2. SYNOPSIS

Study centre(s)

This study was conducted at study centres in 11 countries (France, Italy, Spain, Germany, Poland, Belgium, Denmark, Israel, United Kingdom, Norway, and Canada).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of PFS	Time from randomisation to Investigator-assessed disease progression (according to RECIST 1.1 guidelines) or death (by any cause in the absence of progression)
Secondary	Efficacy	To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of OS	Time from randomisation to death from any cause
Secondary	Efficacy	To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of time to earliest progression by GCIG criteria	Time from randomisation to the earliest of Investigator-assessed disease progression by RECIST or CA-125, or death (by any cause in the absence of progression)
Secondary	Efficacy	To determine the efficacy of Olaparib maintenance retreatment compared to matching placebo by assessment of the use of subsequent therapies and study treatment discontinuation	• TFST • TSST • TDT
Secondary	Efficacy	To determine the HRQoL of Olaparib maintenance retreatment compared to matching placebo as	Change from baseline, time to deterioration and proportion improved

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		measured by the FACT-O TOI	
Secondary	Safety	To evaluate the safety and tolerability of Olaparib maintenance retreatment	AEs/SAEs/AESI Collection of clinical chemistry/haematology parameters
CCI			
CCI			
CCI			

CCI

Abbreviations: AE: Adverse event; AESI: Adverse event of special interest; *BRCA1/2*: Breast cancer susceptibility genes; CA-125: cancer antigen 125; CCI CSP Clinical study protocol; DNA: Deoxyribonucleic acid; FACT-O: Functional Assessment of Cancer Therapy – Ovarian; GCIG: Gynaecologic Cancer Intergroup; HRQoL: Health-related quality of life; OS: Overall survival; PARPi: Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerisation inhibitor; PFS: Progression-free survival; RECIST 1.1: Response Evaluation Criteria in Solid Tumours, version 1.1; SAE: Serious adverse event; TDT: Time from randomisation to study treatment discontinuation or death; TOI: Trial Outcome Index; TFST: Time from randomisation to first subsequent treatment commencement or death, whichever occurred first; TSST: Time from randomisation to second subsequent treatment commencement or death, whichever occurred first.

Study design

This was a Phase IIIb, randomised, double-blind, placebo-controlled, multicentre study that assessed the efficacy and tolerability of Olaparib retreatment, versus matching placebo, in non-mucinous EOC patients (including patients with primary peritoneal and/or fallopian tube cancer). To be eligible, patients must have received maintenance therapy with a PARPi, and must have had at least a partial radiological response to their most recent course of platinum-based chemotherapy, or had NED (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125. All patients had a genetic status for *BRCA1*/*2* assessed locally.

Patients were randomised into 1 of 2 cohorts depending on their known *BRCA1/2* status:

- Cohort 1: patients with confirmed *BRCA1*/2(+ve) status (*sBRCA1*/2 or *gBRCA1*/2)
- Cohort 2: patients with known *gBRCA1*/2(-ve); could include some patients who had an undetected *sBRCA1*/2 mutation.

The study was designed such that each cohort would be randomised and analysed separately. Within each cohort, patients were randomised by prospective allocation in a 2 :1 ratio (Olaparib: matching placebo). Randomisation was stratified by prior use of bevacizumab and number of prior regimens of platinum-containing chemotherapy.

The minimum periods for which patients must have taken maintenance PARPi without progression to be eligible for this retreatment study were: ≥ 18 months following a first line of chemotherapy or ≥ 12 months following a second line or subsequent line of chemotherapy for Cohort 1, and ≥ 12 months following a first line of chemotherapy or ≥ 6 months following a second line or subsequent line of chemotherapy for Cohort 2. Patients should also have received subsequent platinum-based chemotherapy, excluding bevacizumab, following progression during or following prior PARPi therapy and have achieved, in the opinion of the Investigator, at least a partial radiological response, or not have a rising CA-125 following optimal debulking surgery with no measurable disease. In addition, patients had to be randomised into this OReO study within 8 weeks of their last dose of platinum-based chemotherapy (last dose was the day of the last infusion).

Investigators were required to provide tumour assessment information using RECIST 1.1 and HRQoL questionnaires at baseline (a maximum of 28 days prior to randomisation). Following randomisation, patients had to have tumour assessments every 12 weeks (± 7 days) until objective disease progression. Patients were to receive study treatment until objective radiological disease progression as per RECIST 1.1, or as long as, in the Investigator's

opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria. Such patients were also to:

- Not have symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease
- Not have a decline in ECOG performance status that could be attributed to disease progression
- Not have tumour progression at critical anatomical sites that could not be readily managed and stabilised by protocol allowed medical interventions
- Be provided information deferring any standard treatment options that may exist in favour of continuing investigational product treatment at the time of initial progression.

Target patient population and sample size

The benefit of Olaparib maintenance retreatment over matching placebo was evaluated through the primary endpoint of PFS and supporting secondary endpoints. Published data (Study 19, NOVA, SOLO2) of PARPi therapy following a second or subsequent line of platinum-based chemotherapy indicated a median PFS of less than 5.5 months could be expected in the placebo treated patients, irrespective of whether they were *BRCA1/2*(+ve) or *BRCA1/2*(-ve).

In the *BRCA1/2*(+ve) cohort, it was assumed that the median PFS from randomisation for patients in the placebo treatment group would be approximately 4.5 months. In total, 85 progression or death events from 120 patients would have 85% power to demonstrate significant PFS benefit at the 2-sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS was exponentially distributed, and allowing for a 10% drop-out rate. An observed HR of 0.63 or less was required to achieve this level of significance. Assuming 34 months of non-linear recruitment, 85 events were expected to occur approximately 41 months after the first patient was enrolled into this cohort of the study.

In the *BRCA1/2*(-ve) cohort, it was assumed that the median PFS from randomisation for patients in the treatment group would be approximately 4.5 months. In total, 74 progression or death events from 108 patients would have 80% power to demonstrate significant PFS benefit at the 2-sided 5% level if the assumed true treatment effect resulted in a HR of 0.5; this translates to a 4.5 month (100%) increase in median PFS beyond the 4.5 months expected for patients on placebo, if PFS was exponentially distributed, and allowing for a 10% drop-out rate. An observed HR of 0.61 or less would be required to achieve this level of significance. Assuming 36 months of non-linear recruitment, 74 events were expected to occur approximately 42 months after the first patient was enrolled into this cohort of the study.

Considering both cohorts, it was expected that approximately 228 patients in total would be enrolled into the study.

The analyses presented in this CSR are based on the DCO of 15 Feb 2021 and the database lock date of 12 May 2021. At DCO, 103 progression or death events had occurred in the *BRCA1/2*(+ve) cohort and 78 progression or death events had occurred in the *BRCA1/2*(-ve) cohort. Secondary efficacy endpoints were to be assessed at the time of primary analysis for PFS, and after 50% death events in either cohort or 60 months after FPI; whichever was earlier. As the criteria for final DCO (50% death events in either cohort) was also met by the time of the PFS analysis, all analyses are included in this report. The later completion of recruitment to the *BRCA1/2*(-ve) cohort and the subsequent limited follow-up in these patients due to the short time between last patient in and DCO led to a high level of early censoring and a lower maturity for the *BRCA1/2*(-ve) cohort than for the *BRCA1/2*(+ve) cohort.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

	Olaparib/Placebo
Study treatment name:	Olaparib/Placebo
Dosage formulation:	150 mg tablet 100 mg tablet
Route of administration:	Oral
Dosing instructions:	Patients were administered study treatment orally bd at 300 mg bd continually, or lower if 300 mg was not tolerated on initial PARPi treatment. Two × 150 mg Olaparib (or placebo) study treatment tablets were to be taken at the same time each day, approximately 12 hours apart with 1 glass of water. The tablets were to be swallowed whole and not chewed, crushed, dissolved, or divided. Study treatment tablets could be taken with or without food. Study treatment was dispensed to patients on Day 1 and every 28 days for the first 12 weeks, and then 12-weekly thereafter until the patient completed the study, withdrew from the study, or closure of the study.
Packaging and labelling:	For all centres, study treatment tablets were packed in high-density polyethylene bottles with child-resistant closures. Each container contained sufficient medication for at least 28 days plus overage. Study treatment was available as a film-coated tablet containing 150 mg or 100 mg of Olaparib, or placebo. Labels were prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels fulfilled Good Manufacturing Practice Annex 13 requirements for labelling. Label text was translated into local language.
Provider:	AstraZeneca

	Olaparib/Placebo
Batch numbers:	Provided in Appendix 16.1.6 of the CSR

Duration of treatment

Patients were to receive study treatment until objective radiological disease progression as per RECIST 1.1, or as long as, in the Investigator's opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria.

Statistical methods

Analysis sets:

The FAS included all randomised patients and compared the treatment groups according to randomisation. Patients who were randomised but did not subsequently go on to receive study treatment were included in the FAS. Therefore, all efficacy data was summarised and analysed using the FAS on an ITT basis as the primary analysis set.

The safety analysis set included all patients who received at least 1 dose of randomised study treatment, Olaparib or placebo. Patients were summarised according to treatment received. Safety data were summarised and analysed using the safety analysis set.

The PRO analysis set consisted of the FAS patients with a baseline PRO assessment. HRQoL data were summarised and analysed using the PRO analysis set.

Statistical analyses:

- Efficacy analyses: Assessments included PFS (primary endpoint), and OS, TFST, TSST, and TDT, time to earliest progression by RECIST 1.1, CA-125, or death (secondary endpoints). Tumour response was evaluated as per RECIST 1.1. The primary outcome, PFS, was analysed using a stratified log-rank test and the effect of Olaparib compared to placebo was estimated by the HR, associated 95% CI and p-value. K-M plots were presented by treatment group. The analysis of other time-to-event endpoints used the same methodology as PFS.
- Patient reported outcome: Comparison of HRQoL using the FACT-O tool for Olaparib vs placebo was analysed using a MMRM analysis of the change from baseline in TOI score for each scheduled post-baseline visit, based on the PRO analysis set. HRQoL mean scores were analysed accounting for treatment, visit, baseline scores, and the stratification factors. Time to deterioration was analysed using survival analysis methodology as per the PFS endpoint.
- Safety was assessed, in terms of AEs, laboratory data (clinical chemistry, haematology, and urinalysis), vital signs, and exposure, using summary statistics. Shift tables were provided for laboratory variables.

Patient population

***BRCA1/2*(+ve) cohort**

In total, 149 patients were screened in the *BRCA1/2*(+ve) cohort, 37 of which were screen failures. A total of 112 patients were randomised to treatment, 74 to Olaparib and 38 to placebo. Most patients (Olaparib: 67 patients [90.5%]; placebo: 37 patients [97.4%]) discontinued treatment, most commonly due to objective progression according to the RECIST criteria (Olaparib: 60 patients [89.6% of patients discontinuing]; placebo: 37 patients [100% of patients discontinuing]). Eight patients (7.1%) were still ongoing treatment at the time of DCO (Olaparib: 7 patients [9.5%]; placebo: 1 patient [2.6%]).

In total, 9 patients (Olaparib: 5 patients [6.8%]; placebo: 4 patients [10.5%]) in the *BRCA1/2*(+ve) cohort had at least 1 important protocol deviation. The most frequently observed protocol deviation was in the category of "CA-125 at screening was > ULN but was not repeated" and was reported in 3 patients (2.7%). The important protocol deviations were not considered likely to have influenced the primary analysis conclusions.

There were no important protocol deviations due to COVID-19. The COVID-19 pandemic is not determined to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

All 112 patients randomised to study treatment were included in the FAS. In total 112 patients were included in the safety analysis set, and 108 patients were included in the PRO analysis set. No patients in the *BRCA1/2*(+ve) cohort were excluded from safety analysis set.

The median (range) age in the *BRCA1/2*(+ve) cohort was 59.5 (37 to 87) years, and approximately two thirds of the patients were under the age of 65 and distributed in similar percentages in each treatment group. Over 90% of patients identified their race as White. The mean weight was comparable between the treatment groups.

There were no notable differences in disease history between treatment groups. The medical and surgical history reported was generally typical of the co-morbidities seen in this patient population and use of disallowed concomitant medication was reported in 1 (0.9%) patient in the *BRCA1/2*(+ve) cohort.

***BRCA1/2*(-ve) cohort**

In total, 149 patients were screened in the *BRCA1/2*(-ve) cohort, 40 of which were screen failures. A total of 108 patients were randomised to treatment, 72 to Olaparib and 36 to placebo. Most patients (Olaparib: 51 patients [70.8%]; placebo: 30 patients [83.3%]) discontinued treatment, most commonly due to objective progression according to the RECIST criteria (Olaparib: 43 patients [84.3% of patients discontinuing]; placebo: 29 patients

[96.7% of patients discontinuing]). Twenty-seven patients (25.0%) were still ongoing treatment at the time of DCO (Olaparib: 21 patients [29.2%]; placebo: 6 patients [16.7%]).

In total, 20 patients (Olaparib: 15 patients [20.8%]; placebo: 5 patients [13.9%]) in the *BRCA1/2*(-ve) cohort had at least 1 important protocol deviation. The most frequently observed protocol deviation was in the category of "CA-125 at screening was > ULN but was not repeated" and was reported in 6 patients (5.6%). The important protocol deviations were not considered likely to have influenced the primary analysis conclusions.

There were no important protocol deviations due to COVID-19. The COVID-19 pandemic is not determined to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

All 108 patients randomised to study treatment were included in the FAS and in the safety analysis set, and 103 patients were included in the PRO analysis set. No patients in the *BRCA1/2*(-ve) cohort were excluded from safety analysis set.

The median (range) age in the *BRCA1/2*(-ve) cohort was 66.0 (29 to 81) years, and approximately half of the patients were under the age of 65 and distributed in similar percentages in each treatment group. Over 90% of patients identified their race as White. The mean weight was comparable between the treatment groups.

There were no notable differences in disease history between treatment groups. The medical and surgical history reported was generally typical of the co-morbidities seen in this patient population and use of disallowed concomitant medication was reported in 2 (1.9%) patients in the *BRCA1/2*(-ve) cohort.

Summary of efficacy results

***BRCA1/2*(+ve) cohort**

Primary objective: For primary PFS, the required number of progression or death events for the analysis was reached in both cohorts. At DCO, there was 92.0% PFS maturity (103 events/112 patients). There was a statistically significant improvement in PFS for Olaparib compared to placebo with an HR of 0.566 (95% CI: 0.372, 0.868; p-value = 0.0220). Median (95% CI) PFS was 4.3 months (2.79, 5.49) on Olaparib versus 2.8 months (2.73, 4.96) on placebo. The PFS rate (95% CI) at 6 months was 34.7% (24.00%, 45.65%) for Olaparib patients and 13.2% (4.81%, 25.77%) for placebo patients. The PFS rate at 12 months was 19.0% (10.83%, 28.82%) for Olaparib patients and 0% (NC, NC) for placebo patients.

These analyses showed that the PFS benefit was generally seen across the different subgroups.

Sensitivity analyses for primary PFS showed benefits of Olaparib maintenance retreatment remained over placebo for all 3 sensitivity analyses (ie, time assessment bias, attrition bias, and adjustment for additional prognostic factors). Sensitivity analyses were consistent with the primary PFS analyses.

Secondary objectives:

- OS: At time of DCO for primary PFS analysis, there was 54.5% OS maturity (61 events/112 patients) and the HR was 0.881 (95% CI: 0.521, 1.525; p-value = 0.4382). The survival rate (95% CI) at 12 months was 80.4% (69.18%, 87.91%) on Olaparib and 78.9% (62.29%, 88.87%) on placebo.
- There was 92.0% maturity (103 events/112 patients) for progression by RECIST, or CA-125, or death. Median (95% CI) time to earliest progression by RECIST, or CA-125, or death was 2.8 months (2.76, 5.36) on Olaparib versus 2.8 months (2.73, 3.98) on placebo for the *BRCA1/2*(+ve) cohort and the HR was 0.626 (95% CI: 0.411, 0.962; p-value = 0.0579).
- There was 81.3% TFST maturity (91 events/112 patients). Median TFST (95% CI) was 5.8 months (4.67, 9.17) on Olaparib versus 5.1 months (3.58, 6.11) on placebo for the *BRCA1/2*(+ve) cohort and the HR was 0.560 (95% CI: 0.363, 0.877; p-value = 0.0117). There was 70.5% TSST maturity (79 events/112 patients). Median TSST (95% CI) was 13.1 months (11.10, 15.64) on Olaparib versus 11.7 months (8.61, 13.60) on placebo for the *BRCA1/2*(+ve) cohort and the HR was 0.703 (95% CI: 0.446, 1.128; p-value = 0.1798). The TSST free survival rate (95% CI) at 12 months was 58.2% (45.70%, 68.81%) on Olaparib and 47.9% (31.02%, 62.93%) on placebo.
- There was 92.9% TDT maturity (104 events/112 patients). Median TDT (95% CI) was 4.5 months (3.35, 5.59) on Olaparib versus 3.4 months (2.86, 5.49) on placebo for the *BRCA1/2*(+ve) cohort and the HR was 0.617 (95% CI: 0.409, 0.943; stratified log rank p-value = 0.0329).

Patient reported outcomes/quality of life:

- The percentage of patients completing FACT-O (adjusted compliance rates) was ≥75% through to the end of treatment in both arms in the *BRCA1/2*(+ve) cohort. Evaluability rates were 100% across all visits in both arms.
- In the MMRM analysis, the overall adjusted mean (SE) change from baseline in TOI score was -1.27 (0.55) in the Olaparib arm and 1.67 (0.89) with placebo.
- Olaparib and placebo arms in the time to symptom deterioration in swelling, cramps, or pain were similar. Although there were sufficient patients in the arms, there were insufficient events for any meaningful interpretation. Since there were insufficient patients with a baseline score, comparisons were not estimated for bowel control.

***BRCA1/2*(-ve) cohort**

Primary objective: For primary PFS, the required number of progression or death events for the analysis was reached in both cohorts. At DCO, there was 72.2% PFS maturity (78 events/108 patients). There was a statistically significant improvement in PFS for Olaparib compared to placebo, with an HR of 0.430 (95% CI: 0.264, 0.708; p-value = 0.0023). Median (95% CI) PFS was 5.3 months (2.89, 5.55) on Olaparib versus 2.8 months (2.79, 2.89) on placebo.

These analyses showed a consistent PFS treatment effect across the different subgroups.

Sensitivity analyses for primary PFS showed benefits of Olaparib maintenance retreatment remained over placebo for all 3 sensitivity analyses (ie, time assessment bias, attrition bias, and adjustment for additional prognostic factors). Sensitivity analyses were consistent with the primary PFS analyses.

Secondary objectives:

- OS: At the time of DCO for primary PFS analysis, the OS data was immature (21.3%).
- There was 75.0% maturity (81 events/108 patients) for progression by RECIST, or CA-125, or death. Median (95% CI) time to earliest progression by RECIST, or CA-125, or death was 2.9 months (2.79, 5.32) on Olaparib versus 2.8 months (2.63, 2.79) on placebo for the *BRCA1/2*(-ve) cohort and the HR was 0.541 (95% CI: 0.341, 0.869; p-value = 0.0149.
- There was 63.9% TFST maturity (69 events/108 patients). Median TFST (95% CI) was 7.9 months (5.88, 11.07) on Olaparib versus 4.3 months (3.68, 6.41) on placebo for the *BRCA1/2*(-ve) cohort and the HR was 0.389 (95% CI: 0.233, 0.654; p-value = 0.0011. There was 33.3% TSST maturity (36 events/108 patients).
- There was 75.0% TDT maturity (81 events/108 patients). Median TDT (95% CI) was 5.6 months (3.42, 5.78) on Olaparib versus 3.1 months (2.79, 3.91) on placebo for the *BRCA1/2*(-ve) cohort and the HR was 0.492 (95% CI: 0.307, 0.801; p-value = 0.0033.

Patient reported outcomes/quality of life:

- The percentage of patients completing FACT-O (adjusted compliance rates) was ≥75% through to the end of treatment in both arms in the *BRCA1/2*(-ve) cohort. Evaluability rates were 100% across all visits in both arms.
- In the MMRM analysis, the overall adjusted mean (SE) change from baseline in TOI score was -2.08 (0.60) in the Olaparib arm and 0.58 (0.90) with placebo.
- Olaparib and placebo arms in the time to symptom deterioration in swelling, cramps, and pain were similar. Although there were sufficient patients in the arms, there were insufficient events for any meaningful interpretation. Since there were insufficient patients with a baseline score, comparisons were not estimated for bowel control.

Summary of pharmacogenetic results

Results of the exploratory pharmacogenetic objectives will be reported separately from this CSR.

Summary of safety results

***BRCA1/2*(+ve) cohort**

The median total treatment exposure and median actual treatment exposure of Olaparib were 4.73 and 4.44 months, respectively. The median total treatment exposure and median actual treatment exposure of placebo were 3.35 and 3.15 months, respectively. The number (percentage) of patients with Olaparib interruptions and/or dose reductions was 28 (37.8%) and 11 patients, (14.9%) respectively. The number (percentage) of patients with placebo interruptions and/or dose reductions was 9 patients (23.7%) and 1 patient (2.6%), respectively.

In the *BRCA1/2*(+ve) cohort, most patients in both treatment groups had at least 1 TEAE (Olaparib: 64 patients [86.5%]; placebo: 33 patients [86.8%]). Treatment emergent adverse events of CTCAE Grade 3 or higher were reported for 11 patients (14.9%) in the Olaparib group and 2 patients (5.3%) in the placebo group.

Treatment emergent SAEs (including events with outcome of death) were reported for 5 patients (6.8%) in the Olaparib group. No patients in the placebo group reported any treatment emergent SAE. Adverse events of special interest (AESI) in this study were as follows: myelodysplastic syndrome (MDS)/AML, new primary malignancies and pneumonitis. From the start of the study up to the time of DCO, no patients reported an event of MDS/AML in the Olaparib group. In the placebo group, an event of MDS was reported in 1 patient more than 30 days after the last treatment dose. New primary malignancies (other than MDS/AML) were reported in 1 patient (1.4%) in the Olaparib arm and 1 patient (2.6%) in the placebo arm. No patients in either treatment arm reported events of pneumonitis.

A total of 39 patients (52.7%) in the Olaparib group and 22 patients (57.9%) in the placebo group died during the study. The majority of deaths were related to the disease under investigation (Olaparib: 35 patients [47.3%]; placebo: 21 patients [55.3%]). No patients in the *BRCA1/2*(+ve) cohort had an AE with an outcome of death.

Two patients (2.7%) in the Olaparib group had TEAEs leading to study treatment discontinuation. The placebo group did not have any patients with TEAEs leading to study treatment discontinuation.

***BRCA1/2*(-ve) cohort**

The median total treatment exposure and median actual treatment exposure of Olaparib were 3.98 and 3.81 months, respectively. Both the median total treatment exposure and median actual treatment exposure of placebo were 2.86 months. The number (percentage) of patients with Olaparib interruptions and/or dose reductions was 27 patients (37.5%) and 16 patients (22.2%), respectively. The number (percentage) of patients with placebo interruptions and/or dose reductions was 3 patients (8.3%) and 1 patient (2.8%), respectively.

In the *BRCA1/2*(-ve) cohort, most patients in both treatment groups had at least 1 TEAE (Olaparib: 66 patients [91.7%]; placebo: 31 patients [86.1%]). Treatment emergent adverse events of CTCAE Grade 3 or higher were reported for 15 patients (20.8%) in the Olaparib group and 3 patients (8.3%) in the placebo group.

Treatment emergent SAEs (including events with outcome of death) were reported for 11 patients (15.3%) in the Olaparib group and 2 patients (5.6%) in the placebo group. For the AESIs, new primary malignancies (other than MDS/AML) were reported in 1 patient (1.4%) in the Olaparib arm and no patients in the placebo arm. No patients in either arm reported events of MDS/AML or pneumonitis.

A total of 15 patients (20.8%) in the Olaparib group and 8 patients (22.2%) in the placebo group died during the study. The majority of deaths were related to the disease under investigation (Olaparib: 13 patients [18.1%]; placebo: 8 patients [22.2%]). No patients in the *BRCA1/2*(-ve) cohort had an AE with an outcome of death.

One patient (1.4%) in the Olaparib group had a TEAE leading to study treatment discontinuation. The placebo group did not have any patients with TEAE leading to study treatment discontinuation.

Conclusions

The OReO/ENGOT Ov-38 trial showed that, in a heavily pretreated ovarian cancer population, rechallenge with maintenance Olaparib following response to repeat platinum-based chemotherapy provided a statistically significant improvement in PFS compared with placebo, regardless of BRCA mutation status.

- Demographics and disease characteristics are reflective of the intended patient population.
- The study demonstrated an improvement in PFS with Olaparib compared with placebo, in patients with ovarian cancer previously treated with a PARPi and responding to repeat platinum chemotherapy (PFS HR 0.566; 95% CI 0.372, 0.868; median PFS 4.3 versus 2.8 months) in the *BRCA1/2*(+ve) cohort. The PFS rate at 12 months was 19.0% for Olaparib patients and 0% for placebo patients.

- The study demonstrated an improvement in PFS with Olaparib compared with placebo, in patients with ovarian cancer previously treated with a PARPi and responding to repeat platinum chemotherapy (PFS HR 0.430; 95% CI 0.264, 0.708; median PFS 5.3 versus 2.8 months) in the *BRCA1/2*(-ve) cohort.
- No clear difference was noted in the OS K-M curves between treatment groups.
- Review of AE data indicates safety and tolerability consistent with known safety profile of Olaparib.