, double-blind, phase 3 study (SOLO2; ENGOT Ov-21; NCT01874353) evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with mutation in *BRCA1* and/or *BRCA2* (*BRCA1/2*m). Primary endpoint was investigator-assessed progression-free survival (PFS). Patients were randomised 2:1 to olaparib (300 mg twice daily) or placebo.

Findings: 294/295 randomised patients received study treatment (olaparib, n=195; placebo, n=99). PFS was significantly longer with olaparib than placebo when evaluated by investigator assessment (hazard ratio [HR] 0·30, 95% confidence interval [CI] 0·22–0·41; p<0·0001; median 19·1 vs 5·5 months) and blinded independent central review (HR 0·25, 95% CI 0·18–0·35; p<0·0001; median 30·2 vs 5·5 months). Supportive secondary endpoints demonstrated significant benefit for olaparib: time to first subsequent therapy or death, HR 0·28 (p<0.0001); time to second progression (PFS2), HR 0·5 (p=0·0002); time to second subsequent therapy or death, HR 0.37 (p<0·0001). Most common grade ≥3 adverse events: anaemia (olaparib, 38 patients [19·5%]; placebo, 2 patients [2·0%]), fatigue/asthenia (olaparib, 8 patients [4·1%]; placebo, 2 patients [2·0%]), and neutropenia (10 patients, 5.1%; placebo, 4 patients [4·0%]). Toxicities led to olaparib dose reductions in 49 patients (25.1%) and discontinuation in 21 patients (10.8%). Patients' quality of life, measured by the Trial Outcome Index of the Functional Assessment of Cancer Therapy – Ovarian Cancer, showed no appreciable difference between treatment groups.

Interpretation: Olaparib tablet maintenance treatment provided a statistically significant PFS improvement with no detrimental effect on quality of life in patients with platinum-

sensitive, relapsed ovarian cancer and a *BRCA1/2*m. Secondary endpoints of TFST, PFS2, and TSST demonstrated statistically significant benefit in favour of olaparib. Excepting anaemia, toxicities with olaparib were low grade and manageable.

Funding: AstraZeneca

Word count: 299/300

Introduction

Patients with advanced ovarian cancer often respond well to first-line chemotherapy, with the duration of benefit usually ranging from 4 to 6 months.[1–3] Following disease recurrence however, this period becomes progressively shorter with the successive treatments given at each subsequent relapse. There is a significant unmet need for well-tolerated therapies that can improve long-term disease control in patients with recurrent ovarian cancer.

Olaparib is the first-in-class oral poly(ADP-ribose) polymerase (PARP) inhibitor. The inhibition of PARP is a potential synthetic lethal therapeutic strategy for the treatment of cancers characterised by specific DNA-repair defects, such as tumour cells that harbour a *BRCA1* and/or a *BRCA2 (BRCA1/2)* mutation and are rendered deficient in homologous recombination repair.[4,5] In homologous recombination-deficient tumours, PARP inhibition eliminates an alternative DNA repair pathway essential for maintaining viability, leading to tumour cell death. The estimated prevalence of a *BRCA1/2* mutation in patients with newly diagnosed high-grade serous ovarian cancer (HGSOC) is 20–25%; it may be higher in patients with platinum-sensitive, relapsed ovarian cancer.[6–9] Olaparib (capsule formulation) is currently approved in the EU and other countries as maintenance treatment for patients with platinum-sensitive, relapsed ovarian cancer and a germline and/or somatic *BRCA1/2* mutation, and in the USA as monotherapy for advanced ovarian cancer patients with a germline *BRCA1/2* mutation.[10,11]

Previous studies have indicated the effectiveness of olaparib in the setting of platinum-sensitive, relapsed, HGSOC. Study 19 (NCT00753545) was a randomised controlled phase 2 trial of olaparib capsules given as maintenance monotherapy to 265 patients where it provided a significant improvement in progression-free survival (PFS), compared with placebo, in the total study population (hazard ratio [HR] 0·35; 95%

confidence interval [CI] 0·25–0·49; p<0·001). A pre-planned retrospective analysis of Study 19 patients by *BRCA* status suggested that those with a *BRCA1/2* mutation derived the greatest PFS benefit from olaparib treatment (HR 0·18; 95% CI 0·10–0·31; p<0·0001).[2,12] Study 19 also demonstrated the long-term benefit and tolerability profile of olaparib in the maintenance setting.[13]

The SOLO2/ENGOT Ov-21 trial that we describe here was designed to prospectively confirm the findings seen in Study 19 in a similar disease setting: it is a randomised, international, multicentre, phase 3 trial to evaluate olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation. SOLO2 uses a tablet formulation of olaparib that offers patients a reduced daily pill burden compared with capsule. An adaptive-design phase 1 trial of olaparib bioavailability (Study 24) has previously established that olaparib exposure with a 300 mg twice daily [bid] tablet dose was comparable to, or higher than, exposure in patients receiving olaparib 400 mg bid capsule.[14] The findings from Study 24 informed the tablet dose regimen adopted in SOLO2 and other phase 3 olaparib studies.[14]

Efficacy and safety data from the primary analysis of SOLO2/ENGOT Ov-21 are reported.

Methods

Study design and participants

This was a randomised, double-blind, placebo-controlled, international, multicentre, phase 3 study (SOLO2/ENGOT-Ov21, NCT01874353, D0816C00002), conducted by the European Network for Gynaecological Oncological Trial groups (ENGOT) across 123 sites in 16 countries. Eligible patients were aged ≥18 years with histologically confirmed, relapsed, HGSOC or high-grade endometrioid cancer, including primary peritoneal and/or fallopian tube cancer. Patients had received at least two previous lines of platinum-based chemotherapy and were in radiological response (either complete response [CR] or partial response [PR]) to their most recent regimen. In addition, patients were required to have platinum-sensitive disease (disease progression occurring at least 6 months after the last dose of platinum therapy was given) following their penultimate line of chemotherapy before enrolment.

Patients were required to have a predicted deleterious, or suspected deleterious, *BRCA1/2* mutation based on either blood or tumour testing and all patients consented to provide two blood samples for confirmatory germline *BRCA1/2* mutation testing using Myriad BRAC*Analysis*® (Myriad Genetics, Salt Lake City, UT, USA). Patients with a known *BRCA1/2* mutation before randomisation could enter the trial based on this information; patients with unknown *BRCA1/2* mutation status were screened prior to randomisation. All patients randomised in SOLO2 harboured a germline *BRCA1/2* mutation. All patients provided written, informed consent. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.[15] Additional eligibility criteria are provided in the Methods of the Supplementary Appendix.

Randomisation and masking

Eligible patients were randomised (2:1) to receive olaparib tablet maintenance monotherapy, or matching placebo. An adaptive-design phase 1 trial of olaparib bioavailability (Study 24) has previously established that olaparib exposure with a 300 mg twice daily [bid] tablet dose was comparable to, or higher than, exposure in patients receiving olaparib 400 mg bid capsule.[14] The randomisation scheme was produced by a computer software program that generates random numbers (Global Randomisation System) and was loaded into an interactive voice and web response system (IVRS/IWRS) database. Randomisation using IVRS/IWRS was completed within 8 weeks of the patients' last dose of chemotherapy, and was stratified by response to previous chemotherapy (CR or PR) and length of platinum-free interval (6–12 months or ≥12 months). Treatment masking was achieved using individual treatment codes assigned by the IVRS/IWRS. Treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers. Olaparib and placebo tablets looked identical and were presented in the same packaging.

Procedures

Patients received either oral olaparib maintenance monotherapy (300 mg bid, tablets [manufactured by AstraZeneca]) or placebo (bid, tablets) until disease progression or until the investigator deemed that a patient was no longer benefiting from treatment. After a discontinuation of study treatment in SOLO2, the investigator was responsible for selecting a patient's subsequent treatments.

Patients were assessed using computed tomography (CT) or magnetic resonance imaging (MRI) scans every 12 weeks until week 72, and then every 24 weeks thereafter until objective disease progression; CT/MRI scans were also sent to a Clinical Research Organisation for blinded independent central review (BICR). After progression, patients

were followed every 12 weeks for second progression and survival. The primary endpoint for patient-reported health-related quality of life (HRQoL) was Trial Outcome Index (TOI) score, derived from the Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) questionnaire; patient-reported health state utility was assessed as an exploratory objective using the EuroQoL five dimensions five level questionnaire. Questionnaires were collected every 12 weeks for either 24 months or until the data cut-off for the primary analysis (whichever occurred first). Safety was monitored by recording adverse events (AEs), measuring vital signs, and by performing physical examinations. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Outcomes

The primary endpoint for this trial was investigator assessment of PFS, defined as the time from randomisation until objective radiological disease progression or death using modified Response Evaluation Criteria in Solid Tumours v1·1. A sensitivity analysis of PFS was conducted by BICR. Secondary endpoints included investigator assessment of time to second progression (PFS2), determined by objective radiological, CA-125, or symptomatic progression; time to first subsequent therapy or death (TFST); time to second subsequent therapy or death (TSST); overall survival (OS); objective response rate; HRQoL; and safety and tolerability.

Statistical analysis

Analyses were to be performed on a higher number of events than required for a powered superiority analysis for both PFS and PFS2; therefore, the power to show superiority for both endpoints was >90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated HR. PFS

was tested at a two-sided significance level of 5% and analysed with a log-rank test, using the stratification factors used for randomisation. PFS2 and OS were analysed at the time of primary analysis of PFS, using the same methodology. At this initial analysis, statistical significance was to be declared for PFS2 if one-sided $p<0{\cdot}0125$ and for OS if one-sided $p<0{\cdot}0001$. Efficacy data were analysed in the intention-to-treat population, which included all randomised patients (full analysis set). Safety was analysed in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set). The statistical analysis plan is available at Lancet.org. This trial is registered with ClinicalTrials.gov, identifier NCT01874353, and is closed to new participants.

Role of the funding source

The trial design was a collaboration between Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein (GINECO), ENGOT, and the sponsor, AstraZeneca. This article was written by the authors, with medical writing support funded by the sponsor. All authors had full access to the raw data and had roles in data collection, analysis, interpretation, and manuscript writing. The decision to submit the manuscript for publication was made by all the authors. The corresponding author (EP-L) had final responsibility for the decision to submit for publication.

Results

Between 3 September 2013 and 21 November 2014, 295 patients were randomised (figure 1). At the data cut-off (19 September 2016), 294 patients had received study treatment (olaparib group, n=195; placebo group, n=99) and 83/195 (42·6%) patients were receiving ongoing treatment with olaparib, compared with 13/99 (13·1%) patients remaining on placebo. Demographic and baseline characteristics were well balanced between the two groups (table 1). 153/196 patients (78·1%) in the olaparib group and 83/99 patients (83·8%) in the placebo group had a previously known *BRCA1/2* mutation, and could be enrolled based on this information. All patients received a confirmatory *BRCA* test as part of the trial and, overall, 190/196 (96·9%) of patients in the olaparib group and 96/99 (97·0%) in the placebo group had a confirmed germline *BRCA1/2* mutation. No patients had a confirmed somatic *BRCA1/2* mutation. Details of treatment duration and dose intensity are provided in the Results section of the Supplementary Appendix.

Efficacy

This analysis was performed after 187 investigator-assessed events of disease progression or death (63% maturity: olaparib group, 107/196 [54·6%]; placebo group, 80/99 [80·8%]). The actual number of PFS events was 2·6% lower than the number of PFS events detailed in the statistical plan (~192 events). The median follow-up for PFS was 22·1 months (interquartle range [IQR] 21·9–27.4) in the olaparib group and 22·2 months (IQR 8.3–27.5) for placebo. Investigator-assessed PFS showed a statistically significant improvement in favour of olaparib with a HR of 0·30 (95% CI 0·22 to 0·41, p<0·0001; median 19·1 [IQR 8.3–33.2] months olaparib group vs 5·5 [IQR 2.9–10.4] months placebo group) (figure 2A). The proportion of patients who had not experienced disease progression in the olaparib group after 12 months and 24 months was 65·1% and 43·0%, respectively, compared with 20·9% and 15·1%, respectively, in

the placebo group. The sensitivity analysis of PFS by BICR (151/295 events [51% maturity]) also demonstrated a significant improvement for PFS in patients receiving olaparib versus patients on placebo, with a HR of 0·25 (95% CI 0·18 to 0·35, p<0·0001; median 30·2 [IQR 8·4–non calculable] months vs 5·5 [IQR 2.8–10.2 months]) (figure 2B).

Several secondary endpoints also demonstrated a statistically significant improvement for olaparib. Analysis of TFST (171/295 events [58% maturity]) gave a HR of 0·28 (95% CI 0·21 to 0·38, p<0·0001; median 27·9 [IQR 11·3–34·5] months vs 7·1 [IQR 4·9–16·0] months) for olaparib relative to placebo (figure 3A). PFS2 (119/295 events [40% maturity]) demonstrated a HR of 0·50 (95% CI 0·34 to 0·72, p=0·0002; median not reached vs 18·4 [IQR 12·7–27·5] months) in favour of olaparib, and a HR benefit of 0·37 (95% CI, 0·26 to 0·53, p<0·0001; median not reached vs 18·2 [IQR 12·6–not calculable] months) was observed for TSST (128/295 events [43% maturity]) in the direction of olaparib (figure 3B, C). The immature OS data (72/295 events [24% maturity]) showed no detriment for patients receiving olaparib, and a HR that numerically favoured olaparib treatment (HR 0·80; 95% CI 0·50 to 1·31, p=0·4267; medians not reached).

Patient-reported outcomes

Patient-reported outcomes showed no appreciable difference in quality of life for patients receiving olaparib compared with those receiving placebo. The primary analysis measure, the mean change from baseline in TOI of the FACT-O, was similar in both groups over the first 12 months (adjusted mean, –2·90 months [95% CI –4·13 to –1·67] vs –2·87 months [95% CI –4·64 to –1·10]; estimated difference, –0·03 months [95% CI –2·19 to 2·13] p=0·98). Additional quality of life data will be published separately.

Safety and tolerability

AEs (all CTCAE grades) reported in >20% of patients in either treatment group are shown in table 2. The most common toxicities observed (all grades) were nausea (olaparib, 148/195 patients [75·9%]; placebo, 33/99 patients [33·3%]), fatigue/asthenia (olaparib, 128/195 [65·6%]; placebo, 39/99 patients [39·4%]), anaemia (olaparib, 85/195 [43·6%]; placebo 8/99 patients [8.1%]), vomiting (olaparib, 73/195 [37·4%]; placebo, 19/99 patients [19.2%]), and diarrhoea (olaparib, 64/195 [32·8%]; 20/99 patients [20.2%]), however the overall incidence of grade >3 toxicity was low (olaparib, 72/195 patients [36·9%)]; placebo, 18/99 patients [18·2%]). The most common grade ≥3 AE was anaemia (olaparib, 38/195 patients [19·5%]; placebo, 2/99 [2·0%]). 35/195 (17·9%) patients in the olaparib group had a blood transfusion compared with 1/99 (1·0%) patients in the placebo group. The incidence of grade ≥3 neutropenia and thrombocytopenia did not increase on olaparib treatment (table 3): neutropenia, 10/195 patients (5·1%) in the olaparib group versus 4/99 patients (4.0%) in the placebo group; thrombocytopenia, 2/195 (1·0%) patients in the olaparib group versus 1/99 patients (1·0%) in the placebo group.

Serious AEs were experienced by 35/195 (17·9%) patients in the olaparib group and 8/99 (8·1%) patients in the placebo group. One patient (1/195 [0·5%]) in the olaparib group had an AE (acute myeloid leukaemia [AML]) with an outcome of death. The rate of secondary malignancies for the long-term follow-up period was 7/195 patients (3·6%) in the olaparib group and 5/99 patients (5·1%) in the placebo group (supplementary table 1). The incidence of AML, myelodysplastic syndrome (MDS), and chronic myelomonocytic leukaemia (CMML) for the long-term follow-up period was 4/195 patients (2·1%) in the olaparib group (AML, 2/195 patients [1·0%]; MDS, 1/195 patients [0·5%]; CMML, 1/195 patients [0·5%]) and 4/99 patients (4·0%) in the placebo group (AML, 1/99 patients [1·0%]; MDS, 3/99 patients [3·0%]).

The frequency of AEs leading to dose interruptions was 88/195 (45·1%) patients in the olaparib group versus 18/99 (18·2%) patients for placebo (table 3). Dose reductions following AEs were required for 49/195 (25·1%) patients and 3/99 (3·0%) patients in the olaparib and placebo groups, respectively. The proportion of patients that discontinued study treatment because of toxicity was 21/195 (10·8%) in the olaparib group compared with 2/99 (2·0%) patients in the placebo group; anaemia (6/195 patients, 3·1%) and neutropenia (2/195 patients, 1·0%) were the most common AEs leading to discontinuation in the olaparib group.

Discussion

In this randomised, double-blind, phase 3 study, olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer led to a statistically significant improvement in PFS, as evaluated both by the primary endpoint of investigator assessment and by BICR. In addition, analysis of patient-reported outcomes showed that maintenance treatment with olaparib had no detrimental effect on patients' quality of life. The improvement in PFS seen using the olaparib tablet formulation in this disease setting is compelling because patients were able to maintain a good quality of life while experiencing a delay in disease progression and, therefore, the symptoms associated with subsequent chemotherapy treatments.

The effect on PFS observed in our trial is comparable to that reported with other PARP inhibitors in phase 2 and phase 3 trials in similar clinical settings; however, such indirect comparisons cannot be considered definitive, particularly because of differences between the patient populations.[16–18] The sensitivity analysis of PFS by BICR, which was conducted to account for any potential bias from the investigator assessment, was consistent with the investigator-assessed primary endpoint. The HR observed in the sensitivity analysis was numerically slightly superior (0·25 vs 0·30). The larger median PFS derived from the BICR analysis compared with the investigator assessment was possibly driven by informative censoring, whereby some patients who had progressed according to investigator assessment had not yet been shown to progress by BICR because scans were performed every 12 weeks only, prior to submission for BICR assessment. The SOLO2 sensitivity analysis that adjusted conservatively for informative censoring resulted in a median PFS by BICR that was similar to the investigator assessment (further details are available in the Methods and Results of the Supplementary Appendix). Our study also showed a statistically significant improvement in TFST, PFS2 and TSST in favour of olaparib. The timing of TFST typically marks a

significant treatment shift for patients with recurrent ovarian cancer, from an oral PARP inhibitor to intravenous chemotherapy, whilst the analysis of TSST suggests that patients reach their second subsequent treatment without the potential occurrence of chemotherapy resistance countering the benefit they originally received on olaparib maintenance treatment. Of the secondary endpoints presented here, TFST and TSST may therefore be especially clinically meaningful.[19,20] The OS data were immature (24% maturity) at the time of this analysis and an additional analysis is planned at approximately 60% maturity (~177 OS events).

Maintenance monotherapy with olaparib was previously evaluated in Study 19, which demonstrated a significant treatment benefit in both the overall study population (patients with platinum-sensitive, relapsed ovarian cancer) and the subpopulation of patients harbouring a *BRCA1/2* mutation.[2] Our SOLO2 data support the treatment benefit observed in Study 19 for patients with a *BRCA1/2* mutation, using a two-tablet bid dosing schedule of olaparib.

Overall, the safety profile of the olaparib tablet was similar to that observed with the approved capsule formulation of olaparib.[12] The rate of grade ≥3 anaemia was higher in SOLO2, however these data could be explained by the longer exposure to olaparib for patients in SOLO2, versus Study 19. The incidence of olaparib discontinuation (21 patients, [10.8%]) due to AEs showed that toxicity related to the 300 mg bid maintenance olaparib tablet dose was manageable in most of these patients with dose modifications. Use of the 300 mg bid tablet dose in SOLO2 reduces the pill burden from 16 capsules to 4 tablets per day, providing a more convenient regimen for patients.[14] Several of the most common adverse events observed in patients receiving olaparib in SOLO2, namely fatigue, nausea, anemia, and vomiting, are considered to be class effects with a PARP inhibitor.[16–18] The rates of grade ≥3 neutropenia were comparable between the olaparib and placebo groups in SOLO2. Notably, some common grade ≥3

AEs, such as thrombocytopenia, tachycardia, and liver enzyme elevation (alanine aminotransferase or aspartate aminotransferase increased), which has been reported by >10% of PARP inhibitor-treated patients in other trials, was reported in ≤1% of olaparib-treated patients in our trial.[16–18] The rates of tachycardia, hypertension, anxiety, and insomnia were not increased in the olaparib group verus placebo. Taken together, these data highlight that olaparib does not show a significant interaction with liver or cardiovascular function, and does not have an appreciable direct negative effect on psychological function. Long-term follow-up data demonstrated that the incidence of secondary malignancies, including MDS/AML/CMML, was also comparable between both treatment groups in SOLO2.

Conclusions

SOLO2/ENGOT Ov-21 provides the first phase 3 data for olaparib tablets as maintenance treatment in patients with platinum-sensitive, relapsed, serous ovarian cancer. Our results confirm that olaparib can achieve a significant prolongation of PFS with no detrimental effect on quality of life in this patient population. The favorable safety profile in SOLO2 enabled the majority of patients receiving olaparib to maintain full dosing throughout their maintenance treatment.

Research in context

Evidence before this study

We conducted searches of PubMed and the databases of the American Society of Clinical Oncology, European Cancer Organisation, European Society of Gynaecological Oncology, European Society for Medical Oncology, and Society of Gynaecological Oncology to find journal publications and conference abstracts published between 1 January 2016 and 1 January 2017, including the search terms “poly(ADP-ribose) polymerase inhibitor” or “PARP inhibitor” and “ovarian cancer”, using no language restrictions. PARP inhibitors in late clinical development are olaparib, niraparib, rucaparib, talazoparib, and veliparib. In a phase 2 study (NCT00753545, D0810C00019 [Study 19]), patients with platinum-sensitive, relapsed ovarian cancer treated with the oral PARP inhibitor olaparib as maintenance monotherapy (capsule formulation) had significantly increased PFS compared with those treated with placebo, with the greatest PFS benefit seen in patients with a *BRCA1/2* mutation.

Added value of this study

Study 19 provided evidence in phase 2 that patients with platinum-sensitive, relapsed ovarian cancer can benefit from olaparib maintenance treatment with the capsule formulation of olaparib. Patients with a *BRCA1/2* mutation derived the greatest PFS improvement in Study 19, as demonstrated by a pre-specified, retrospective analysis. This phase 3 study (NCT01874353, SOLO2, ENGOT Ov-21), the largest study of olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer, has recruited patients with a *BRCA1/2* mutation. Efficacy data for SOLO2 shows a statistically significant improvement in median PFS with maintenance olaparib compared with placebo, by investigator assessment and BICR, which substantially exceeded the PFS benefit seen with olaparib in Study 19. We also observed significant

improvement in PFS2, and a statistically significant and clinically meaningful improvement in TFST and TSST. Patients received a new tablet formulation of olaparib in SOLO2. Olaparib tablets reduce the pill burden from 16 capsules to four tablets per day whilst maintaining comparable or higher exposure, providing patients with a simpler, more convenient treatment regime. Maintenance treatment with the olaparib tablet formulation was well tolerated, with no new safety signals and manageable toxicities. In addition, no significant difference in patients' quality of life was reported with olaparib compared with placebo.

Implications of all of the available evidence

We report here the first phase 3 data for the newer tablet formulation of olaparib as monotherapy, rather than the capsule formulation, and the first phase 3 data for olaparib in patients with ovarian cancer. The sensitivity analysis of PFS by BICR showed the greatest median improvement in PFS observed to date for a PARP inhibitor in this clinical setting, and resulted in a lower HR (HR=0·25, 95% CI 0·18–0·35) than the investigator-assessed primary endpoint (HR=0·30, 95% CI 0·22–0·41). Both assessments of PFS demonstrated a PFS benefit with olaparib that substantially exceeded that seen in phase 2 investigation in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation in Study 19. The SOLO2 data support use of the olaparib tablet formulation, which was shown to have a similar safety profile to that previously seen with the approved capsule formulation of olaparib. The tablet dose used in SOLO2 significantly reduces the pill burden from 16 capsules to four tablets per day, providing a convenient olaparib regimen that may contribute to improved patient compliance. Given the limited treatment options available for patients with platinum-sensitive, relapsed ovarian cancer, the data for olaparib as maintenance therapy in SOLO2 are notable: patients demonstrated a delay in disease progression while

experiencing no change in their quality of life. Additional clinical studies using the olaparib tablet formulation are ongoing.

Acknowledgments

We would like to thank the patients for their participation in this study, and their families, plus all investigators and onsite personnel. We thank Lizzie Wilkins, PhD, from Mudskipper Business Ltd who provided medical writing assistance funded by the sponsor. We thank Nathalie Le Fur, ARCACY-GINECO, for her role in project management and John Salter, AstraZeneca, for his role in statistical analysis.

Declaration of interest

EPL reports personal fees from Astra Zeneca, personal fees from Roche, and personal fees from Pfizer, outside the submitted work; JAL reports grants and personal fees from AstraZeneca, outside the submitted work; FS reports personal fees from Roche, personal fees from AstraZeneca, outside the submitted work; VG reports grants from The University of Sydney during the conduct of this study; RTP reports personal fees from AstraZeneca, during the conduct of the study; AO has nothing to disclose; JK has nothing to disclose; TH has nothing to disclose; AP reports consulting and advisory roles from Advaxis, AstraZeneca, PharmaMar and Roche; SP reports personal fees from AstraZeneca, during the conduct of the study; grants from AstraZeneca, outside the submitted work; MF reports grants, personal fees and advisory board membership from AstraZeneca outside the submitted work; NC reports grants and personal fees from AstraZeneca, during the conduct of the study, personal fees from Roche, personal fees from PharmaMar, personal fees from Clovis, personal fees from Pfizer, personal fees from Tesaro, outside the submitted work; PH reports personal fees from AstraZeneca during the conduct of the study, personal fees from Roche, personal fees from Tesaro, personal fees from Clovis, personal fees from PharmaMar, outside the submitted work;

KF reports grants and personal fees from Daiichi Sankyo, during the conduct of the study; grants from Kaken , grants from Shionogi, grants from Chugai, grants and personal fees from AstraZeneca, grants and personal fees from Pfizer, grants and personal fees from Eisai, grants and personal fees from MSD, grants and personal fees from Taiho, grants and personal fees from Zeria, grants and personal fees from Ono, grants and personal fees from GSK, grants and personal fees from Lilly, grants from Immunogen, grants from Oncotherapy, personal fees from Nihon Kayaku, personal fees from Novartis, personal fees from Kyowahakko Kirin, personal fees from Janssen, personal fees from Asahikasei Medical, outside the submitted work; IRQ reports advisory board membership from AstraZeneca outside the submitted work; SB reports personal fees and non-financial support from Tesaro, non-financial support from Clovis, grants and non-financial support from AstraZeneca, outside the submitted work; JL reports study funding from AstraZeneca, during the conduct of the study; honoraria and advisory board membership from AstraZeneca, advisory board membership from Tesaro, advisory board membership from Genentech/Roche, outside the submitted work; EL reports full time employment from AstraZeneca during the conduct of this study; RB reports full time employment from AstraZeneca during the conduct of this study; PP has nothing to disclose.

References

1 Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann Oncol* 2012; **23**: 2605-12.

2 Ledermann J, Harter P, Gourley C, et al. 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. *Lancet Oncol* 2014; **15**: 852-61.

3 Ledermann JA, Rustin GJ, Hackshaw A, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol* 2011; **29**: 3798-804.

4 Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005; **434**: 913-17.

5 Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005; **434**: 917-21.

6 Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012; **30**: 2654-63.

7 Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; **474**: 609-15.

8 Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol* 2011; **121**: 353-57.

9 Dann RB, DeLoia JA, Timms KM, et al. BRCA1/2 mutations and expression: response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. *Gynecol Oncol* 2012; **125**: 677-82.

10 European Medicines Agency. Lynparza summary of product characteristics. 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003726/WC500180151.pdf. Last accessed: 3-8-2016.

11 FDA. Lynparza: highlights of prescribing information. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf. Last accessed: 3-8-2016.

12 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; **366**: 1382-92.

13 Ledermann JA, Harter P, Gourley C, et al. 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. *Lancet Oncol* 2016; **17**: 1579-89.

14 Mateo J, Moreno V, Gupta A, et al. An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. *Target Oncol* 2016; **11**: 401-15.

15 European Medicines Agency. ICH topic E6(R1): Guideline for good clinical practice. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. July. 2002. Available at: http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf

16 U.S. Food & Drug Administration. Drug Approval Package: Zejula (niraparib). Multi-Discipline Review/Summary, Clinical, Non-Clinical. 2017. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447_zejula_toc.cfm. Last accessed: 9-5-2017.

17 Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016; **375**: 2154-64.

18 Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017; **18**: 75-87.

19 Matulonis UA, Oza AM, Ho TW, Ledermann JA. Intermediate clinical endpoints: a bridge between progression-free survival and overall survival in ovarian cancer trials. *Cancer* 2015; **121**: 1737-46.

20 Wilson MK, Pujade-Lauraine E, Aoki D, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol* 2017; **28**: 727-32.

21 AstraZeneca. Global Policy: Bioethics. 2015. Available at: https://www.astrazeneca.com/sustainability/responsible-research.html. Last accessed: 8-7-2016.

Table 1: **Baseline and demographic characteristics**

Characteristic		**Olaparib 300 mg bid (n=196)**	**Placebo (n=99)**
Age, years		56 (51–63)	56 (49–63)
ECOG performance status	0	162 (82·7%)	77 (77·8%)
	1	32 (16·3%)	22 (22·2%)
	Missing	2 (1·4%)	0
Primary tumour location	Ovary	164 (83·7%)	86 (86·9%)
	Fallopian tubes or primary peritoneal	31 (15·8%)	13 (13·1%)
	Missing	1 (0·5%)	0
Histology type	Serous	183 (93·4%)	86 (86·9%)
	Endometrioid	9 (4·6%)	8 (8·1%)
	Mixed	3 (1·5%)	5 (5·1%)
	Missing	1 (0·5%)	0
Patients with >2 cm target lesions at baseline	Yes	30 (15·3%)	18 (18·2%)
Confirmed germline *BRCA* mutation	*BRCA1*	132 (67·3%)	61 (61·6%)
	BRCA2	58 (29·6%)	35 (35·4%)
	Both	0	0
	Missing*	6 (3·1%)	3 (3·0%)
Response to previous platinum therapy	CR	91 (46·4%)	47 (47·5%)
	PR	105 (53·6%)	52 (52·5%)
Number of prior platinum regimens	2	110 (56·1%)	62 (62·6%)
	3	60 (30·6%)	20 (20·2%)

Characteristic		Olaparib 300 mg bid (n=196)	Placebo (n=99)
	4	18 (9·2%)	12 (12·1%)
	≥5	7 (3·5%)	5 (5·0%)
Platinum-free interval	>6–12 months	79 (40·3%)	40 (40·4%)
	>12 months	117 (59·7%)	59 (59·6%)

Data are number (%) or median (IQR). CR=complete response. ECOG=Eastern Cooperative Oncology Group. PR=partial response. *Denotes patients with a confirmed germline *BRCA1/2* mutation by local testing, but without confirmed germline *BRCA1/2* mutation status as part of this trial.

Table 2: **Non-haematological adverse events (any grade) in ≥20% of patients in either treatment group and haematological AEs (any grade) occurring in ≥10% of patients are shown, together with the respective incidence of grade ≥3 adverse events**

Event*	Olaparib (n=195)		Placebo (n=99)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any adverse event	192 (98·5%)	72 (36·9%)	94 (94·9%)	18 (18·2%)
Non-haematological adverse events				
Nausea	148 (75·9%)	5 (2·6%)	33 (33·3%)	0
Fatigue/asthenia*	128 (65·6%)	8 (4·1%)	39 (39·4%)	2 (2·0%)
Vomiting	73 (37·4%)	5 (2·6%)	19 (19·2%)	1 (1·0%)
Diarrhoea	64 (32·8%)	2 (1·0%)	20 (20·2%)	0
Dysgeusia	52 (26·7%)	0	7 (7·1%)	0
Headache	49 (25·1%)	1 (0·5%)	13 (13·1%)	0
Abdominal pain	47 (24·1%)	5 (2·6%)	31 (31·3%)	3 (3·0%)
Decreased appetite	43 (22·1%)	0	11 (11·1%)	0
Constipation	40 (20·5%)	0	23 (23·2%)	3 (3·0%)
Haematological adverse events				
Anaemia†	85 (43·6%)	38 (19·5%)	8 (7·1%)	2 (2·0%)
Neutropenia‡	38 (19·5%)	10 (5·1%)	6 (6·1%)	4 (4·0%)

Thrombocytopenia[§]	27 (13·8%)	2 (1·0%)	3 (3·0%)	1 (1·0%)

Data are number (%). Where indicated, the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for some adverse events have been combined. *Includes patients with fatigue and patients with asthenia; [†]includes patients with anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased. [‡]Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased, granulocytopenia, and granulocyte count decreased. [§]Includes patients with thrombocytopenia, platelet count decreased, and plateletcrit decreased.

Table 3: **Dose modifications owing to adverse events and dose discontinuations owing to adverse events**

Patient compliance, n (%)	**Olaparib (n=195)**	**Placebo (n=99)**
Dose interruptions	88 (45·1%)	18 (18·2%)
Dose reductions	49 (25·1%)	3 (3·0%)
Discontinuations	21 (10·8%)	2 (2·0%)

Figure legends

Figure 1: **Patient enrolment and outcomes**

Figure 2: **Kaplan–Meier estimates of (A) PFS by investigator assessment (B) PFS by BICR**

BICR=blinded independent central review. PFS=progression-free survival.

Figure 3: **Kaplan–Meier estimates of (A) TFST (B) PFS2 and (C) TSST**

CI=confidence interval. PFS2=time to second progression. NR=not reported. TFST=time to first subsequent therapy or death. TSST=time to second subsequent therapy or death.

Figure 1.

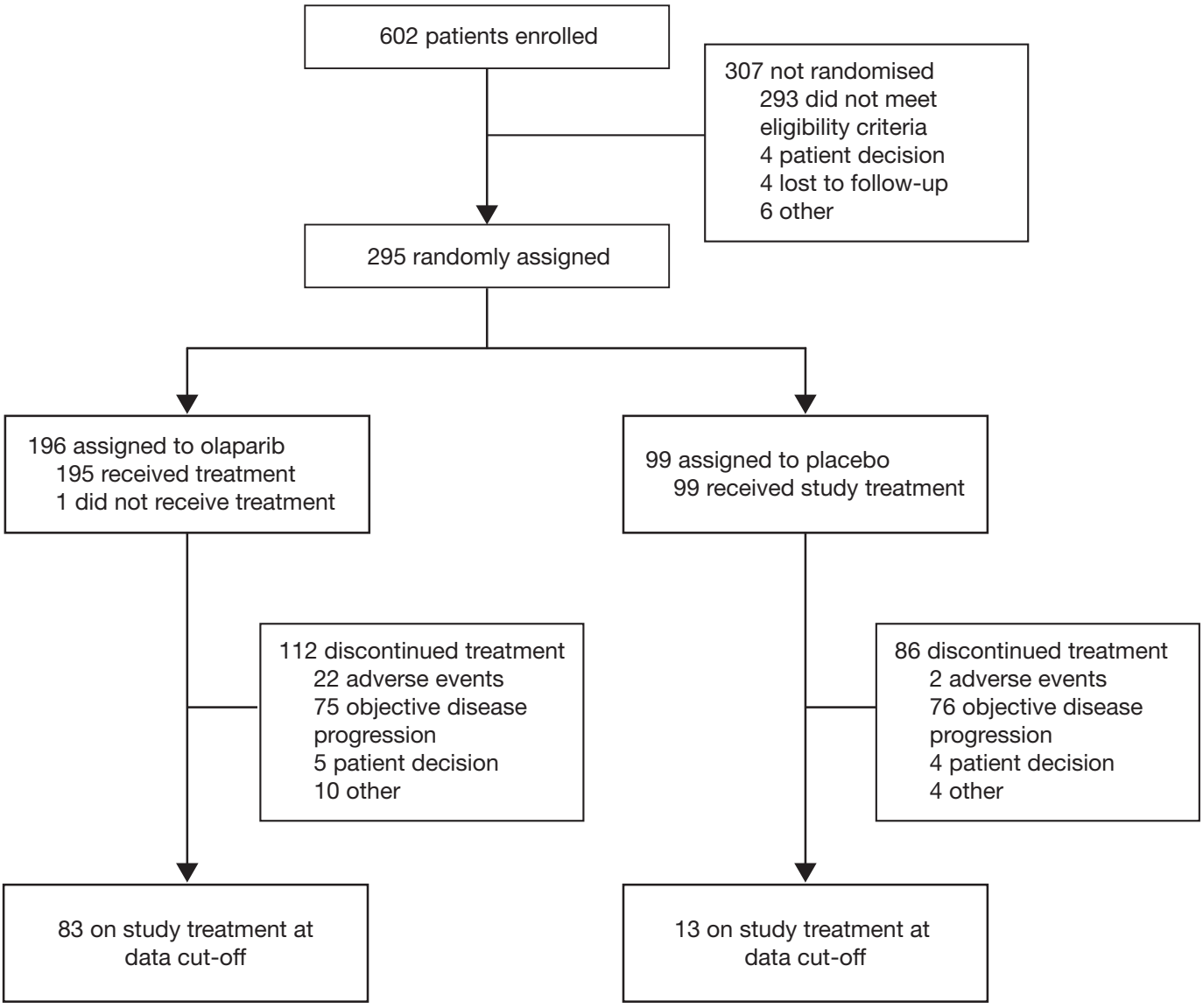
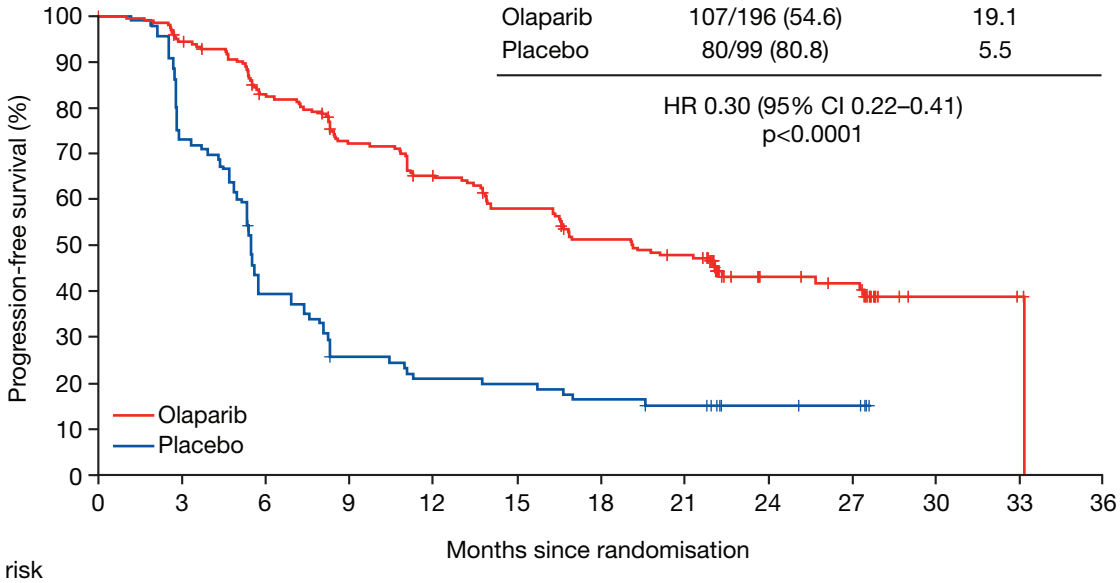

602 patients enrolled
307 not randomised
293 did not meet eligibility criteria
4 patient decision
4 lost to follow-up
6 other
295 randomly assigned
196 assigned to olaparib
195 received treatment
1 did not receive treatment
99 assigned to placebo
99 received study treatment
112 discontinued treatment
22 adverse events
75 objective disease progression
5 patient decision
10 other
86 discontinued treatment
2 adverse events
76 objective disease progression
4 patient decision
4 other
83 on study treatment at data cut-off
13 on study treatment at data cut-off

Figure 2A.

	Events/total patients, n (%)	Median PFS, months
Olaparib	107/196 (54.6)	19.1
Placebo	80/99 (80.8)	5.5

HR 0.30 (95% CI 0.22–0.41)
p<0.0001



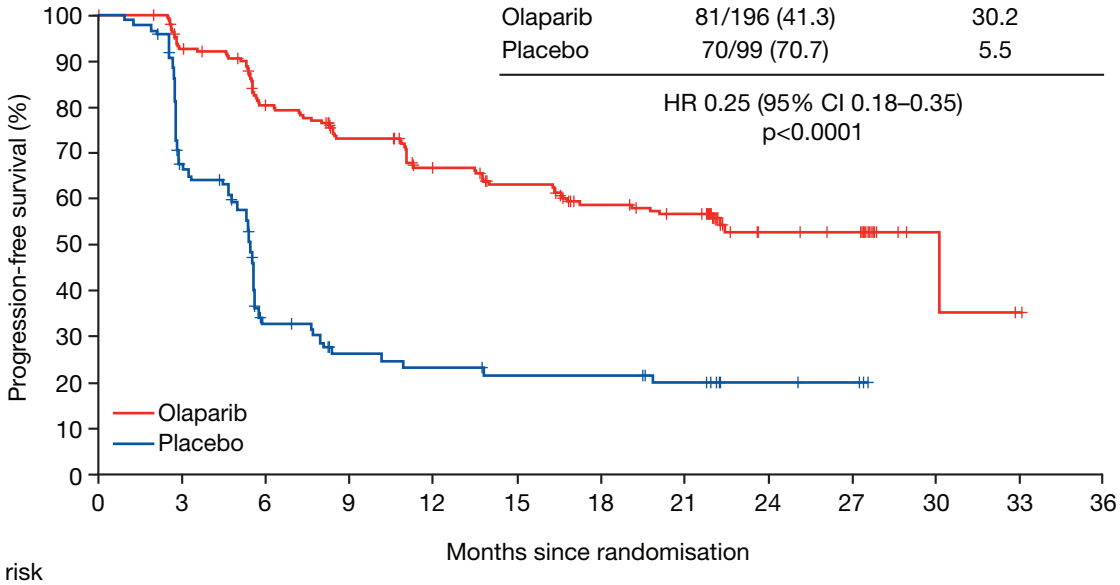
No. at risk

Olaparib	196	182	156	134	118	104	89	82	32	29	3	2	0
	(0)	(3)	(7)	(9)	(12)	(13)	(16)	(17)	(61)	(63)	(87)	(88)	(89)
Placebo	99	70	37	22	18	17	14	12	7	6	0	0	0
	(0)	(3)	(4)	(6)	(6)	(6)	(6)	(7)	(12)	(13)	(19)	(19)	(19)

Figure 2B.

	Events/total patients, n (%)	Median PFS, months
Olaparib	81/196 (41.3)	30.2
Placebo	70/99 (70.7)	5.5

HR 0.25 (95% CI 0.18–0.35)
p<0.0001



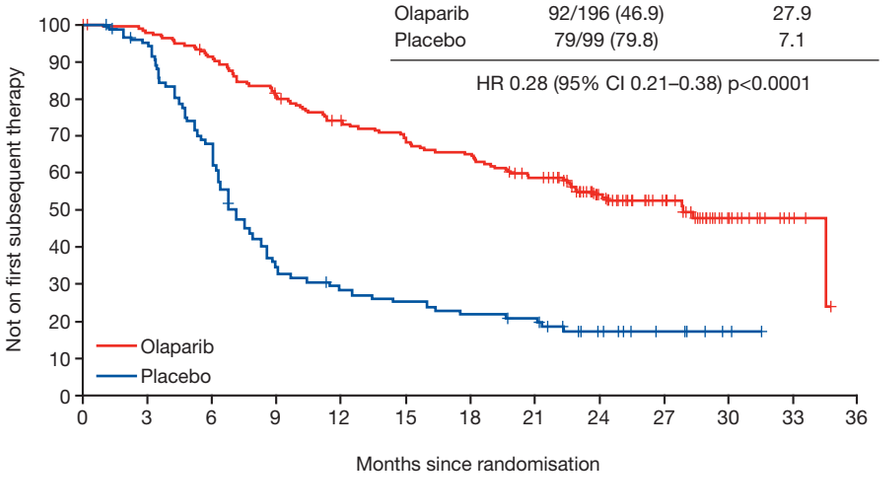
No. at risk

Olaparib	196	176	148	128	112	103	88	82	30	28	3	2	0
	(0)	(6)	(12)	(18)	(23)	(14)	(34)	(37)	(86)	(88)	(113)	(114)	(115)
Placebo	99	62	26	18	16	14	14	11	6	5	0	0	0
	(0)	(6)	(12)	(15)	(15)	(16)	(16)	(18)	(23)	(24)	(29)	(29)	(29)

Figure 3A.

	Events/total patients, n (%)	Median PFS, months
Olaparib	92/196 (46.9)	27.9
Placebo	79/99 (79.8)	7.1

HR 0.28 (95% CI 0.21–0.38) p<0.0001



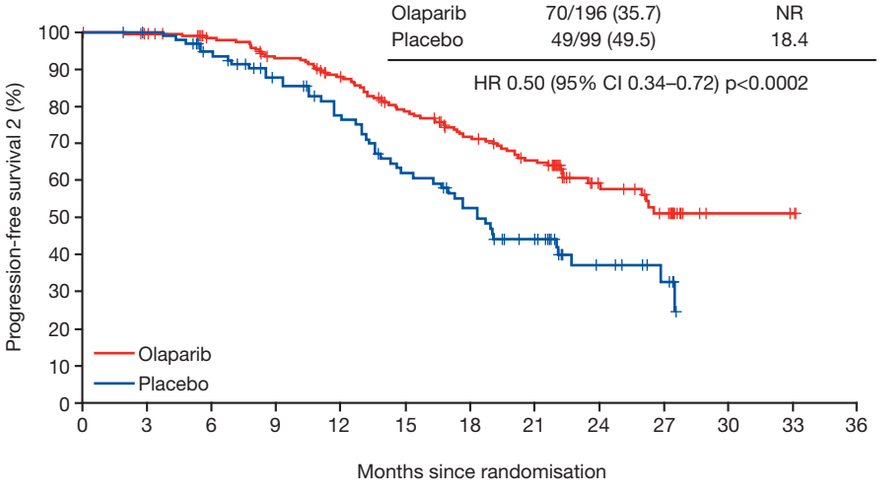
No. at risk (censored)

Olaparib	196 (0)	190 (2)	176 (3)	155 (4)	139 (7)	130 (7)	122 (7)	107 (10)	64 (46)	40 (68)	16 (89)	4 (101)	0 (104)
Placebo	99 (0)	92 (2)	65 (2)	33 (3)	26 (4)	23 (4)	20 (4)	19 (4)	11 (9)	6 (14)	2 (18)	0 (20)	0 (20)

Figure 3B.

	Events/total patients, n (%)	Median PFS, months
Olaparib	70/196 (35.7)	NR
Placebo	49/99 (49.5)	18.4

HR 0.50 (95% CI 0.34–0.72) p<0.0002



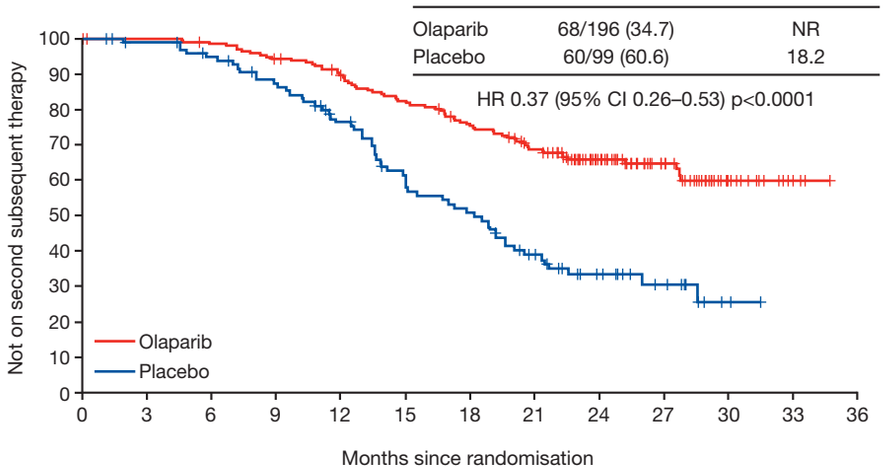
No. at risk (censored)

Olaparib	196 (0)	191 (4)	180 (13)	167 (16)	152 (22)	132 (26)	114 (33)	100 (37)	39 (92)	30 (96)	3 (123)	2 (124)	0 (126)
Placebo	99 (0)	95 (4)	84 (9)	71 (17)	59 (20)	47 (21)	38 (23)	28 (27)	13 (39)	7 (44)	0 (50)	0 (50)	0 (50)

Figure 3C.

	Events/total patients, n (%)	Median PFS, months
Olaparib	68/196 (34.7)	NR
Placebo	60/99 (60.6)	18.2

HR 0.37 (95% CI 0.26–0.53) p<0.0001



No. at risk (censored)

Olaparib	196 (0)	194 (2)	190 (3)	181 (4)	169 (7)	155 (7)	141 (9)	123 (14)	75 (57)	43 (88)	17 (111)	4 (124)	0 (128)
Placebo	99 (0)	95 (3)	90 (4)	81 (6)	67 (10)	51 (12)	43 (12)	30 (15)	17 (24)	10 (30)	2 (37)	0 (39)	0 (39)

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival