Overall survival with maintenance olaparib in BRCA1/2-mutated platinum-sensitive relapsed ovarian cancer (SOLO2/ENGOT-Ov21): a randomised, placebo-controlled, phase 3 trial

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Summary

Background

The PARP inhibitor olaparib significantly improved progression-free survival versus placebo (HR 0·30 [95% CI 0·22–0·41]) in BRCA-mutated platinum-sensitive relapsed ovarian cancer patients in the SOLO2/ENGOT-Ov21 trial. We report the final overall survival (OS) analysis.

Methods

This double-blind, randomised trial was performed across 123 sites (16 countries). Eligible patients had histologically confirmed, relapsed, high-grade serous ovarian or endometrioid cancer and received ≥2 previous platinum regimens. Patients were randomised 2:1 to olaparib tablets (300 mg twice daily) or placebo through a web or voice-response system, with stratification by response to previous chemotherapy (complete or partial) and length of platinum-free interval (>6-12 or >12 months). Masking occurred in patients, treatment providers, and data assessors. OS (secondary endpoint) was analysed in the intention-to-treat population. Safety analyses included patients who received ≥1 treatment dose. This trial, registered with ClinicalTrials.gov (NCT01874353), is not recruiting patients.

Findings

295 patients, enrolled between September 3, 2013, and November 21, 2014, received olaparib (n=196) or placebo (n=99). One patient (randomised in error) did not receive olaparib. Median follow-up was 65·7 months (IQR 63·6–69·3) with olaparib and 64·5 months (IQR 63·4–68·7) with placebo. Median OS was longer with olaparib

(51·7 months [95% CI 41·5–59·1]) versus placebo (38·8 months [95% CI 31·4–48·6]; HR 0·74 [95% CI 0·54–1·00], p=0·054; unadjusted for subsequent PARP inhibitor therapy). The most common grade ≥3 treatment-emergent adverse event (TEAE) was anaemia (41 [21%] of 195 olaparib patients; 2 [2%] of 99 placebo patients). Fifty (26%) olaparib patients and eight (8%) placebo patients reported serious TEAEs. TEAEs with a fatal outcome occurred in eight (4%) olaparib patients.

Interpretation

In SOLO2, the first phase 3 trial to our knowledge that provides final OS data on maintenance olaparib, olaparib prolonged median OS by 12·9 months over placebo (unadjusted for subsequent PARP inhibitor therapy).

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Introduction

Patients with relapsed ovarian cancer usually receive multiple lines of chemotherapy, with time to relapse typically shortening with each successive line of treatment.[1] Treatment goals in the relapsed setting include delaying symptomatic disease progression and prolonging survival.[2] Improvements in overall survival (OS) are difficult to demonstrate in ovarian cancer trials due to crossover and longer post-progression survival associated with post-progression therapies.[3,4]

The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib is approved in numerous countries as maintenance therapy for patients with platinum-sensitive relapsed ovarian cancer, regardless of *BRCA1* and/or *BRCA2* (BRCA) mutation status.[5-8] Olaparib is also approved as maintenance therapy in the newly diagnosed setting.[5,6,9,10]

In the primary analysis of the phase 3 SOLO2/ENGOT Ov-21 trial, maintenance olaparib provided a significant progression-free survival (PFS) benefit versus placebo (hazard ratio [HR] 0·30 [95% confidence interval [CI] 0·22–0·41], p<0·0001; median 19·1 months [95% CI 16·3–25·7] *vs* 5·5 months [95% CI 5·2–5·8]) in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.[11] Olaparib tablets had a manageable tolerability profile.

Here, we report final OS and long-term safety data of maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.

Methods

Study design and participants

This international, randomised, double-blind, placebo-controlled, phase 3 trial (SOLO2/ENGOT-Ov21; NCT01874353) was performed according to the European Network for Gynaecological Oncological Trial groups (ENGOT) Model C,[12] across 123 sites in 16 countries (appendix pp 2–3). The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics.[13]

Eligible patients were aged ≥18 years, had an Eastern Cooperative Oncology Group performance status 0–1 and histologically confirmed, relapsed, high-grade serous ovarian cancer (including primary peritoneal or fallopian tube cancer) or high-grade endometrioid cancer. Patients had received at least two previous lines of platinum-based chemotherapy, were in objective response (according to modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1·1 or CA-125 levels) to their most recent platinum regimen, and had platinum-sensitive disease (disease progression ≥6 months after the last dose of platinum-based chemotherapy) following the penultimate line of chemotherapy before enrolment.

Eligible patients had a documented deleterious, or suspected deleterious, BRCA mutation based on either blood or tumour testing. All patients consented to providing two blood samples for confirmatory germline BRCA mutation testing using the Myriad BRACAnalysis® test (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA). Patients with a known BRCA mutation before randomisation could enter the trial based on this information; patients with unknown BRCA mutation status were

screened prior to randomisation. Although patients with either somatic or germline BRCA mutations were eligible for randomisation, all patients randomised in SOLO2 were found to harbour a germline BRCA mutation.

Patients were ineligible if they were previously treated with a PARP inhibitor or had received any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) were ineligible.

The appendix contains the full eligibility criteria (pp 4–6) and latest protocol. All patients provided written, informed consent. The trial is not recruiting patients.

Randomisation and masking

Patients were randomised 2:1 to maintenance olaparib tablets or placebo. A computer software program (AstraZeneca's Global Randomization System) that generates random numbers produced the randomisation scheme; this was loaded into the interactive web or voice-response system database. Investigators or nominated assistants contacted the interactive web or voice-response system centralised randomisation centre for allocation of randomised treatment. Randomisation was performed within 8 weeks of patients' last dose of chemotherapy, with stratification by response to previous chemotherapy (complete or partial) and length of platinum-free interval (>6–12 or >12 months).

Treatment masking was achieved using individual treatment codes provided by the interactive web or voice-response system. Patients, treatment providers, data collectors, and analysers were masked to the treatment assignment. Olaparib tablets

were manufactured at three sites: AbbVie Deutschland GmbH and Co. KGa (Ludwigshafen, Germany), AbbVie Limited (Barceloneta, Puerto Rico), and AstraZeneca AB (Södertälje, Sweden). Placebo tablets were manufactured at Penn Pharmaceutical Services Limited (Gwent, United Kingdom). Olaparib and placebo tablets appeared identical and were presented in the same packaging. Unmasking was only permitted in medical emergencies where knowledge of the treatment assignment is required for patient management.

Procedures

Patients were randomised to receive oral olaparib tablets (300 mg twice daily) or matching placebo tablets (twice daily) until objective disease progression (modified RECIST version 1·1) or until other discontinuation criteria were met (appendix p 6). Treatment could continue beyond progression if the investigator deemed the patient was experiencing benefit and did not meet other discontinuation criteria. Repeat dose interruptions were permitted for a maximum of 14 days on each occasion (and were required for grade 3–4 treatment-emergent adverse events [TEAEs]; National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4·0) until reversion to grade ≤1 or complete patient recovery. If toxicities reoccurred after re-challenge with study treatment, and if further dose interruptions were considered inadequate for toxicity management, dose reductions (to 250 mg twice daily and then, if required, to 200 mg twice daily) or permanent treatment discontinuation could be considered. Treatment switching from placebo to olaparib was not permitted; however, patients could receive subsequent PARP inhibitor therapy as part of clinical practice.

Adverse events (AEs) were graded using National Cancer Institute CTCAE version 4·0. Tumor assessments were performed with computed tomography or magnetic resonance imaging every 12 weeks until week 72, then every 24 weeks thereafter until disease progression. Physical examinations and measurements of vital signs were performed on day 1, then every 4 weeks until week 72, then every 12 weeks thereafter. Measurements of haematology and clinical chemistry were conducted on day 1, then every week until day 29, then every 4 weeks until week 72, then every 12 weeks. After the data cut-off (DCO) for the primary analysis, all patients were followed for disease progression and survival. Patients receiving study treatment were followed up at least every 12 weeks for safety assessments and disease progression. MDS/AML events and new primary malignancies were actively solicited throughout the follow-up for overall survival.

Outcomes

We have previously reported data for PFS (defined as the time from randomisation until objective radiological disease progression or death), which represented the primary endpoint for this study.[11]

Key secondary endpoints included in this final analysis are OS, time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST), time to study treatment discontinuation or death (TDT), exposure to olaparib in patients receiving olaparib, and safety and tolerability.

Statistical analysis

Final OS analysis was planned for 60% maturity (~177 events). Survival outcomes for the two interventions were compared using a log-rank test stratified by the stratification

factors and based on a two-sided significance level of 5%. Kaplan-Meier methods were used to generate time-to-event curves, from which medians and survival proportions were calculated. HRs and CIs were calculated with Cox proportional hazards models, adjusting for the stratification factors. The same methods were used to assess TFST, TSST, and TDT. For subgroup analyses of OS, a Cox proportional hazards model including treatment, subgroup of interest and subgroup by treatment interaction was used. SAS® version 9·4 (SAS Institute, Cary, NC, USA) was used for the analyses.

Final OS, TFST, TSST, and TDT were analysed in the full analysis set (FAS; all randomised patients). Duration of exposure to treatment and safety were analysed in the safety analysis set (patients who received at least one treatment dose).

A prespecified exploratory OS analysis was performed using the rank preserving structural failure time model (re-censored), to adjust for subsequent PARP inhibitor therapy in the placebo group. Prespecified OS sensitivity analysis was conducted in patients with a germline BRCA mutation confirmed by the Myriad BRACAnalysis® test. A post-hoc OS sensitivity analysis used electronic case report form (eCRF) stratification variables to correct for patients who were mis-stratified at randomisation (appendix, p 6). The 95% CIs of the HRs of the OS sensitivity, TFST, and TSST analyses were unadjusted for multiplicity and inferences may not be reproducible.

An external independent data monitoring committee reviewed accumulating safety data. The latest statistical analysis plan is available in the appendix.

Role of the funding source

The trial was designed by ENGOT and its lead group, GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens), in collaboration with the sponsor, AstraZeneca. This article was written by the authors, with medical writing support funded by the sponsor. All authors had access to the raw data and had roles in data collection, analysis, and interpretation. The corresponding author had full access to all the raw data and had final responsibility for the decision to submit for publication.

Results

From September 3, 2013 to November 21, 2014, 602 patients were screened for eligibility, of whom 295 patients were enrolled and randomised. Of 196 patients assigned to olaparib, 195 received olaparib; one patient was randomised in error (due to ineligibility for the trial) and did not receive olaparib. All 99 patients assigned to the placebo group received placebo (figure 1). Final DCO occurred on February 3, 2020.

Baseline characteristics appeared well balanced between the two groups (appendix p 7). A confirmed Myriad germline BRCA mutation was present in 190 (97%) of 196 patients in the olaparib group and 96 (97%) of 99 patients in the placebo group. Subsequent anticancer therapy modalities received following discontinuation of study treatment are provided in the appendix (p 7). Following progression, 20 (10%) and 38 (38%) patients in the olaparib and placebo groups, respectively, received subsequent PARP inhibitor therapy as either maintenance therapy following platinum-based chemotherapy or as monotherapy (appendix p 8).

The mean total treatment duration was 29·1 (standard deviation [SD] 24·7; interquartile range [IQR] 8·2–56·8) months for olaparib and 13·1 (SD 18·6; IQR 3·7–11·0) months for placebo. At the primary analysis, the mean total treatment duration was 17·4 months (SD 9·8) for olaparib and 9·0 months (SD 8·1) for placebo. At the primary analysis, median follow-up for PFS was 22·1 months (IQR 21·9–27·4) with olaparib and 22·2 months (IQR 8·3–27·5) with placebo in censored patients. At the final analysis, median follow-up for OS was 65·7 months (IQR 63·6–69·3) with olaparib and 64·5 months (IQR 63·4–68·7) with placebo.

The final OS analysis was performed after 181 of 295 patients had died (61% maturity: 116 [59%] of 196 patients [olaparib] and 65 [66%] of 99 patients [placebo]). Median OS was 51·7 months (95% CI 41·5–59·1) with olaparib and 38·8 months (95% CI 31·4–48·6) with placebo (HR 0·74 [95% CI 0·54–1·00], p=0·054; FAS; figure 2A and appendix p 8). The predefined threshold for statistical significance was not met. By Kaplan-Meier estimates, 42% (95% CI 35–49) of patients in the olaparib group and 33% (95% CI 24–43) of patients in the placebo group were alive at 5 years.

In the prespecified exploratory OS analysis that adjusted for subsequent PARP inhibitor therapy in the placebo group in the FAS (181 events in 295 patients: 116 events in 196 olaparib patients and 65 events in 99 placebo patients; 61% maturity), median OS was 51·7 months (95% CI 41·5–59·1) with olaparib and 35·4 months (95% CI 24·2–43·5) with placebo (HR 0·56 [95% CI 0·35–0·97]; figure 2B and appendix p 8). In the prespecified sensitivity analysis in patients with a germline BRCA mutation confirmed by Myriad BRACAnalysis® test (175 events in 286 patients: 111 events in 190 olaparib patients and 64 events in 96 placebo patients; 61% maturity), median OS was 52·4 months (95% CI 41·5–61·4) with olaparib and 37·4 months (95% CI 29·8–

44·2) with placebo (HR 0·71 [95% CI 0·52–0·97], p=0·031; appendix pp 8, 16). In the sensitivity analysis of OS using eCRF stratification variables in the FAS (181 events in 295 patients: 116 events in 196 olaparib patients and 65 events in 99 placebo patients; 61% maturity), median OS was 51·7 months (95% CI 41·5–59·1) with olaparib and 38·8 months (95% CI 31·4–48·6) with placebo (HR 0·70 [95% CI 0·52–0·96], p=0·023; appendix p 8). This analysis corrected for patients mis-stratified at randomisation based on response to previous chemotherapy and length of platinum-free interval.

OS subgroup analyses are shown in the appendix (p 17). Median OS was 67·4 months (95% CI 53·4–not calculable) with olaparib (n=91) and 49·2 months (95% CI 34·0–not calculable) with placebo (n=47) for patients in complete response to prior chemotherapy (HR 0·73 [95% CI 0·45–1·22]), and 39·2 months (95% CI 32·1–45·2) with olaparib (n=105) and 34·0 months (95% CI 21·9–40·1) with placebo (n=52) for patients in partial response (HR 0·79 [95% CI 0·54–1·18). Median OS was 56·3 months (95% CI 43·9–67·4) with olaparib (n=110) and 37·4 months (95% CI 27·1–60·3) with placebo (n=62) in patients who had received two previous lines of platinum-based chemotherapy (HR 0·78 [95% CI 0·53–1·18); 41·5 months (95% CI 35·1–not calculable) with olaparib (n=60) and 38·8 months (95% CI 21·5–49·3) with placebo (n=19) in patients who had received three previous lines (HR 0·68 [95% CI 0·37–1·30]); and 43·6 months (95% CI 22·7–59·1) with olaparib (n=25) and 40·1 months (95% CI 21·2–49·2) with placebo (n=18) in patients who had received at least four previous lines (HR 0·90 [95% CI 0·45–1·87]).

In the final analysis, median TFST (225 events in 295 patients: 139/196 [71%] in the olaparib group *vs* 86/99 [87%] in the placebo group; 76% maturity) was

27·4 months (95% CI 22·6–31·1) with olaparib and 7·2 months (95% CI 6·3–8·5) with placebo (HR 0·37 [95% CI 0·28–0·48], p<0·0001; unadjusted for multiplicity; appendix p 18). By Kaplan-Meier estimates, 28% (95% CI 22·1–34·8) of patients in the olaparib group and 13% (95% CI 7·0–20·3) of patients in the placebo group were alive and had still not received a first subsequent treatment at 5 years. Median TSST (209 events in 295 patients: 130/196 [66%] in the olaparib group *vs* 79/99 [80%] in the placebo group; 71% maturity) was 35·8 months (95% CI 29·4–43·9) with olaparib and 18·9 months (95% CI 15·5–21·5) with placebo (HR 0·51 [95% CI 0·39–0·68], p<0·0001; unadjusted for multiplicity; appendix p 18). Results for TDT are shown in the appendix (p 7).

Cumulative exposure of ≥5 years was seen in 43/195 (22%) patients in the olaparib group and 9/99 (9%) patients in the placebo group, and cumulative exposure of ≥2 years was seen in 87/195 (45%) and 13/99 (13%) patients, respectively (figure 3).

The most common grade 1–2 TEAEs were nausea, fatigue/asthenia, anaemia, and vomiting (table 1 and appendix pp 9–12). The most common grade ≥3 TEAE in the olaparib group was anaemia (table 1).

Serious TEAEs were reported in 50/195 (26%) patients receiving olaparib and 8/99 (8%) patients receiving placebo. At the primary analysis (DCO September 19, 2016), 35/195 (18%) patients receiving olaparib and 8/99 (8%) patients receiving placebo had serious TEAEs. The most common serious TEAE was anaemia (eight [4%] patients) in the olaparib group; and constipation (two [2%] patients) and small intestinal obstruction (two [2%] patients) in the placebo group (appendix p 13).

At the primary analysis, one patient in the olaparib group had a TEAE with an outcome of death. At the final analysis, 116/196 (59%) patients in the olaparib group

and 65/99 (66%) patients in the placebo group died during the trial; deaths related to the disease under investigation occurred in 98/196 (50%) and 54/99 (55%) patients, respectively. The causes of death for 2/196 (1%) patients in the olaparib group and 8/99 (8%) patients in the placebo group were recorded as unknown. TEAEs with an outcome of death occurred in eight (4%) patients in the olaparib group and no patients in the placebo group within the safety follow-up period (between first dose and 30 days after the final treatment dose); in the olaparib group these were attributed to MDS/AML (n=6), gastric adenocarcinoma (n=1), and plasma cell myeloma (n=1), which occurred within the safety follow-up period. MDS/AML events were actively solicited after the safety follow-up period. AEs with an outcome of death occurred in five (3%) patients in the olaparib group after the safety follow-up period; these were all attributed to MDS/AML. AEs with an outcome of death occurred in three (3%) patients in the placebo group after the safety follow-up period; these were attributed to AML (n=1), septic shock with MDS as a secondary cause of death (n=1), and respiratory distress with MDS as a secondary cause of death (n=1). Three deaths, unrelated to AEs or the disease under investigation, occurred in the olaparib group after the safety follow-up period; these were attributed to intestinal obstruction (n=1), myocardial infarction (n=1), and ovarian cancer (n=1, this patient was misclassified as having death not caused by disease progression).

At the primary analysis, MDS/AML occurred in four (2%) patients in the olaparib group (median follow-up: 22·1 months) and four (4%) patients in the placebo group (median follow-up: 22·2 months). At the final analysis in the olaparib group (median follow-up: 65·7 months), MDS/AML occurred in 16 (8%) patients; of these, nine (5%) patients developed MDS/AML after the safety follow-up period. In the placebo group

(median follow-up: 64·5 months), all four (4%) cases of MDS/AML occurred after the safety follow-up period (appendix p 14).

One (6%) olaparib patient and one (25%) placebo patient who developed MDS/AML received subsequent chemotherapy and PARP inhibitor therapy. Five (31%) olaparib patients and two (50%) placebo patients who developed MDS/AML received subsequent chemotherapy only. A swimmer plot summarising the duration of study treatment, subsequent therapy, and onset of MDS/AML is provided in the appendix (p 19). The median time to onset of MDS/AML from randomisation was 3·0 years (IQR 2·3–3·8) with olaparib and 1·4 years (IQR 0·8–2·0) with placebo in the FAS.

New primary malignancies occurred in eight (4%) patients in the olaparib group and two (2%) patients in the placebo group, and pneumonitis occurred in three (2%) patients and no patients, respectively (appendix p 14).

Dose interruptions because of TEAEs occurred in 97 (50%) patients in the olaparib group and 19 (19%) patients in the placebo group at the final analysis, and 88 (45%) patients and 18 (18%) patients, respectively, at the primary analysis. Dose reductions because of TEAEs occurred in 54 (28%) patients in the olaparib group and three (3%) patients in the placebo group at the final analysis, and in 49 (25%) patients and three (3%) patients, respectively, at the primary analysis. Treatment discontinuations because of TEAEs occurred in 33 (17%) patients in the olaparib group and three (3%) patients in the placebo group at the final analysis, and in 21 (11%) patients and two (2%) patients, respectively, at the primary analysis. Details of

TEAEs leading to dose interruptions, dose reductions, and treatment discontinuations are provided in the appendix (pp 14–16).

Discussion

This analysis demonstrated a median OS improvement of 12·9 months with olaparib over placebo (HR 0·74 [95% CI 0·54–1·00], p=0·054), despite 38% of patients in the placebo group receiving subsequent PARP inhibitor therapy, although the predefined threshold for statistical significance was not met. By Kaplan-Meier estimates, 28% of patients in the olaparib group were alive and had still not received a first subsequent treatment at 5 years, representing a patient-centred benefit of olaparib.

The final OS and sensitivity analyses show consistent OS benefits with olaparib versus placebo. The treatment effect of olaparib was apparent in the analysis adjusted for subsequent PARP inhibitor therapy in the placebo group, the analysis of patients with a Myriad germline BRCA mutation, and the analysis that corrected for patients who were mis-stratified at randomisation; the 95% CIs for the OS HR had upper limits of 0·97, 0·97, and 0·96, respectively.

The longer-term tolerability profile of olaparib in this analysis was generally consistent with that reported previously,[11,14] and will be further explored. There was only a small increase in TEAEs, dose modifications, and treatment discontinuations with olaparib compared with the primary analysis, despite the longer treatment duration.

MDS/AML events were actively solicited throughout the study treatment and follow-up. At the final analysis of SOLO2, which investigates patients with BRCA-

mutated platinum-sensitive relapsed ovarian cancer who had received ≥2 previous lines of platinum-based chemotherapy and received study treatment until disease progression, MDS/AML occurred in 16 (8%) olaparib patients and four (4%) placebo patients with a 5-year follow-up. In the olaparib group, nine (5%) patients developed MDS/AML after the safety follow-up period (>30 days after the final dose of olaparib, and during the survival follow-up). In the olaparib group, cumulative exposure of ≥2 years was seen in 45% of patients. The increased incidence of MDS/AML with olaparib versus placebo was observed in the context of the late onset of these events and the extended OS observed with olaparib versus placebo. In the overall clinical trial program across all indications, MDS/AML events occurred in <1·5% of patients at any time after starting olaparib, including cases that were actively solicited during the long-term follow up for overall survival.[5,14,15] In the first-line setting, the risk of MDS/AML remains at <1·5% at 5-year follow-up when maintenance olaparib treatment is provided for a duration of 2 years in patients who had received one previous line of platinum-based chemotherapy.[14,15] The association between MDS/AML and olaparib is being further explored.

Prior to this analysis, there had been difficulties in demonstrating OS improvements in ovarian cancer patients since platinum-based chemotherapy was introduced in the first-line[16] and relapsed[17] settings. Two phase 3 trials on molecularly targeted therapy had not demonstrated significant OS improvements with the addition of bevacizumab to platinum-based chemotherapy, followed by bevacizumab, in women with platinum-sensitive relapsed ovarian cancer.[18,19] Median OS was 33·6 months in the bevacizumab arm versus 32·9 months in the chemotherapy control arm in OCEANS (HR 0·95 [95% CI 0·77–1·18], p=0·65),[18] and 42·2 months (95% CI

37·7–46·2) versus 37·3 months (95% CI 32·6–39·7), respectively, in GOG-0213 (HR 0·83 [95% CI 0·68–1·01], p=0·056).[19] In the intention-to-treat population of newly diagnosed ovarian cancer patients from the phase 3 GOG-0218 trial, the bevacizumab concurrent arm (HR 1·06 [95% CI 0·94–1·20]) and bevacizumab concurrent plus maintenance arm (HR 0·96 [95% CI 0·85–1·09]) did not provide an OS advantage compared with the chemotherapy control arm.[20] In an exploratory analysis of patients with Stage IV disease, median OS was 42·8 months in the bevacizumab concurrent plus maintenance arm versus 32·6 months in the chemotherapy control arm (HR 0·75 [95% CI 0·59–0·95]).[20]

In the phase 2 Study 19 trial (NCT00753545), median OS was 34·9 months (95% CI 29·2–54·6) with maintenance olaparib capsules and 30·2 months (95% CI 23·1–40·7) with placebo in patients with a BRCA mutation (HR 0·62 [95% CI 0·42–0·93], p=0·021).[21] In SOLO2, median OS was 51·7 months (95% CI 41·5–59·1) with maintenance olaparib tablets and 38·8 months (95% CI 31·4–48·6) with placebo (HR 0·74 [95% CI 0·54–1·00], p=0·054), although the predefined threshold for statistical significance was not met. Eleven (15%) of 74 patients with a BRCA mutation in Study 19 and 43 (22%) of 195 patients in SOLO2 received olaparib for at least 5 years, demonstrating the patient-centred treatment benefit that olaparib provides in the relapsed setting.[21]

OS improvements are difficult to demonstrate in ovarian cancer trials because of crossover and longer post-progression survival associated with post-progression therapies.[3,4] The PFS benefit translating into OS prolongation with maintenance olaparib in SOLO2 supports the potential use of PFS as a surrogate for OS in the evaluation of PARP inhibitor therapy in ovarian cancer patients. While OS is the gold

standard efficacy endpoint in ovarian cancer trials, it is evaluated in combination with PFS and intermediate clinical endpoints (such as time to second disease progression and TSST) as the long post-progression survival and post-progression therapies of ovarian cancer patients lead to difficulty in demonstrating OS improvements.[22] Additionally, a consensus statement on recurrent ovarian cancer reported that the preferred endpoint for clinical trials is OS when the expected median OS is ≤12 months and PFS when the expected median OS is >12 months.[4]

In this analysis, the absolute gain in OS was greater in patients in the olaparib group who had received two or three previous lines of platinum-based chemotherapy than in those who had received at least four previous lines. This favours the earlier use of olaparib to achieve greater benefit in the relapsed setting. In the first-line setting, the early introduction of olaparib could offer the greatest benefit. Substantial PFS benefits were seen with olaparib versus placebo in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation in the phase 3 SOLO1 trial (NCT01844986),[14] and with olaparib plus bevacizumab versus bevacizumab in patients with newly diagnosed advanced ovarian cancer who were positive for homologous recombination deficiency in the phase 3 PAOLA-1 trial (NCT02477644).[23] Enduring PFS benefits were seen in patients following their completion of olaparib therapy at 24 months in SOLO1 and PAOLA-1.[14,23] In SOLO1, median PFS was 56·0 months with maintenance olaparib (median follow-up: 4·8 years) and 13·8 months (median follow-up: 5·0 years) with placebo (HR 0·33 [95% CI 0·25–0·43]); 48% of olaparib patients versus 21% of placebo patients remained free from disease progression or recurrence at 5 years.[15] This represents a significant milestone for PARP inhibitor therapy in the newly diagnosed setting.

SOLO2 is the first phase 3 trial to our knowledge that provides final OS data on maintenance olaparib, the only PARP inhibitor with long-term follow-up data, in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation. In this analysis, maintenance olaparib provided an unprecedented OS improvement of 12·9 months over placebo.

Contributors

AP was responsible for writing the manuscript. AF, JAL, RA, RTP, AMO, JK, TH, SP, MF, AB, T-WP-S, KT, GSS, AL, J-HK, EAF, IV, and EP-L were responsible for recruiting patients, conducting the trial, and obtaining the data. TM, ESL, and PR analysed the data. All authors interpreted the data, and reviewed the draft and final versions of the manuscript.

Study groups

Grupo Español de Investigación en Cáncer de Ovario (GEICO): AP. Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO): AF, EP-L. National Cancer Research Institute (NCRI): JAL. National Health and Medical Research Council (NHMRC) Clinical Trials Centre: RA. SOLO2 US Consortium: RTP. Princess Margaret Hospital Consortium: AMO. Israeli Society of Gynecologic Oncology (ISGO): JK. International Hereditary Cancer Center: TH. Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO): SP. Australia New Zealand Gynecological Oncology Group (ANZGOG): MF. Mario Negri Gynecologic Oncology Group (MANGO): AB. German Society of Gynecological Oncology (AGO): T-WP-S. National Cancer Center Hospital: KT. Dutch Gynecological Oncology Group (DGOG): GSS. St Petersburg City Clinical Oncology Dispensary: AL. Korean

Gynecologic Oncology Group (KGOG): J-HK. Instituto do Câncer do Estado São Paulo-Faculdade de Medicina da Universidade de São Paulo: EAF. Belgium and Luxembourg Gynaecological Oncology Group (BGOG): IV.

Declaration of interests

Authors have completed the ICMJE form for disclosure of potential conflicts of interest and the author statement form.

Data sharing

The redacted study protocol and statistical analysis plan is shared in the online appendix of this Article.

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Research in context

Evidence before this study

We searched PubMed using the search terms “poly(ADP-ribose) polymerase inhibitor” or “PARP inhibitor”, “ovarian cancer”, “maintenance”, and “platinum-sensitive

relapsed", using no date or language restrictions. We found one trial design (olaparib phase 3b OPINION study), primary and secondary results from the olaparib phase 2 Study 19, and primary results from the present olaparib phase 3 study, SOLO2.

Added value of this study

To our knowledge, olaparib is the only poly(ADP-ribose) polymerase (PARP) inhibitor with long-term follow-up data and SOLO2 is the first phase 3 trial that provides final overall survival (OS) data on maintenance therapy with a PARP inhibitor (olaparib) in patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation. Improvements in OS are difficult to demonstrate in ovarian cancer trials due to crossover and use of post-progression therapies. However, this analysis showed an unprecedented OS improvement of 12·9 months with maintenance olaparib over placebo.

Implications of all the available evidence

Patients with relapsed ovarian cancer represent a challenging population to treat, and usually receive multiple lines of chemotherapy, with time to relapse typically shortening with each successive line of treatment. Prior to this analysis, limited progress had been made in demonstrating OS improvements in ovarian cancer since the introduction of platinum-based chemotherapy. The SOLO2 final analysis shows significant OS benefit of maintenance olaparib for patients with platinum-sensitive relapsed ovarian cancer and a BRCA mutation.

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601 **Table 1: Summary of treatment-emergent adverse events**

602

	Olaparib (n=195)			Placebo (n=99)		
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 1–2**	**Grade 3**	**Grade 4**
Nausea	142 (72·8%)	6 (3·1%)	0	35 (35·4%)	0	0
Fatigue/asthenia*	119 (61·0%)	11 (5·6%)	0	37 (37·4%)	2 (2·0%)	0
Anaemia†	48 (24·6%)	39 (20·0%)	2 (1·0%)	8 (8·1%)	2 (2·0%)	0
Vomiting	73 (37·4%)	5 (2·6%)	0	19 (19·2%)	1 (1·0%)	0
Diarrhoea	65 (33·3%)	2 (1·0%)	0	20 (20·2%)	0	0
Abdominal pain	49 (25·1%)	6 (3·1%)	0	28 (28·3%)	3 (3·0%)	0
Headache	49 (25·1%)	1 (0·5%)	0	14 (14·1%)	0	0
Constipation	46 (23·6%)	0	0	20 (20·2%)	3 (3·0%)	0
Decreased appetite	43 (22·1%)	1 (0·5%)	0	11 (11·1%)	0	0
Leukopenia‡	27 (13·8%)	4 (2·1%)	3 (1·5%)	2 (2·0%)	0	0
Neutropenia§	32 (16·4%)	11 (5·6%)	3 (1·5%)	2 (2·0%)	3 (3·0%)	1 (1·0%)
Dysgeusia	38 (19·5%)	0	0	6 (6·1%)	0	0

Cough	36 (18·5%)	1 (0·5%)	1 (0·5%)	6 (6·1%)	0	0
Dizziness	33 (16·9%)	1 (0·5%)	0	6 (6·1%)	0	0
Back pain	31 (15·9%)	0	0	12 (12·1%)	2 (2·0%)	0
Thrombocytopenia¶	28 (14·4%)	3 (1·5%)	1 (0·5%)	3 (3·0%)	1 (1·0%)	0
Arthralgia	31 (15·9%)	0	0	14 (14·1%)	0	0
Dyspepsia	29 (14·9%)	0	0	9 (9·1%)	0	0
Hypomagnesaemia	28 (14·4%)	1 (0·5%)	0	10 (10·1%)	0	0
Pyrexia	28 (14·4%)	0	0	6 (6·1%)	0	0
Nasopharyngitis	25 (12·8%)	0	0	11 (11·1%)	0	0
Dyspnoea	23 (11·8%)	2 (1·0%)	0	1 (1·0%)	0	0
Upper abdominal pain	23 (11·8%)	1 (0·5%)	0	13 (13·1%)	0	0
Elevated blood creatinine	21 (10·8%)	0	0	1 (1·0%)	0	0
Urinary tract infection	17 (8·7%)	3 (1·5%)	0	10 (10·1%)	0	0

603 Data are n (%). Data are shown for TEAEs that occurred in at least 10% of patients in either treatment group during study
604 treatment or up to 30 days after discontinuation of the intervention. The TEAEs were graded using CTCAE version 4·0. Where
605 indicated, the *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms for some adverse events have been

606 combined. TEAE= treatment-emergent adverse event. *Includes patients with fatigue and patients with asthenia. †Includes
607 patients with anaemia, decreased haemoglobin level, decreased haematocrit, or decreased red blood cell count. ‡Includes
608 patients with leukopenia and decreased white blood cell count. §Includes patients with neutropenia, febrile neutropenia,
609 neutropenic sepsis, or decreased neutrophil count. ¶Includes patients with thrombocytopenia or decreased platelet count.
610

Figure legends

Figure 1: Trial profile

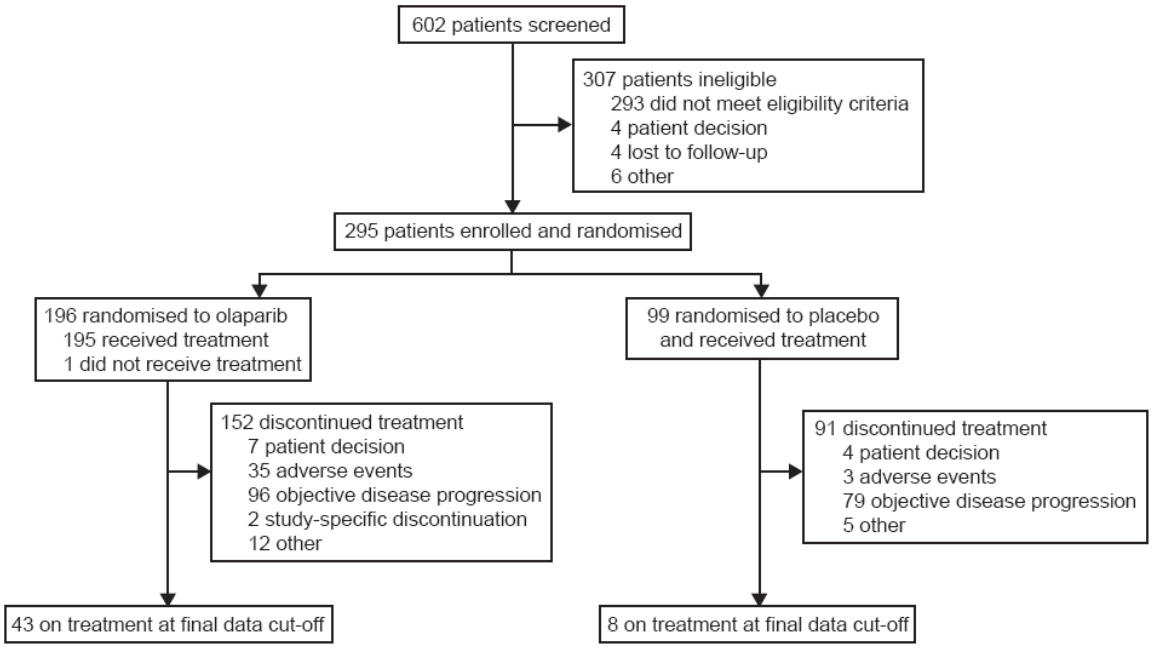
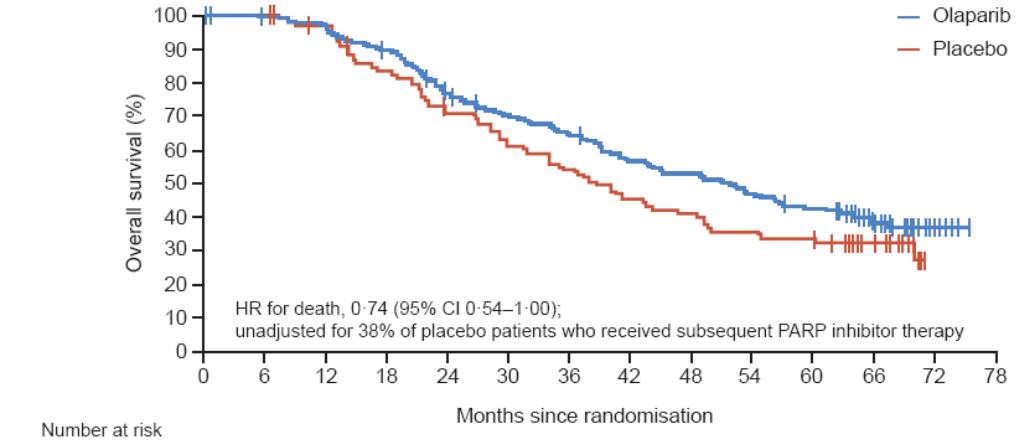
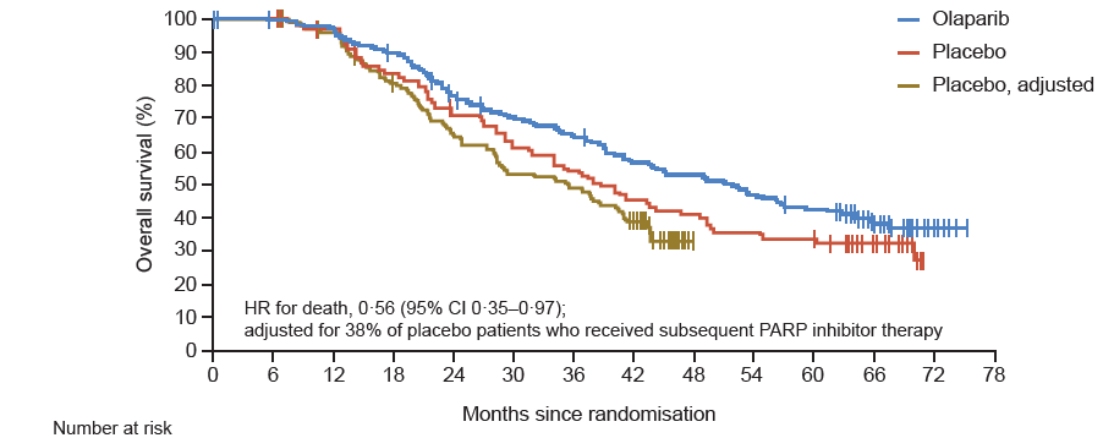


Figure 2: Kaplan-Meier estimates of (A) overall survival in the full analysis set and (B) overall survival in the full analysis set, adjusted for subsequent PARP inhibitor therapy in the placebo group



Number at risk (number censored)

Olaparib	196(0)	192(3)	187(3)	172(4)	145(6)	130(8)	120(8)	105(9)	98(9)	86(9)	77(10)	39(42)	7(73)	0(80)
Placebo	99(0)	99(0)	93(3)	79(4)	66(5)	57(5)	50(5)	42(5)	38(5)	33(5)	31(5)	16(19)	0(34)	0(34)

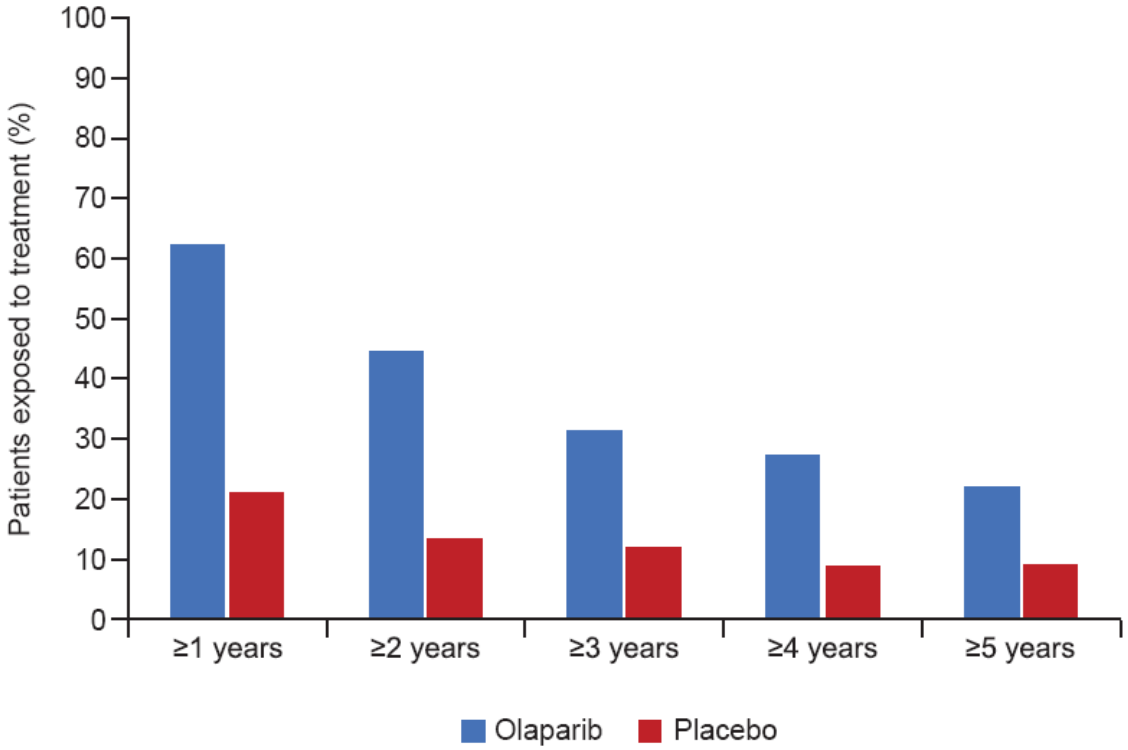


Number at risk (number censored)

Olaparib	196(0)	192(3)	187(3)	172(4)	145(6)	130(8)	120(8)	105(9)	98(9)	86(9)	77(10)	39(42)	7(73)	0(80)
Placebo	99(0)	99(0)	93(3)	79(4)	66(5)	57(5)	50(5)	42(5)	38(5)	33(5)	31(5)	16(19)	0(34)	0(34)
Placebo, adjusted	99(0)	99(0)	92(3)	75(5)	60(5)	50(5)	46(5)	34(7)	0(38)	0(38)	0(38)	0(38)	0(38)	0(38)

The rank preserving structural failure time model (re-censored) was used to adjust for subsequent PARP inhibitor therapy in the placebo group. CI=confidence interval. HR=hazard ratio. PARP=poly(ADP-ribose) polymerase.

623 **Figure 3: Duration of exposure to treatment in the safety analysis set**



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