Clinical Study Report Synopsis	
Drug Substance	Olaparib
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A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

Final Analysis of Overall Survival and Safety Update

Study dates: First subject enrolled: 6 August 2013
Data cut-off date: 03 February 2020
The analyses presented in this report are based on a database lock date of 27 February 2020

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This is a clinical study report (CSR) addendum to the CSR for Study D0816C00002 (hereafter referred to as the SOLO2 study). The results of the progression-free survival (PFS) analysis were based on a data cut-off (DCO) date of 19 September 2016 and were reported along with the data for the secondary efficacy endpoints, global health status/quality of life, pharmacokinetics, and safety data in the CSR for the SOLO2 PFS analysis, dated 16 January 2017. This CSR addendum reports the final analysis of overall survival (OS), as well as final analyses of the following:

- Time to first subsequent therapy or death (TFST)
- Time to second subsequent therapy or death (TSST)
- Time to study treatment discontinuation or death (TDT)
- Updated safety data

The data in this CSR addendum are based on a DCO of 03 February 2020, for the overall study population, and for the subset of patients who had their germline breast cancer susceptibility gene (gBRCA) mutation (gBRCAm) status confirmed by the Myriad test.

Study centres

This was an international multicentre study conducted in 119 sites in 16 countries: United States (19 centres), France (12 centres), Germany (11 centres), Brazil (10 centres), Spain (10 centres), Japan (9 centres), United Kingdom (8 centres), Canada (7 centres), Italy (7 centres), Poland (5 centres), Korea (4 centres), Netherlands (4 centres), Russia (4 centres), Australia (3 centres), Belgium (3 centres), and Israel (3 centres). In addition, a separate cohort of 32 patients was randomised in China but was not included in the main analyses; final OS results from this cohort will be reported outside of this CSR addendum.

The international co-ordinating investigator was Redacted ARCAGY-GINECO, Hôpital Hôtel-Dieu, Redacted 75004 Paris, France.

Publications

Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Sep;18(9):1274-1284. Erratum in Lancet Oncol. 2017 Sep;18(9):e510.

Friedlander M, Gebski V, Gibbs E, Davies L, Bloomfield R, Hilpert F,et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation

(SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet Oncol. 2018 Aug;19(8):1126-1134

Korach J, Freyer G, Banerjee S, Asher R, Cosin J, Oza AM, et al. Long-term tolerability of olaparib tablets as maintenance therapy for platinum-sensitive relapsed ovarian cancer (PSR OC): Phase III SOLO2 trial. Ann Oncol. 2018 Oct;29 Suppl 8:viii340-viii341.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation reported in this synopsis are summarised in Table S1. At the DCO for this addendum, only the endpoints of OS, TFST, TSST, TDT, and safety are reported.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum based chemotherapy [a].	PFS: the time from randomization until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression.
Secondary	Efficacy	To determine the efficacy of Olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy by assessment of OS; time to earliest progression by modified RECIST 1.1 or CA-125, or death; and PFS2.	OS: the time from the date of randomisation until death due to any cause. Time to earliest progression by modified RECIST 1.1 or CA-125 or death: the time from randomization to the earlier date of modified RECIST 1.1 or CA-125 progression or death by any cause [a]. PFS2: the time from the date of randomisation to the earliest of the progression event subsequent to that sed for the primary variable PFS or death [a].
Secondary	Efficacy	To obtain additional assessments of the anti-tumour activity of olaparib by evaluation of TFST, TSST, and TDT.	TFST: the time to first subsequent therapy or death. TSST: the time to second subsequent therapy or death. TDT: the time to study drug discontinuation or death.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To collect PRO data to explore disease-related symptoms and HRQoL as assessed by the TOI of the FACT-O[a].	FACT-O: a questionnaire, which includes the following subscales: physical, social/family, emotional and functional well-being, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. TOI: the trial outcome index derived from the FACT-O, which targets the most relevant symptoms together with functional and physical well-being and can be directly related to signs and symptoms and AEs.
Secondary	Efficacy	To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future *BRCA* mutation assays (gene sequencing and large rearrangement analysis) [a]	The following efficacy variables were reanalysed and reported in this CSR addendum for patients whose *gBRCAm* status was confirmed by the Myriad Test: OS, TDT, TFST and TSST.
Secondary	PK	To determine the patients' exposure to olaparib [a].	Individual plasma concentration data. Where possible the following PK parameters were determined: $C_{max,ss}$, AUC_{ss}, and $C_{min,ss}$.
Safety	Safety	To assess the safety and tolerability of olaparib maintenance monotherapy in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum based chemotherapy.	AEs, SAEs, DAEs, OAEs, laboratory vital signs, and ECGs.
Exploratory	Efficacy	To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L) [a].	EQ-5D-5L: a standardised measure of health status providing a simple, generic measure of health for clinical and economic appraisal.
Exploratory	Efficacy	To explore the impact of treatment and disease on resource use [a].	Resource use outcome variables include: length of hospital stay and reasons for hospitalisation, length of any time spent in the ICU.
Exploratory	Efficacy	To explore the effects of Olaparib maintenance monotherapy compared to placebo on HRQoL as assessed by the individual domains of the TOI of the FACT-O [a].	FACT-O: new patient-centric endpoints: disease-related symptoms, treatment-related toxicities, physical functioning and overall HRQoL.
Exploratory	Efficacy	To explore the efficacy of olaparib by assessment of OS adjusting for the impact of spontaneous switching (outside of study design) to PARP inhibitors or other potentially active investigational agents [a].	OS

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Other	To determine the frequency of and describe the nature of *BRCA mutation*/s in tumour samples and to compare this with germline *BRCA* mutation status [a].	*BRCA* mutation status by local, Myriad germline and Myriad tumour; deleterious and suspected deleterious mutation types in germline and tumour *BRCA* patients.
Exploratory	Other	To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory), tumour biopsy and blood sample at baseline and on progression (optional) [a].	To be determined
Exploratory	Other	Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability, or safety) may be performed on the collected and stored archival tumour samples that were mandatory for entry into the study or on optional tumour biopsy samples collected during the course of the study [a].	To be determined
Exploratory	Other	To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional) [a].	To be determined

[a] Reported outside of this CSR addedndum.
AE = adverse event; AUC_{ss} = area under plasma concentration-time curve during any dosing interval at steady state; *BRCA* = breast cancer susceptibility gene; *BRCAm* = breast cancer susceptibility gene mutated/mutation; CA-125 = Cancer Antigen-125; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{min,ss}$ = minimum plasma concentration at steady state; CSR = clinical study report; DAE = discontinuation of study drug due to adverse events; ECG = electrocardiogram; EQ-5D-5L = EuroQoL five dimensions, five level; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; *gBRCAm* = germline *BRCA* mutated; HRQoL = Health-related Quality of Life; ICU = intensive care unit; OAE = other adverse event; OS = overall survival; PARP = polyadenosine 5'diphosphoribose polymerase; PFS = progression-free survival; PFS2 = time from randomisation to second progression or death; PK = pharmacokinetic; PRO = patient reported outcomes; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; SAE = serious adverse event; TDT = time to study drug discontinuation or death; TFST = time to first subsequent therapy or death; TOI = trial outcome index; TSST = time to second subsequent therapy or death.

Study design

The study was a Phase III, randomised, double-blind, placebo-controlled, multi-centre study in platinum sensitive relapsed high-grade serous ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with breast cancer susceptibility gene (*BRCA*) mutations who had responded following platinum based

chemotherapy. Patients were determined to be platinum sensitive after completion of their penultimate platinum-based chemotherapy prior to enrolment on this study. Platinum-sensitivity was determined as >6 months (at least 183 days) after completion of their final platinum chemotherapy dose until disease progression (as determined by the investigator).

Patients must have completed at least 2 previous lines of platinum-based therapy before entry to the study, with no non-platinum regimen allowed to treat progression of the disease between the penultimate and the last chemotherapy course. Patients must not have received bevacizumab during the chemotherapy course immediately prior to randomisation.

Maintenance treatment was allowed at the end of the penultimate platinum regimen, including bevacizumab.

In addition, patients needed to demonstrate an objective partial response (PR) or complete response (CR) at baseline (per Response Evaluation Criteria in Solid Tumours [RECIST] and/or Cancer Antigen-125 [CA-125]) after completion of their last platinum regimen prior to enrolment in this study, or have no evidence of disease (NED; if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125. Patients had to be randomised within 8 weeks after their last dose of chemotherapy.

All patients were required to have documented mutation in *BRCA1* or *BRCA2* that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients known to have *BRCA* mutation/s from germline or a tumour specimen, prior to randomisation could enter the study based on this result. Patients with unknown *BRCA* status had to consent to provide 2 blood samples for germline *BRCA* testing.

Patients were randomised (using an Interactive Voice Response/Interactive Web Response system [IVRS]) in a 2:1 ratio (olaparib:matching placebo) to receive either olaparib 300 mg twice daily (bd) tablets or matching placebo.

Target subject population and sample size

It was intended to randomise a total of approximately 264 patients (176 in the olaparib group and 88 in the placebo group) with platinum sensitive relapsed high grade serious ovarian cancer or high grade endometrioid cancer with a documented mutation in *BRCA1* or *BRCA2* that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function), who had responded following platinum based chemotherapy, with an estimated life expectancy of at least 16 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

The global recruitment to the study closed when 295 patients were randomised, approximately 36 months after the first patient was enrolled. The DCO for the PFS analysis (19 September 2016) took place when 187 progression events had occurred (63.4% maturity). The DCO for

the final analysis of OS; (03 February 2020), took place when 181 patients had died [61.4% maturity]).

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

Patients were planned to be randomised (using an IVRS system in a 2:1 ratio to the treatments as specified below:

- olaparib tablets orally 300 mg bd
- placebo tablets orally bd

Duration of treatment

Patients continued to receive study treatment until objective radiological disease progression per RECIST as assessed by the investigator 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

The final OS analysis was performed with a DCO of 03 February 2020. Overall survival was analysed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6 to 12 months and >12 months) in the penultimate platinum-based chemotherapy prior to enrolment for generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) was estimated from a Cox proportional hazards model (with ties=Efron and the stratification variables as covariates) and the CI was calculated using a profile likelihood approach. The HR (olaparib vs placebo) together with its corresponding 95% CI and p-value was presented (a HR <1 represented the reduction in risk for those patients allocated olaparib). Kaplan-Meier (KM) plots of OS were presented by treatment group. Where the observed p-value for treatment difference was <0.05 (2 sided), the result was regarded as statistically significant.

Subgroup analyses were also conducted comparing OS between treatments to assess the consistency of treatment effect across potential or expected prognostic factors. If there were too few events available for a meaningful analysis of a particular subgroup (<20 events), the relationship between that subgroup and OS was not formally analysed. In this case, only descriptive summaries were provided. If there were less than 20 events in a particular subgroup, consideration was given to combining relevant subgroups if appropriate to do so.

The following subgroups of the full analysis set (FAS) were analysed:

- • Response to last platinum chemotherapy
- • Time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment

- • Baseline *BRCA* testing
- • *gBRCAm* status
- • ECOG performance status at baseline
- • Prior cytoreductive surgery for most recent progression
- • Lines of prior platinum therapy
- • Baseline CA-125 value
- • Age at randomisation
- • *gBRCA* mutation type by Myriad testing
- • Prior use of bevacizumab
- • Region 1 (North America or Rest of World)
- • Region 2 (Brazil, Poland, Russia, Japan, Korea or Rest of World)
- • Race

As a key sensitivity, the analysis of OS was repeated in those patients whose *gBRCAm* status was confirmed by the Myriad BRACAnalysis CDx® test. In addition, a sensitivity analysis of time to censoring was performed, where the censoring indicator of the primary OS was reversed. As there were patients who were mis-stratified, a post-hoc sensitivity analysis was carried out using the (correct) baseline data collected in the electronic case report form (eCRF); this used the same methodology and model as the main analysis of OS.

Subject population

Of the 602 patients enrolled into the study, 307 patients were not randomised as they were screening failures. All of the 295 patients randomised into the study were included in the FAS.

All except one olaparib patient (195) and all placebo patients (99) received study treatment and were included in the Safety Analysis Set. One patient in the olaparib arm ([Redacted]) did not receive treatment as the patient was randomised in error on the final day of dosing of platinum-based chemotherapy; it became apparent that the patient did not fulfil the eligibility criteria, including not having a baseline RECIST scan, and not having a minimum chemotherapy-free interval of 21 days.

At the final DCO (03 February 2020), 43 patients (22.1%) and 8 patients (8.1%) in the olaparib and placebo arms, respectively, were still receiving study treatment; 152 patients (77.9%) and 91 patients (91.9%) in the olaparib and placebo groups, respectively, had discontinued study treatment. The majority of patients who discontinued study treatment did so due to worsening of the condition under investigation (96 patients [49.2%] in the olaparib arm and 79 patients [79.8%] in the placebo arm). A greater number of patients discontinued study treatment due to adverse events (AEs) in the olaparib group than in the placebo group (35 patients [17.9%] in the olaparib arm and 3 patients [3.0%] in the placebo arm). A similar percentage of patients in both treatment groups voluntarily discontinued treatment (7 patients

[3.6%] olaparib versus 4 [4.0%] placebo). A similar percentage of patients in both groups had "Other" reasons for discontinuing study treatment (12 [6.2%] olaparib vs 5 [5.1%] placebo), which in most cases related to disease progression as assessed by, for example, CA-125 values, biopsy or imaging methods.

The 2 treatment groups were well balanced in terms of age, race, and ethnicity. The majority (89.5%) of patients were White and the median age was 56 years. Disease characteristics were generally well balanced between treatment groups. The majority of patients in both treatment groups had their primary tumour in the ovary (162 [82.7%] and 86 [86.9%] patients, respectively, in the olaparib and placebo groups). A similarly small proportion of patients (<10%) in both arms had either primary peritoneal cancer or fallopian tube cancer. The stratification factors of time to disease progression from the penultimate platinum-containing therapy prior to study enrolment and objective response to the last platinum containing regimen prior to study enrolment were well balanced.

Summary of efficacy results

The results of the PFS analysis were based on a DCO of 19 September 2016. The study met its primary objective, demonstrating a large, clinically meaningful, and statistically significant improvement in PFS with olaparib tablets 300 mg bd maintenance therapy compared with placebo (PFS HR 0.30; 95% CI 0.22, 0.41; p<0.0001; median PFS 19.1 months versus 5.5 months). The sensitivity analysis of PFS by blinded independent central review (BICR) was consistent with the PFS analysis (HR 0.25; 95% CI 0.18, 0.35; p<0.0001; median PFS 30.2 months versus 5.5 months). There was also a statistically significant and clinically meaningful delay in the secondary efficacy endpoint of time to second progression (PFS2) (HR 0.50; 95% CI 0.34, 0.72; p=0.0002).

At the final analysis DCO (03 February 2020), the majority of patients (82.7%) had discontinued study treatment and OS data were 61.4% mature (181/295 events). The HR of 0.74 indicated a clinically meaningful 26% reduction in risk of death with olaparib vs placebo.

Based on KM estimates (Table S2 and Figure S1), the percentage of patients who remained alive in the olaparib arm was 76.6%, 64.3%, 52.9%, and 42.1% at 24, 36, 48, and 60 months, respectively, compared with 70.6%, 53.5%, 40.6%, and 33.2%, respectively, in the placebo arm.

Although OS did not demonstrate a statistically significant difference between treatment arms at the DCO for the final OS analysis (HR 0.74; 95% CI 0.54, 1.00; p=0.0537), the final OS data are supportive of the clinically meaningful and statistically significant PFS treatment benefit observed at the time of the PFS analysis. The median OS improvement was 12.9 months in favour of olaparib (51.7 months compared with 38.8 months for olaparib and placebo, respectively).

The improvement in OS occurred despite 38.4% of patients in the placebo arm receiving a polyadenosine 5'diphosphoribose polymerase (PARP) inhibitor as subsequent therapy.

Table S2 Summary of Analysis of Overall Survival (FAS); DCO 03 February 2020

	Olaparib 300 mg bd (N=196)	**Placebo (N=99)**
n (%) of deaths [a]	116 (59.2)	65 (65.7)
Median (IQR) follow-up for overall survival (months) [b]	65.7 (63.6,69.3)	64.5 (63.4,68.7)
Treatment effect		
Median OS [e]	51.7	38.8
95% CI	41.5, 59.1	31.4, 48.6
HR [c]	0.74	
95% CI [c]	0.54, 1.00	
2-sided p-value [d]	0.0537	
Alive at 24 months (95% CI), % [e]	76.6 (69.9, 81.9)	70.6 (60.3, 78.7)
Alive at 36 months (95% CI), % [e]	64.3 (57.0, 70.6)	53.5 (42.9, 62.9)
Alive at 48 months (95% CI), % [e]	52.9 (45.6, 59.8)	40.6 (30.7, 50.3)
Alive at 60 months, (95% CI) % [e]	42.1 (35.0, 49.1)	33.2 (23.9, 42.7)
Alive at 72 months, (95% CI) % [e]	36.6 (29.3, 43.9)	-

[a] Overall survival was defined as the time from randomisation until death.

[b] Time from randomisation to date of censoring

[c] Estimated from Cox proportional hazards model including stratification variables as covariates.

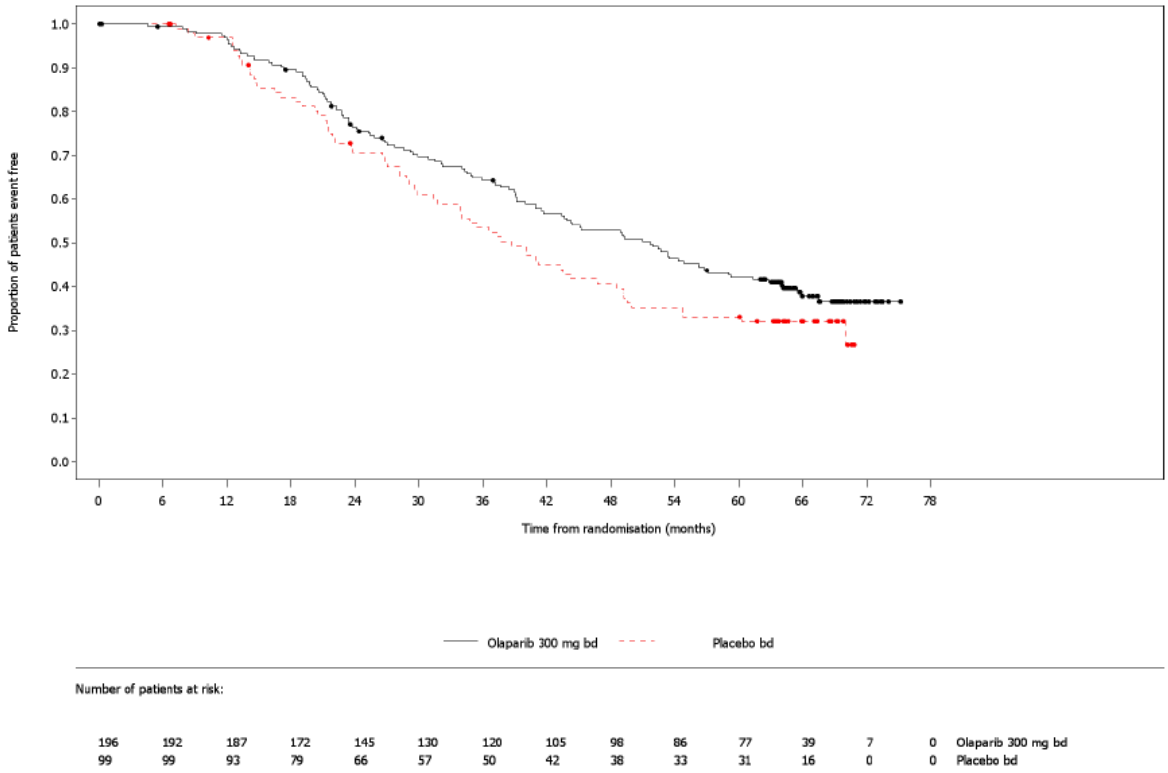
[d] Determined using log-rank test stratified by response to last platinum chemotherapy and time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment.

[e] Calculated using KM techniques.

bd = twice daily; CI = confidence interval; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; IQR = interquartile range; KM = Kaplan-Meier; OS = overall survival.

Data derived from Table 14.2.3.2.

Figure S1 Overall Survival, Kaplan-Meier plot (FAS); DCO 03 February 2020



Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was known to be alive.

bd = twice daily; DCO = data cut-off; FAS = full analysis set.

Data derived from Figure 14.2.3.1

The pre-specified sensitivity analysis of OS in Myriad *gBRCAm* patients (HR=0.71; 95% CI:0.52, 0.97; p=0.0306) was consistent with the FAS. The proportion of patients who were censored for OS prior to DCO was balanced between the treatment arms, both for those censored >12 weeks prior to DCO and those censored ≤12 weeks prior to DCO.

A sensitivity analysis of OS, using eCRF stratification variables (HR=0.70; 95% CI: 0.52, 0.96; p=0.0231) was consistent with the overall OS analysis.

Analysis of OS by Subgroups

Overall, the OS subgroup analyses were generally consistent with the FAS, with the exception of ECOG performance status of "restricted activity" and patients aged ≥65 years, which could be due to the small sample sizes in these subgroups (resulting in wide CIs around an HR estimate that included 1), and their overall exploratory nature, definitive conclusions cannot be drawn. Moreover, PFS benefit was demonstrated in both of those subgroups.

The global interaction test of OS was statistically significant at the 10% level (p=0.0942). The only interaction identified was ECOG performance status at baseline; however, further modelling did not provide sufficient evidence of a qualitative interaction (treatment effects in opposite direction).

Time for First and Second Subsequent Therapies

Although not controlled for multiplicity, there were statistically significant and clinically meaningful delays in the time to both first (HR 0.37; 95% CI 0.28, 0.48; p<0.0001) and second (HR 0.51; 95% CI 0.39, 0.68; p<0.0001) subsequent therapy or death in the olaparib arm compared with the placebo arm.

Time to study treatment discontinuation or death

Although not controlled for multiplicity, there was a statistically significant and clinically meaningful improvement in TDT (HR 0.37; 95% CI 0.28, 0.49; p<0.0001).

Summary of Safety Results

- At the final DCO, the total treatment duration in the olaparib arm was approximately 1.7 times longer than that at the DCO for the PFS analysis. The total median exposure to study treatment was more than 3 times longer in the olaparib arm (19.4 months) than in the placebo arm (5.6 months), consistent with the delay in PFS.
- At the final DCO (03 February 2020), 22.1% of olaparib-treated patients and 8.1% of placebo-treated patients remained on study treatment. In the olaparib arm, 62.1%, 44.6%, 31.3%, 27.2%, 22.1% and 2.1% of patients had been treated for ≥1 year, ≥2 years, ≥3 years, ≥4 years, ≥5 years and ≥6 years, respectively. In the placebo arm, 21.1%, 13.1%, 12.1%, 9.1% and 9.1% of patients had been treated for ≥1 year, ≥2 years, ≥3 years, ≥4 years and ≥5 years, respectively.
- The olaparib safety profile observed in this study was generally consistent with that observed in previous studies of olaparib monotherapy. The most commonly reported AEs in the olaparib arm were nausea, anaemia, fatigue, vomiting, diarrhoea and asthenia. These events were manageable by a strategy that included olaparib treatment interruption, dose reduction and therapeutic interventions. The safety profile is supportive of the use of olaparib 300 mg bd in the maintenance setting.
- More patients in the olaparib compared with placebo arm reported AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (46.2% olaparib, 19.2% placebo), with the most commonly reported being anaemia in the olaparib arm.
- More patients in the olaparib arm (49.7%) compared with the placebo arm (19.2%) required a temporary interruption to treatment due to an AE; the most common reasons (reported in >5% olaparib-treated patients) in the olaparib arm were anaemia, vomiting, nausea, and neutropenia.
- More patients in the olaparib arm (27.7%) compared with the placebo arm (3.0%) required a dose reduction due to an AE. The AEs most commonly leading to dose reduction (reported in >2 olaparib-treated patients) in the olaparib arm were anaemia, fatigue, asthenia, leukopenia, and neutropenia.

- The majority of deaths in the study were due to the disease under investigation. In the olaparib arm, a total of 18 patients had a cause of death that was not related to disease progression only. In the majority of these patients (in 11 of 18 patients [61.1%]) death was attributed to, or associated with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). Of the remaining 7 patients, cause of death was unknown Redacted, a disease progression event that was misclassified Redacted or associated with other AEs Redacted. In the placebo arm, 11 patients had a cause of death that was not related to disease progression only. In the majority of these patients (in 8 of 11 patients [72.7%]) cause of death was unknown Redacted. Events of MDS/AML were the primary or secondary cause of death in the remaining 3 patients. The majority of all fatal events that were not related to disease under investigation (in 13 of 18 olaparib-treated patients [72.2%] and in 11 of 11 placebo-treated patients) occurred more than 30 days after discontinuation of study treatment.
- More patients in the olaparib arm reported serious adverse events (SAEs) compared with the placebo arm (SAEs; 25.6% olaparib, 8.1% placebo).
- The adverse events of special interest (AESIs) for olaparib are MDS/AML, new primary malignancies and pneumonitis. There is extended follow-up for the AESIs of MDS/AML and new primary malignancies throughout the entire survival follow-up period. At the DCO for the final analysis (03 February 2020):
  - Sixteen patients (8.2%) randomised to the olaparib arm and 4 patients (4.0%) randomised to the placebo arm had an event of MDS/AML; of these, 12 olaparib-treated patients had AESIs of MDS/AML in the period between the DCO for the PFS analysis (16 September 2016) and the DCO for the final analysis, compared with no patients in the placebo arm.
  - Seven patients (3.6%) on the olaparib arm and 3 patients (3.0%) in the placebo arm had developed new primary malignancy events; of these, 4 olaparib-treated patients had developed new primary malignancies in the period between the DCO for the primary PFS analysis (16 September 2016) and the DCO for the final analysis, compared with 2 patients in the placebo arm. Redacted
  - Three patients in the olaparib arm and no patients in the placebo arm had events of pneumonitis; all of these events occurred prior to the DCO for the PFS analysis (16 September 2016).
- With the exception of haemoglobin, changes in haematology parameters were generally mild or moderate and transient. In the majority of patients, the worst maximum CTCAE Grade was 0, 1 or 2. No hepatobiliary or renal safety concerns were identified from review of the laboratory and AE data.

- No clinically important changes from baseline in vital signs were observed over time with olaparib treatment.

Conclusion(s)

SOLO2 demonstrated a positive benefit/risk profile for olaparib maintenance treatment in patients with platinum-sensitive relapsed *BRCAm* ovarian cancer. This is evidenced by the following:

- The results of the PFS analysis were based on a DCO of 19 September 2016. The study met its primary objective, demonstrating a large, clinically meaningful and statistically significant improvement in PFS with olaparib tablets 300 mg bd maintenance therapy compared with placebo (PFS HR 0.30; 95% CI 0.22, 0.41; p<0.0001; median PFS 19.1 months versus 5.5 months). The sensitivity analysis of PFS by BICR was consistent with the PFS analysis (HR 0.25; 95% CI 0.18, 0.35; p<0.0001; median PFS 30.2 versus 5.5 months). There was also a statistically significant and clinically meaningful delay in the secondary efficacy endpoint of PFS2 (HR 0.50; 95% CI 0.34, 0.72; p=0.0002).
- At the final analysis of OS data (DCO 03 February 2020; 61.4% maturity) a higher proportion of patients were alive and in follow up in the olaparib arm than in the placebo arm. Although OS did not demonstrate a statistically significant difference between treatment arms at the DCO for the final OS analysis, the final OS data are supportive of the clinically meaningful and statistically significant PFS treatment benefit observed at the time of the PFS analysis. The median OS improvement was 12.9 months in favour of olaparib (51.7 months compared with 38.8 months for olaparib and placebo, respectively).
- The improvement in OS occurred despite 38.4% of patients in the placebo arm receiving a PARP inhibitor as subsequent therapy.
- Other secondary efficacy endpoints assessed in this study were also supportive of the final OS analysis. Although not controlled for multiplicity, there were statistically significant and clinically meaningful delays in TFST (median TFST 27.4 months in the olaparib arm and 7.2 months in the placebo arm; HR 0.37; 95% CI 0.28, 0.48; p<0.0001) and TSST (median TSST 35.8 months in the olaparib arm and 18.9 months in the placebo arm; HR 0.51; 95% CI 0.39, 0.68; p<0.0001); and a statistically significant and clinically meaningful improvement in TDT (median TDT 19.4 months in the olaparib arm and 5.6 months in the placebo arm; HR 0.37; 95% CI 0.28, 0.49; p<0.0001).

The olaparib tolerability profile observed in this study was generally consistent with that observed in previous studies of olaparib monotherapy. However, MDS/AML was reported at a higher rate in both arms of this study than has previously been reported in olaparib clinical trials and occurred at a higher rate in olaparib treated patients than those who received placebo. It is considered possible that olaparib might have contributed to the development of MDS/AML in patients with platinum sensitive relapsed *BRCAm* ovarian cancer, who have been treated with at least 2 prior lines of platinum-based chemotherapy and who received olaparib until disease progression (the proportions of patients with a duration of olaparib treatment ≥2 years and ≥5 years were 45% and 22%, respectively). Moreover, these findings

should be interpreted in the context of extended survival on the olaparib arm and late onset of MDS/AML events. Despite this finding, the prolonged PFS and OS demonstrated with olaparib therapy continues to support the use of olaparib as a long-term maintenance treatment

Clinical Study Report Synopsis	
Drug Substance	Olaparib
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Edition Number	1
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A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum-Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum-based Chemotherapy: China Cohort

Final Analysis of Overall Survival and Safety Update

Study dates: First patient enrolled in China cohort: 07 April 2015
The analyses presented in this report are based on a data cut-off date of 03 February 2020

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

SYNOPSIS

This is a CSR Addendum to the China clinical study report (CSR) for Study D0816C00002 (hereafter referred to as the SOLO2 study). The CSR for the SOLO2 PFS analysis China cohort, dated 05 June 2017 contains the results of the progression-free survival (PFS) analysis based on a data cut-off (DCO) date of 16 January 2017 along with the data for the secondary efficacy endpoints and safety data. This CSR Addendum reports the final analysis of overall survival (OS) in the China cohort, as well as final analyses of the following:

- Time to first subsequent therapy or death (TFST)
- Time to second subsequent therapy or death (TSST)
- Time to study treatment discontinuation or death (TDT)
- Updated safety data

The data in this CSR Addendum are based on a DCO of 03 February 2020, for the China cohort.

Study Centre(s)

SOLO2 was an international multicentre study conducted in 119 sites in 16 countries. In addition to global enrolment, the study screened/enrolled patients at 16 sites in China; a separate cohort of 32 patients was randomised from 13 sites in China and is reported in this CSR Addendum.

Publications

There are no publications for the China cohort data at the time of writing this report.

Objectives and Criteria for Evaluation

The study objectives and criteria for evaluation reported in this synopsis are summarised in Table S1.

Table S1 Objectives and Endpoints

Objectives	Outcome variable/description
Primary (efficacy)	
• To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST 1.1) of olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy. [a]	• PFS: the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anti-cancer therapy prior to progression.

Table S1 Objectives and Endpoints

Objectives	Outcome variable/description
Secondary (efficacy)	
• To determine the efficacy of olaparib maintenance monotherapy compared to placebo in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy by assessment of OS; time to earliest progression by modified RECIST 1.1 or CA-125, or death; and PFS2.	• OS: the time from the date of randomisation until death due to any cause. • Time to earliest progression by modified RECIST 1.1 or CA-125 or death: the time from randomisation to the earlier date of modified RECIST 1.1 or CA-125 progression or death by any cause. [a] • PFS2: the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. [a]
• To obtain additional assessments of the anti-tumour activity of olaparib by evaluation of TFST, TSST, and TDT.	• TFST: the time to first subsequent therapy or death. • TSST: the time to second subsequent therapy or death. • TDT: the time to study drug discontinuation or death.
• To collect PRO data to explore disease related symptoms and HRQoL as assessed by the TOI of the FACT-O. [a, b]	• FACT-O: a questionnaire, which includes the following subscales: physical, social/family, emotional and functional well-being, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. • TOI: the trial outcome index derived from the FACT-O, which targets the most relevant symptoms together with functional and physical well-being and can be directly related to signs and symptoms and AEs.
• To assess efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future *BRCA* mutation assays (gene sequencing and large rearrangement analysis). [a, b]	• OS, TDT, TFST, and TSST in patients whose *gBRCAm* status was confirmed.
Secondary (PK)	
• To determine the patients' exposure to olaparib. [a, b]	• Individual plasma concentration data. • Where possible the following PK parameters were determined: $C_{max,ss}$, AUC_{ss}, and $C_{min,ss}$.
Safety	
• To assess the safety and tolerability of olaparib maintenance monotherapy in *BRCAm* relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy.	• AEs, SAEs, DAEs, OAEs, laboratory vital signs, and ECGs.

Table S1 Objectives and Endpoints

Objectives	Outcome variable/description
Exploratory (efficacy)	
• To explore the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level (EQ-5D-5L). [a, b]	• EQ-5D-5L: a standardised measure of health status providing a simple, generic measure of health for clinical and economic appraisal.
• To explore the impact of treatment and disease on resource use. [a, b]	• Resource use outcome variables include: length of hospital stay and reasons for hospitalisation, length of any time spent in the ICU.
• To explore the effects of olaparib maintenance monotherapy compared to placebo on HRQoL as assessed by the individual domains of the TOI of the FACT-O. [a, b]	• FACT-O: new patient-centric endpoints: disease-related symptoms, treatment-related toxicities, physical functioning, and overall HRQoL.
• To explore the efficacy of olaparib by assessment of OS adjusting for the impact of spontaneous switching (outside of study design) to PARP inhibitors or other potentially active investigational agents. [a, b]	• OS
Exploratory (other)	
• To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status. [a, b]	• *BRCA* mutation status by local, Myriad germline and Myriad tumour; deleterious and suspected deleterious mutation types in germline and tumour *BRCA* patients.
• To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples - archival tumour (mandatory), tumour biopsy and blood sample at baseline and on progression (optional). [a, b]	• To be determined.
• Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability, or safety) may be performed on the collected and stored archival tumour samples that were mandatory for entry into the study or on optional tumour biopsy samples collected during the course of the study. [a, b]	• To be determined.
• To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to study treatments and or susceptibility to disease (optional). [a, b]	• To be determined.

[a] Reported outside of this CSR Addendum.

[b] Objective not assessed in the China cohort.

AE = Adverse event; AUC_{ss} = Area under plasma concentration-time curve during any dosing interval at steady state; *BRCA* = Breast cancer susceptibility gene; *BRCAm* = Breast cancer susceptibility gene mutated/mutation; CA-125 = Cancer Antigen-125; $C_{max,ss}$ = Maximum plasma concentration at steady state; $C_{min,ss}$ = Minimum plasma concentration at steady state; CSR = Clinical study report; DAE = Discontinuation of study drug due to adverse events; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL five dimensions, five level; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; *gBRCAm* = Germline *BRCA* mutated; HRQoL = Health-related Quality of Life; ICU = Intensive care unit; OAE = Other adverse event; OS = Overall survival; PARP = Polyadenosine 5'diphosphoribose polymerase; PFS = Progression-free survival; PFS2 = Time from randomisation to second progression or death; PK = Pharmacokinetic; PRO = Patient reported outcomes; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; SAE = Serious adverse event; TDT = Time to study drug discontinuation or death; TFST = Time to first subsequent therapy or death; TOI = Trial outcome index; TSST = Time to second subsequent therapy or death.

Study Design

The study was a Phase III, randomised, double-blind, placebo-controlled, multi-centre study in platinum-sensitive relapsed high-grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with breast cancer susceptibility gene (*BRCA)* mutations who had responded following platinum-based chemotherapy. Patients were determined to be platinum-sensitive after completion of their penultimate platinum-based chemotherapy prior to enrolment on this study. Platinum-sensitivity was determined as >6 months (at least 183 days) after completion of their final platinum chemotherapy dose until disease progression (as determined by the investigator). Patients must have completed at least 2 previous lines of platinum-based therapy before entry to the study, with no non-platinum regimen allowed to treat progression of the disease between the penultimate and the last chemotherapy course. Patients must not have received bevacizumab during the chemotherapy course immediately prior to randomisation. Maintenance treatment was allowed at the end of the penultimate platinum regimen, including bevacizumab.

In addition, patients needed to demonstrate an objective partial response or complete response at baseline (per Response Evaluation Criteria in Solid Tumours [RECIST] and/or Cancer Antigen-125 [CA-125]) after completion of their last platinum regimen prior to enrolment in this study, or have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125. Patients had to be randomised within 8 weeks after their last dose of chemotherapy.

All patients were required to have a documented mutation in *BRCA1* or *BRCA2* that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients known to have *BRCA* mutation/s from germline or a tumour specimen prior to randomisation could enter the study based on this result. Patients with unknown *BRCA* status had to consent to provide 2 blood samples for germline *BRCA* testing. Patients were randomised (using an Interactive Voice Response/Interactive Web Response

system) in a 2:1 ratio (olaparib:matching placebo) to receive either olaparib 300 mg twice daily (bd) tablets or matching placebo.

Target Population and Sample Size

It was planned to randomise approximately 33 patients in the SOLO2 China cohort. Patients were to have platinum-sensitive relapsed HGSOC or high grade endometrioid cancer with a documented mutation in *BRCA1* or *BRCA2* that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function; note this is referred to as pathogenic or likely pathogenic in the BGI *gBRCA* test performed in China [analysis of the *BRCA1* and *BRCA2* genes performed by the BGI Clinical Laboratories (Shenzhen) performed in China]). In addition, patients were to have responded following platinum-based chemotherapy, with an estimated life expectancy of at least 16 weeks and an Eastern Cooperative Oncology Group performance status of 0 to 1.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Olaparib tablets were manufactured by AbbVie on behalf of AstraZeneca, as 150 mg and 100 mg green, film-coated tablets. Placebo tablets were manufactured by Penn Pharma on behalf of AstraZeneca, with the appearance to match each strength of olaparib.
Olaparib tablets were dosed at 300 mg bd orally. The following batch numbers of olaparib and olaparib matching placebo were used prior to the PFS DCO (16 January 2017):

- Olaparib: 1000073207, 31187B900, 37203B900, 39210B900, 39214B900, 41224B900, 44237B900, 46244B900
- Placebo: 007624, 009511

The following batch numbers of olaparib and olaparib matching placebo were used between the PFS DCO (16 January 2017) and the final OS DCO (03 February 2020):

- Olaparib: 1000118083/L004959, 1000094393, 1000131766/L005700, 1000088515
- Placebo: 009974

Duration of Treatment

Patients continued to receive study treatment until objective radiological disease progression per RECIST as assessed by the investigator 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

The final OS analysis was performed with a DCO of 03 February 2020. Overall survival was analysed using a log-rank test (unstratified), using the Breslow approach for handling ties. The hazard ratio (HR) and confidence interval (CI) was estimated from a Cox proportional hazards

model (with ties=Efron) and the CI was calculated using a profile likelihood approach. The HR (olaparib versus placebo) together with its corresponding 95% CI and p-value was presented (an HR <1 represented the reduction in risk for those patients allocated olaparib). Kaplan-Meier (KM) plots of OS were presented by treatment arm.

The secondary efficacy endpoints of TFST, TSST, and TDT were analysed using the same methodology and model as used for the final analysis of OS.

The China cohort sample size was small, and the China cohort analysis was not included in the multiple testing procedure, thus no alpha was assigned to the China cohort analysis. All treatment comparisons were descriptive in nature only and no formal statistical analysis was carried out. Thus, any p-values are nominal only.

Study Population

Of the 127 patients enrolled into the study in the China cohort, 95 patients were not randomised as they were screening failures. All of the 32 patients randomised into the study were included in the China Full Analysis Set (FAS). All patients (32) received study treatment and were included in the China Safety Analysis Set. Twenty-two patients received olaparib and 10 patients received placebo.

In the China cohort, the first patient was enrolled on 07 April 2015 and the last patient was enrolled on 28 October 2015. At the final OS DCO (03 February 2020), 5 patients in the olaparib arm were still receiving study treatment compared with no patients in the placebo arm; 17 patients (77.3%) and 10 patients (100%) in the olaparib and placebo groups, respectively, had discontinued study treatment. The majority of patients who discontinued study treatment did so due to worsening of the condition under investigation (14/17 patients [82.4%] in the olaparib arm and 6/10 patients [60.0%] in the placebo arm). No patients, in either arm, discontinued study treatment due to adverse events (AEs). A smaller proportion of patients discontinued treatment due to patient decision in the olaparib arm than in the placebo arm (2/17 patients [11.8%] olaparib versus 4/10 patients [40.0%] placebo). In the olaparib arm, 1/17 patients (5.9%) discontinued study treatment due to “other” reasons.

The 2 treatment groups were well balanced in terms of age. The median age was 49 years in the olaparib arm and 47 years in the placebo arm. Disease characteristics were generally well balanced between treatment groups. All patients had their primary tumour in the ovary, except for one olaparib-treated patient who had primary peritoneal cancer.

Summary of Efficacy Results

Progression-free Survival

The PFS analysis in China cohort (DCO 16 January 2017) showed that SOLO2 was a positive study, which met its primary objective of improved PFS (PFS HR 0.44; 95% CI 0.17, 1.19; p=0.0776; median PFS 13.8 months versus 5.5 months).

Overall Survival

At the final analysis DCO (03 February 2020), OS data were 62.5% mature (20 events/32 patients). An estimated OS HR of 0.93 (95% CI 0.38, 2.49) was observed. The median OS was longer in the olaparib arm compared with the placebo arm (41.7 months compared with 36.4 months for olaparib and placebo arms, respectively). Based on KM estimates (Table S2 and Figure S1), the percentage of patients who remained alive in the olaparib arm was 63.6%, 59.1%, 43.0%, and 35.8% at 24, 36, 48, and 54 months, respectively, compared with 80.0%, 50.0%, 40.0%, and 26.7%, respectively, in the placebo arm.

Visual assessments of the KM curves suggest non-proportionality of hazards, therefore, caution is required in interpreting the OS via the HR estimate obtained under the proportional hazard assumptions. The low number of events in this analysis should be taken into consideration.

Table S2 Summary of Analysis of Overall Survival (China FAS); DCO 03 February 2020

	Olaparib 300 mg bd (N=22)	**Placebo (N=10)**
n (%) of deaths [a]	13 (59.1)	7 (70.0)
Median (IQR) follow-up for overall survival, months [b]	50.8 (46.9, 52.5)	49.9 (47.1, 55.5)
Treatment effect		
Median OS (95% CI), months [c]	41.7 (17.6, NR)	36.4 (13.2, NR)
HR [d]	0.93	
95% CI [d]	0.38, 2.49	
2-sided p-value [e]	0.8831	
Alive at 24 months (95% CI), % [c]	63.6 (40.3, 79.9)	80.0 (40.9, 94.6)
Alive at 36 months (95% CI), % [c]	59.1 (36.1, 76.2)	50.0 (18.4, 75.3)
Alive at 48 months (95% CI), % [c]	43.0 (21.7, 62.7)	40.0 (12.3, 67.0)
Alive at 54 months (95% CI), % [c]	35.8 (15.4, 56.9)	26.7 (4.8, 56.3)

[a] Overall survival was defined as time from randomisation until death.

[b] Time from randomisation to date of censoring.

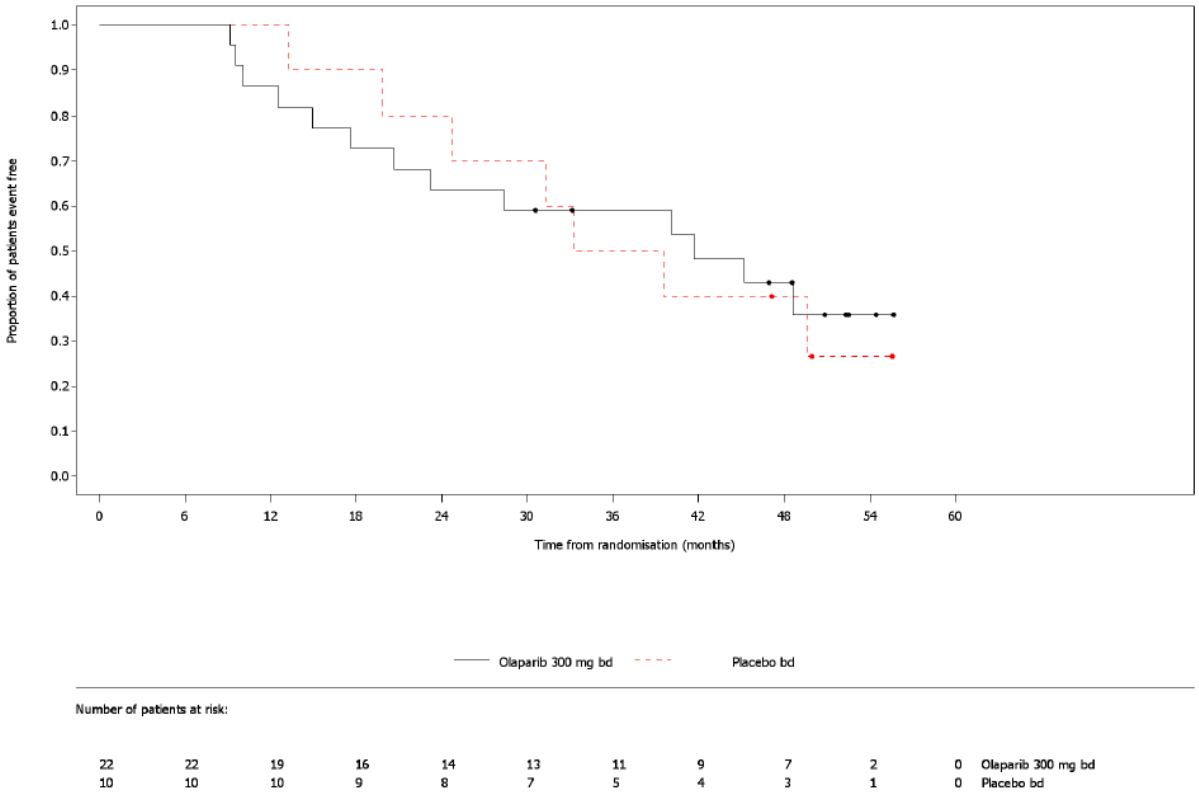
[c] Calculated using Kaplan-Meier techniques.

[d] Estimated from a Cox proportional hazards model with a treatment factor only.

[e] Determined using a log-rank test.

bd = Twice daily; CI = Confidence interval; DCO = Data cut-off; FAS = Full Analysis Set; HR = Hazard ratio; IQR = Interquartile range; NR = Not reached; OS = Overall survival.

Figure S1 Overall Survival, Kaplan-Meier Plot (China FAS); DCO 03 February 2020

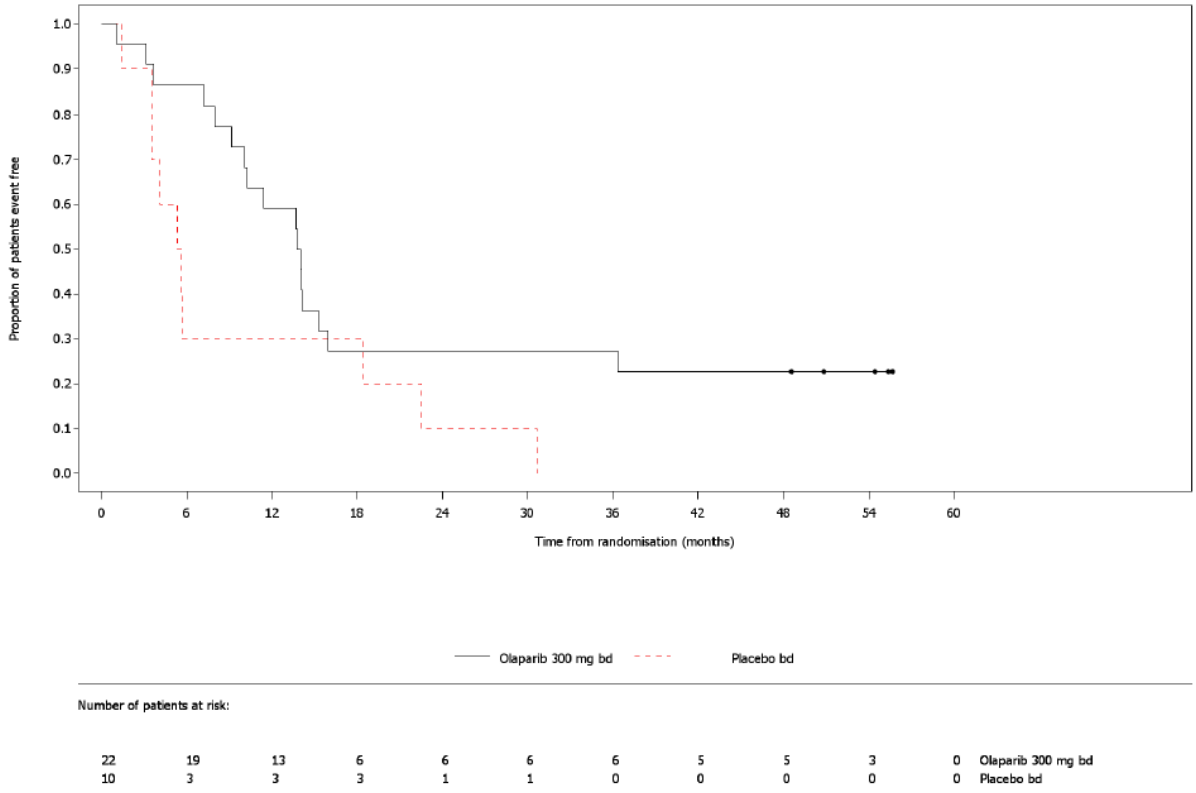


bd = Twice daily; DCO = Data cut-off; FAS = Full Analysis Set.

Time to First and Second Subsequent Therapies

There was a delay in TFST in the olaparib arm compared with the placebo arm (HR 0.47; 95% CI 0.21, 1.08; median TFST in the olaparib arm was 13.9 months versus 5.5 months in the placebo arm; Figure S2), consistent with the benefit observed for PFS in the China cohort. The low number of events in this analysis should be taken into consideration.

Figure S2 **Time to First Subsequent Cancer Therapy, Kaplan-Meier Plot (China FAS); DCO 03 February 2020**

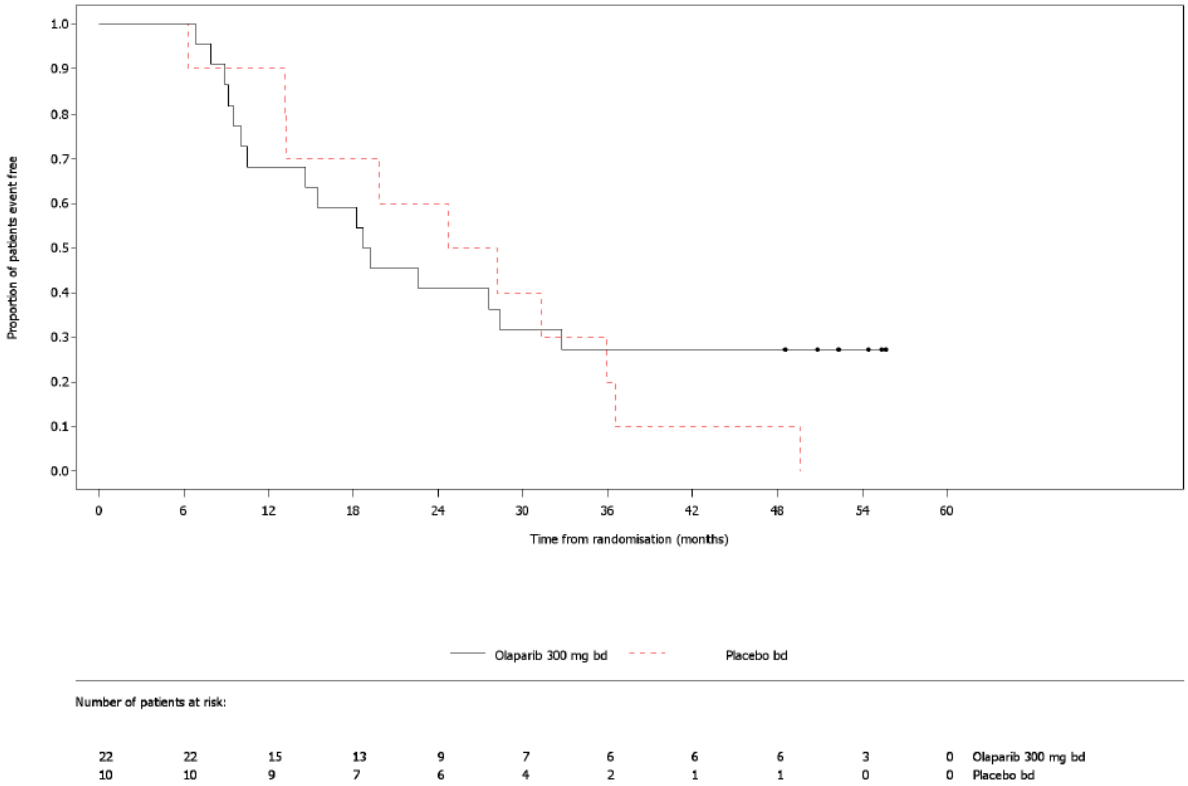


bd = Twice daily; DCO = Data cut-off; FAS = Full Analysis Set.

An estimated TSST HR of 0.81 (95% CI 0.37, 1.85) was observed. The median TSST was 19 months in the olaparib arm compared with 26.4 months in the placebo arm (Figure S3).

Visual assessments of the KM curves suggest non-proportionality of hazards, therefore, caution is required in interpreting the TSST via the HR estimate obtained under the proportional hazard assumptions. The low number of events in this analysis should be taken into consideration.

Figure S3 Time to Second Subsequent Cancer Therapy, Kaplan-Meier Plot (China FAS); DCO 03 February 2020

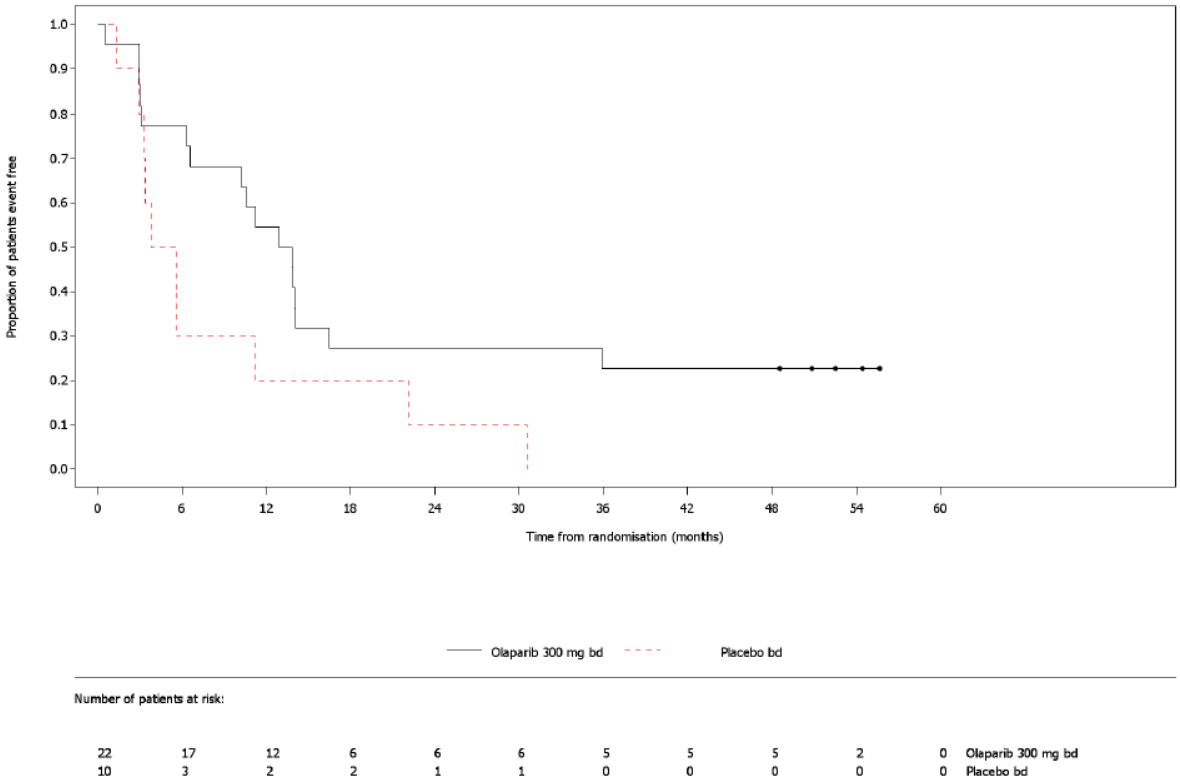


bd = Twice daily; DCO = Data cut-off; FAS = Full Analysis Set.

Time to Study Treatment Discontinuation or Death

There was an improvement in TDT in the olaparib arm compared with the placebo arm (HR 0.45; 95% CI 0.20, 1.04); median TDT in the olaparib arm was 13.4 months compared with 4.7 months in the placebo arm.

Figure S4 **Time to Study Treatment Discontinuation or Death, Kaplan-Meier Plot (China FAS); DCO 03 February 2020**



bd = Twice daily; DCO = Data cut-off; FAS = Full Analysis Set.

Summary of Safety Results

The median exposure to study treatment was 13.4 months and 4.7 months in the olaparib and placebo arms, respectively. The median relative dose intensity was 97.5% and 98.1% and the median percentage intended dose was 97.6% and 98.6%, in the olaparib and placebo groups, respectively. The majority of patients in the olaparib treatment arm received a mean daily dose of 600 mg olaparib.

All patients in both treatment arms reported AEs. In the olaparib arm, the most common AEs (reported by ≥30% patients) were nausea, anaemia, decreased appetite, vomiting, fatigue, and upper respiratory tract infection. In the placebo arm, the most common AE reported by ≥30% patients was abdominal distension.

The majority of AEs were Common Toxicity Criteria for Adverse Events (CTCAE) Grade 1 or 2. A higher percentage of patients had AEs of CTCAE Grade ≥3 in the olaparib arm (36.4%) compared with the placebo arm (10.0%). In the olaparib arm, the most frequently

reported AE of CTCAE Grade ≥3 was anaemia (3 patients [13.6%]). The only AE of CTCAE Grade ≥3 in the placebo arm was gastroenteritis (one patient [10.0%]).

Serious adverse events (SAEs) were reported by 5 patients (22.7%) in the olaparib arm and one patient (10.0%) in the placebo arm. The most common SAE was anaemia (reported in 2 patients [9.1%] in the olaparib arm and no patients in the placebo arm); all other SAEs were reported in one patient each (4.5% and 10.0% in the olaparib arm and placebo arm, respectively).

Of the 32 patients in the China FAS, 20 patients died during the study; 13 patients (59.1%) and 7 patients (70.0%) in the olaparib and placebo arms, respectively. Redacted

Adverse events leading to dose interruption were reported for 10 patients (45.5%) in the olaparib arm and no patients in the placebo arm. The most common AEs leading to dose interruption were anaemia (3 patients [13.6%]), diarrhoea, neutrophil count decreased, vomiting, and white blood cell count (WBC) decreased (each in 2 patients [9.1%]). Adverse events leading to dose reduction were reported for one patient in the olaparib arm; these were haemoglobin decreased, neutrophil count decreased, and WBC count decreased. There were no AEs leading to dose reduction in the placebo arm.

There were no AEs leading to discontinuation of study treatment in either treatment arm.

Adverse events of special interest in this study were the important identified risk of myelodysplastic syndrome/acute myeloid leukaemia, and the important potential risks of new primary malignancies and pneumonitis; there were no reports of these events in the China cohort.

Anaemia, neutropenia, and lymphopenia are known to be adverse drug reactions for olaparib treatment. Changes in the associated laboratory parameters on olaparib therapy were generally mild or moderate in severity, with low numbers of patients with a maximum CTCAE Grade of 3 or 4. Median absolute creatinine levels remained consistent and within normal range throughout the treatment period. No clinically relevant trends in vital signs were reported during the study. Redacted

Conclusions

The global SOLO2 study met its primary endpoint, showing a statistically significant and clinically meaningful improvement in PFS for platinum-sensitive relapsed *BRCAm* ovarian cancer patients receiving olaparib maintenance treatment compared with placebo (DCO 19 September 2016). The China cohort was enrolled after the recruitment in the global cohort was complete. The small China cohort was planned to be analysed separately and showed generally consistent results to the global study, both in terms of efficacy and safety (DCO 16 January 2017). No alpha was assigned to the statistical analyses of the China cohort data; therefore, these analyses are descriptive only, and due to the small sample size, confidence intervals around estimates are wide.

- The results of the PFS analysis in the China cohort were based on a DCO of 16 January 2017 and showed a 56% reduction in the risk of disease progression or death by investigator assessment with olaparib 300 mg bd maintenance therapy compared with placebo in *BRCAm* platinum-sensitive relapsed ovarian cancer patients who were in response following platinum containing chemotherapy (HR 0.44; 95% CI 0.17, 1.19; median PFS 13.8 months versus 5.5 months).
- At the final analysis of OS (DCO 03 February 2020; 62.5% maturity [20 events/32 patients]) there was a lower proportion of deaths in the olaparib arm (59.1%) compared with the placebo arm (70.0%). An estimated OS HR of 0.93 (95% CI 0.38, 2.49) was observed. The median OS was longer in the olaparib arm compared with the placebo arm (41.7 months compared with 36.4 months for olaparib and placebo arms, respectively).
- Other secondary efficacy endpoints assessed in this study demonstrated a delay in TFST (median TFST 13.9 months in the olaparib arm and 5.5 months in the placebo arm; HR 0.47; 95% CI 0.21, 1.08) and an improvement in TDT (median TDT was 13.4 months and 4.7 months in the olaparib arm and placebo arm, respectively; HR 0.45; 95% CI 0.20, 1.04). An estimated TSST HR of 0.81 (95% CI 0.37, 1.85) was observed (median TSST was 19.0 months in the olaparib arm compared with 26.4 months in the placebo arm).
- The olaparib safety and tolerability profile observed in the China cohort of this study was consistent with that observed in previous studies of olaparib monotherapy and is supportive of the use of olaparib 300 mg bd in the maintenance setting in Chinese patients.