Clinical Study Report Addendum 2 Synopsis	
Drug Substance	AZD2281
Study Code	D0816C00010
Edition Number	Final
Date	13 October 2021
EudraCT Number	2014-003438-20
NCT Number	NCT02282020

A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy versus Physician's Choice Single Agent Chemotherapy in the Treatment of Platinum Sensitive Relapsed Ovarian Cancer in Patients Carrying Germline *BRCA1/2* Mutations

Final Overall Survival Analysis and Safety Update

Study dates: First subject enrolled: 24 February 2015
Last subject last visit: 16 April 2021

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:
PPD
Massachusetts General Hospital
PPD
Boston, MA 02114, USA.

Sponsor's Responsible Medical Officer:
PPD
AstraZeneca PPD
Cambridge, CB2 8PA, UK.

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

Study Centres

This was an international multicentre study conducted in 78 study centres in 13 countries worldwide.

Publications

Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA III, Bidziński M, et al. Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial. J Clin Oncol. 2020;38(11):1164-74.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Measure
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the efficacy of olaparib vs physician's choice single agent chemotherapy by assessment of ORR using BICR	ORR by BICR using RECIST 1.1 [a]
Secondary	Efficacy	To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy	PFS by BICR using RECIST 1.1 [a] PFS2 by investigator assessment of radiological, clinical or CA-125 progression OS Time to earliest progression by RECIST 1.1 or CA-125 or death [a] TFST TSST TDT DoR by BICR using RECIST 1.1 criteria for evaluable patients [a] TTR by BICR using RECIST 1.1 criteria for evaluable patients [a]
Secondary	Efficacy	To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy on the HRQoL as measured by the TOI of the Functional Assessment of Cancer Therapy – Ovarian	Mean change from baseline in TOI score [a] Proportion improved (in the absence of subsequent cancer therapy) in TOI score [a]

Objective			Outcome Measure
Priority	**Type**	**Description**	**Description**
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 (eg, gene sequencing and large rearrangement analysis)	ORR[a] (by BICR), PFS[a] (by BICR), PFS2, OS, TDT, TFST and TSST, analyses will be performed in those patients whose *gBRCAm* status is confirmed by the central Myriad test (only required if populations differ from the MDAS [for ORR] or FAS [for PFS] populations) Development and delivery of a *BRCA* mutation companion diagnostic [a]
Secondary	Pharmacokinetic	To determine exposure to olaparib following dosing at the 300 mg bd tablet dose	Olaparib plasma concentration data and PK analyses [a]
Secondary	Safety	To assess the safety and tolerability of single agent olaparib vs physician's choice single agent chemotherapy	Adverse events, physical examination, vital signs including blood pressure, pulse, electrocardiogram and laboratory findings including clinical chemistry and haematology
Exploratory	Exploratory	To assess the effect on patient self-reported feelings about side-effects of single agent olaparib vs physician's choice of single agent chemotherapy using the 'Feelings about side-effects' domain of the CTSQ-16	Treatment satisfaction score (as measured by the Satisfaction with Therapy scale of the CTSQ-16) [a] Patient-reported feelings measured by the 'feelings about side-effects' domain of the CTSQ-16 [a]
Exploratory	Exploratory	To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay [a] Health state utility derived from the HRQoL instrument, the EuroQoL EQ-5D-5L [a]
Exploratory	Exploratory	To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent PARP inhibitors or imbalances between the treatment arms for other potentially active agents	OS adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals) [b]
Exploratory	Exploratory	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	*BRCA1* and/or *BRCA2* mutation status in tumour [c]

Objective			Outcome Measure
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacogenetic	To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional) 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 (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)	Potential retrospective tissue biomarker research [c]

[a] Outcome measure reported in the full CSR.

[b] In light of the final OS analysis (DCO 16 April 2021), this planned exploratory analysis is not relevant, hence will not be performed.

[c] Exploratory analysis has not been performed to date.

BICR, blinded independent central review; *BRCA*, breast cancer susceptibility gene; *BRCAm*, germline or somatic *BRCA* mutated; CA-125, cancer antigen-125; CSR, Clinical Study Report; CTSQ-16, Cancer Therapy Satisfaction Questionnaire; DCO, data cut-off; DNA, deoxyribonucleic acid; DoR, duration of response; EuroQoL, European Quality of Life; FAS, Full Analysis Set; *gBRCA,* germline *BRCA*; HRQoL, Health-related Quality of Life; MDAS, Measurable Disease Analysis Set; ORR, objective response rate; OS, overall survival; PARP, Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase; PFS, progression-free survival; PFS2, time from randomisation to second progression or death; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumours; TDT, time from randomisation to study treatment discontinuation or death; TFST, time from randomisation to first subsequent therapy or death; TOI, Trial Outcome Index; TSST, time from randomisation to second subsequent therapy or death; TTR, time to response; vs, versus.

Study Design

The study was a Phase III, open-label, randomised, controlled, multi-centre study to assess the efficacy and safety of treatment with olaparib monotherapy versus physician's choice of

single agent standard of care chemotherapy (ie, weekly paclitaxel, topotecan, pegylated liposomal doxorubicin [PLD], or gemcitabine) in patients with platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy, who had progressed at least 6 months after their last platinum-based chemotherapy and who carried a germline deleterious or suspected deleterious breast cancer susceptibility gene (*BRCA1/2*) mutation.

Patients were randomised using an Interactive Voice Response System (IVRS)/Interactive Web Response System in a 2:1 ratio to receive either olaparib 300 mg tablet orally twice daily (bd) continuously, or chemotherapy (weekly paclitaxel, topotecan, PLD, or gemcitabine). The randomisation scheme was stratified based on: selected chemotherapy (weekly paclitaxel vs topotecan vs PLD vs gemcitabine); number of prior chemotherapy regimens for ovarian cancer (2 or 3 prior lines of chemotherapy vs 4 or more); time to disease progression after the end of the last platinum-based chemotherapy (6 to 12 months vs >12 months).

Following randomisation, patients in both treatment arms were to attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22, and 29), then every 4 weeks up to 48 weeks (if not progressed and still on treatment), then every 12 weeks. Visits for patients who remained on treatment post progression took place every 12 weeks.

Patients were to have Response Evaluation Criteria in Solid Tumors (RECIST) assessments until documented evidence of objective radiological progression in accordance with RECIST 1.1, irrespective of treatment decisions (ie, RECIST follow-up until progression even if a patient discontinued study treatment prior to progression and/or received a subsequent therapy prior to progression). RECIST assessments were scheduled every 8 weeks (±1 week) from randomisation for 48 weeks and every 12 weeks (±1 week) thereafter. Following objective disease progression, patients could continue study treatment if the investigator believed that the patient continued to receive benefit, the patient was not experiencing serious toxicity, and there was no available better alternative treatment that could benefit the patient.

Target Subject Population and Sample Size

Patients ≥ 18 years of age with relapsed high-grade epithelial (serous or endometrioid) ovarian, primary peritoneal, or fallopian tube cancer who had received at least 2 prior platinum-based lines of chemotherapy for ovarian cancer, and who required a new line of chemotherapy to treat their current disease progression were eligible. Patients had to be suitable for treatment of relapsed disease with single agent chemotherapy based on physician's choice of weekly paclitaxel, topotecan, PLD, or gemcitabine, and to have not been previously exposed to the selected chemotherapy as a single agent. Patients could be either partially platinum-sensitive (defined as progression 6 to 12 months after the end of the last platinum-based chemotherapy) or platinum-sensitive (defined as progression >12 months after the end of the last platinum-based chemotherapy). Patients who had platinum-resistant or

refractory disease were not eligible for the study. Patients had to have documented germline *BRCA1* and/or *BRCA2* mutation that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).

A minimum of 250 patients were planned to be randomised 2:1 (olaparib: chemotherapy). A total of 266 patients were randomised (178 olaparib; 88 chemotherapy).

The sample size calculation was based on the primary endpoint objective response rate (ORR). At least 223 patients with measurable disease at baseline were required for the study to have >80% power to show a statistically significant difference in ORR at the 2-sided 5% level, assuming a response rate of 25% in the chemotherapy arm and at least 45% in the olaparib arm for patients with measurable disease at baseline according to blinded independent central review (BICR). It was anticipated that approximately 90% of patients would have measurable disease at baseline according to BICR and therefore to ensure adequate power, the sample size of at least 250 patients was required.

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

Olaparib: Olaparib was provided as 100 mg or 150 mg film-coated tablets manufactured by Soliqs or AbbVie on behalf of AstraZeneca. Patients randomised to olaparib received olaparib 300 mg bd orally.

Batch numbers: 46242B900, 37204B900, 44236B900, L002742/1000073095, 39211B900, 1000073198, L003627/1000086259/41193K15, 37201B900, 1000110211/L004724, 1000126307/L005445, L006267/1000146600, L005863/1000134861, 39214B900, 1000088520/L004048, 1000118082/L004957, 37201B900/L003185, 34197B900/L005494, 37202B900, 1000146593/L006264, L006267/100014660, 34195B900, Q1096214/L009946, Q1094667/L009824, 1000146597/L006266, Q1096215/L009947, Q1102236/L011523, AAAD/L012694, Q1094664/L009834.

Physician's choice of chemotherapy: Prior to randomisation in the IVRS, investigators declared their choice of 1 of the following regimens for each patient:

- Weekly paclitaxel 80 mg/m^2 intravenously (iv) on Day 1, 8, 15, and 22 every 4 weeks
- PLD 50 mg/m^2 iv on Day 1 every 4 weeks
- Topotecan 4 mg/m^2 iv on Day 1, 8, and 15 every 4 weeks
- Gemcitabine 1000 mg/m^2 iv on Day 1, 8, and 15 every 4 weeks

Paclitaxel, topotecan, PLD, and gemcitabine were provided centrally in Argentina, Brazil, Hungary, Israel, Italy, Mexico, Poland, Republic of Korea, and Spain and locally by the

investigator in Belgium, Canada, Czech Republic, and the United States of America (USA). All the chemotherapies were administered as per standard practice guidelines.

Batch numbers: Paclitaxel: 4GN0083, 6GN5013/L005110, DH124080/PW03790; PLD: FBZSZ00, L004695, FJZSN01, GEZSG01/L006255, FJZSN01/L004695, GKZT600/L007895, EEBS400, L009362/HCZTN00, L004202/FHZSW00, GCZTA00/L006046; Topotecan: R14614, GE2318/L005474; Gemcitabine: 43J0081, 53J5141/L005095.

Duration of Treatment

Patients were to continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the investigator, or until the patient experienced unacceptable toxicity or met any other discontinuation criteria.

Statistical Methods

The primary outcome variable for the study of ORR by BICR assessment using RECIST 1.1 was assessed at the primary data cut-off (DCO: 10 October 2018) on the measurable disease analysis set population. An ad hoc updated descriptive overall survival (OS) analysis was requested by the Food and Drug Administration to occur when approximately 45% maturity was reached (DCO 10 January 2020), which is reported in the Clinical Study Report (CSR) Addendum 1 (dated 08 July 2020). This CSR Addendum 2 reports the final OS analysis for the study which was to occur when approximately 60% maturity was reached (DCO 16 April 2021). In both CSR Addendum 1 and 2, secondary endpoints of time from randomisation to second progression or death (PFS2), OS, time from randomisation to first subsequent therapy or death (TFST), time from randomisation to second subsequent therapy or death (TSST) and time from randomisation to study treatment discontinuation or death (TDT) were analysed for the Full Analysis Set (FAS) using a log rank test stratified in accordance with the pre-defined pooling strategy for each endpoint and were also analysed for the confirmed Myriad germline *BRCA* mutated (*gBRCAm*) subset.

Study Population

The study was conducted in 78 sites in 13 countries worldwide: USA (19 centres), Spain (7 centres), Israel (8 centres), Brazil (7 centres), Italy (7 centres), Republic of Korea (6 centres), Poland (6 centres), Hungary (5 centres), Czech Republic (4 centres), Canada (3 centres), Belgium (2 centres), Mexico (2 centres), and Argentina (2 centres). The 6 top recruiting countries were Italy (18.4%), USA (15.4%), Republic of Korea (12.4%), Poland (12.0%), Czech Republic (7.9%), and Mexico (7.9%).

A total of 678 patients were enrolled in the study, of these 266 patients were randomly assigned to treatment with olaparib (n = 178) or chemotherapy (n = 88) (FAS); 178 olaparib patients and 76 chemotherapy patients received their allocated treatment (Safety Analysis

Set). Twelve chemotherapy patients withdrew consent from the full study prior to receiving treatment. The majority of patients discontinued study treatment in both treatment arms. At the time of the DCO (16 April 2021), 19 patients (10.7%) in the olaparib arm and no patients in the chemotherapy arm were still receiving study treatment; 135 patients (75.8%) in the olaparib arm and 68 patients (77.3%) in the chemotherapy arm had terminated from the study; 24 patients (13.5%) in the olaparib arm and 20 patients (22.7%) in the chemotherapy arm were continuing in the study off-treatment. The percentage of patients who terminated from the study prior to death was approximately 2.3 times higher in the chemotherapy arm than in the olaparib arm (25.0% vs 10.7%, respectively).

Disease progression was the most common reason for treatment discontinuation in both treatment arms. A higher percentage of patients discontinued study treatment due to an adverse event (AE) in the chemotherapy arm (17.0%) compared to the olaparib arm (10.1%), and a higher percentage of patients discontinued due to patient decision in the chemotherapy arm (11.4%) compared with the olaparib arm (3.9%).

Demography and baseline disease characteristics were generally well balanced between treatment arms.

Summary of Efficacy Results

At the time of the primary analysis DCO (10 October 2018), the study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in ORR for patients with measurable disease at baseline as assessed by BICR in the olaparib arm (72.2%) compared with the chemotherapy arm (51.4%). The planned final analysis of progression-free survival (PFS) also demonstrated a statistically significant improvement in PFS (hazard ratio [HR]: 0.62; 95% Confidence Internal [CI]: 0.43, 0.91; p = 0.013) as assessed by BICR for patients on the olaparib arm compared to patients on the chemotherapy arm.

At the time of the final OS analysis (DCO 16 April 2021), there were 162 PFS2 events (61.0% maturity) with a higher proportion of PFS2 events in the olaparib arm than the chemotherapy arm (64.0% vs 54.5 %, respectively). A higher proportion of patients in the chemotherapy arm (23.9%) withdrew consent without a second progression compared with those in the olaparib arm (8.4%), and therefore could not be followed-up for PFS2 and were censored. The PFS2 HR of 0.80 (95% CI: 0.56, 1.15; p = 0.229) numerically favoured olaparib compared with the chemotherapy arm but did not reach statistical significance. There was a 4-month improvement in median PFS2 in the olaparib arm compared with the chemotherapy arm (23.6 months vs 19.6 months, respectively).

At the time of the final OS analysis, the OS data were 61.0% mature (162 events/266 patients); 24.2% of olaparib patients and 22.7% of chemotherapy patients were alive and in

survival follow-up. The OS hazard ratio of 1.07 (95% CI: 0.76, 1.49; p = 0.714) suggested no difference between olaparib versus chemotherapy. The median OS was 34.9 months in the olaparib arm compared with 32.9 months in the chemotherapy arm. The Kaplan-Meier curves cross on several occasions and largely overlap with similar survival rates at each timepoint. The percentage of patients who terminated from the study prior to death was 2.3 times higher in the chemotherapy arm than in the olaparib arm (25.0% vs 10.7%, respectively). As these percentages include patients with unknown survival status, this may explain the observed lower incidence of deaths in the chemotherapy arm at the time of the DCO (52.3%) compared with the olaparib arm (65.2%).

A higher percentage of patients in the chemotherapy arm received subsequent polyadenosine 5'diphosphoribose polymerase (PARP) inhibitors compared with patients in the olaparib arm (37.5% vs 5.1%, respectively). Of the patients who received any subsequent anti-cancer therapy post discontinuation of study treatment, 61.1% of patients in the chemotherapy arm received a PARP inhibitor as a subsequent therapy, compared with only 7.6% in the olaparib arm, which is likely to have impacted the PFS2 and OS results.

There was a clinically meaningful delay in TFST in the olaparib arm (15.4 months) versus the chemotherapy arm (10.9 months; HR: 0.49; 95% CI: 0.35, 0.69). The delay in median TFST is consistent with the benefit observed in PFS at the primary analysis.

The TSST hazard ratio of 0.75 (95% CI: 0.53, 1.05) numerically favoured the olaparib arm versus the chemotherapy arm. The median TSST in the olaparib arm was 25.2 months vs 19.9 months in the chemotherapy arm.

There was a clinically meaningful delay in TDT (HR: 0.20; 95% CI: 0.14, 0.29). The median TDT in the olaparib arm was 13.1 months versus 5.1 months in the chemotherapy arm. However, this result should be interpreted with caution because, despite the protocol instructing that treatment was to be given until disease progression, in clinical practice, chemotherapy is frequently given for a fixed number of cycles or as tolerated by the patient.

Efficacy outcomes PFS2, OS, TFST, TSST, and TDT in the confirmed Myriad *gBRCAm* subset were consistent with those seen in the FAS.

Summary of Safety Results

At the time of the final OS analysis, total treatment duration was 268.93 years for olaparib, and was 40.33 years for chemotherapy. Median total duration of exposure was 13.09 months in the olaparib arm and 5.73 months in the chemotherapy arm.

The most commonly reported AEs (≥ 20% of patients) in the olaparib arm were nausea, anaemia, vomiting, fatigue, diarrhoea, abdominal pain, and asthenia. The most commonly

reported AEs (≥ 20% of patients) in the chemotherapy arm palmar-plantar erythrodysaesthesia syndrome, nausea, neutropenia, fatigue, anaemia, vomiting, and constipation.

Serious AEs (SAEs) were reported by a higher proportion of patients in the olaparib arm than the chemotherapy arm (25.8% vs 18.4%, respectively), however these results should be viewed in the context of exposure in the olaparib arm being twice as long as for the chemotherapy arm. The most common SAEs (occurring in > 2 patients) were anaemia (3.4%), deep vein thrombosis, pleural effusion, and vomiting (1.7% each) in the olaparib arm, and vomiting (3.9%) in the chemotherapy arm.

Approximately half of the patients in both arms had AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 (52.8% in the olaparib arm and 48.7% in the chemotherapy arm). CTCAE version 4.0 was used for severity grading in the study. The majority of these events were reported in low numbers of patients. Adverse events of CTCAE Grade ≥ 3 reported at ≥ 5% were anaemia reported in 23.0% vs 0%, neutropenia in 5.6% vs 10.5%, and neutrophil count decreased reported in 3.9% vs 5.3% in the olaparib arm vs chemotherapy arm, respectively. Palmar-plantar erythrodysaesthesia syndrome of CTCAE Grade ≥ 3 was reported in 11.8% of chemotherapy-treated patients and was not observed for olaparib-treated patients.

The incidence of AEs leading to discontinuation of study treatment was lower in the olaparib arm (10.1%) than in the chemotherapy arm (19.7%). The most common AEs leading to discontinuation of study treatment (≥ 2 patients) were anaemia (1.7%), thrombocytopenia and vomiting (1.1% each) in the olaparib arm; and palmar-plantar erythrodysaesthesia syndrome (9.2%), mucosal inflammation, neutropenia, and peripheral neuropathy (2.6% each) in the chemotherapy arm.

A total of 162 patients in the FAS died during the study, 116 patients (65.2%) in the olaparib arm and 46 patients (52.3%) in the chemotherapy arm; the majority (144/162) of deaths were attributed to the disease under investigation only. The number of fatal AEs was numerically higher in the olaparib arm: 6 patients treated with olaparib experienced fatal AEs PPD [redacted]; 1 patient in the chemotherapy arm experienced a fatal AE PPD [redacted].

Adverse events of special interest in this study were MDS/AML, new primary malignancies, and pneumonitis. Events of MDS/AML occurred in relatively similar numbers across treatment arms; 5 patients (2.8%) in the olaparib treatment arm, and 3 patients (3.9%) in the chemotherapy arm had MDS/AML. Two of the 3 patients in the chemotherapy arm developed the MDS/AML event after receiving a subsequent therapy that included a PARP inhibitor. There were 5 events of new primary malignancy: 4 events occurred in 4 olaparib-treated

patients PPD and 1 event PPD occurred in 1 patient in the chemotherapy arm PPD. The event PPD was pre-existing at the time olaparib treatment was initiated. There was 1 event PPD reported in the olaparib treatment arm and none in the chemotherapy arm.

Haematology changes were generally consistent with the reported AE profile. There were no other meaningful differences in haematology changes from baseline in either arm. There were no meaningful differences in chemistry changes from baseline in both treatment arms, other than those consistent with known adverse drug reactions. Overall the clinical chemistry profiles were similar between the 2 treatment arms. No hepatobiliary or renal safety concerns were identified from a review of laboratory and AE data.

Conclusions

- At the time of the primary analysis (DCO 10 October 2018), the study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in ORR for patients with measurable disease at baseline as assessed by BICR in the olaparib arm compared with the chemotherapy (72.2% vs 51.4%, respectively; OR: 2.53; 95% CI: 1.40, 4.58; p = 0.002). The planned final analysis of PFS also demonstrated a statistically significant improvement in PFS as assessed by BICR for patients on the olaparib arm compared to patients on the chemotherapy arm (HR: 0.62; 95% CI: 0.43, 0.91; p = 0.013).
- At the time of the final OS analysis (DCO 16 April 2021), the PFS2 data were 61.0% mature. The PFS2 hazard ratio numerically favoured the olaparib arm compared with the chemotherapy arm but did not reach statistical significance (HR: 0.80; 95% CI: 0.56, 1.15; p = 0.229). There was a 4-month improvement in median PFS2 for olaparib versus chemotherapy (23.6 months vs 19.6 months, respectively).
- The OS data were 61.0% mature at the time of the final OS analysis; 24.2% of olaparib patients and 22.7% of chemotherapy patients were alive and in survival follow-up. The OS hazard ratio of 1.07 (95% CI: 0.76, 1.49; p = 0.714) suggested no difference between olaparib versus chemotherapy. The median OS was 34.9 months in the olaparib arm versus 32.9 months in the chemotherapy arm. The percentage of patients who terminated from the study prior to death was approximately 2.3 times higher in the chemotherapy arm than in the olaparib arm (25.0% vs 10.7%, respectively).
- Although not controlled for multiplicity, at the time of the final OS analysis the difference observed in favour of the olaparib arm compared to the chemotherapy arm in TFST (HR: 0.49; 95% CI: 0.35, 0.69) was clinically meaningful.
- At the time of the final OS analysis, the TSST hazard ratio of 0.75 (95% CI: 0.53, 1.05) numerically favoured the olaparib arm versus the chemotherapy arm.
- Although not controlled for multiplicity, at the time of the final OS analysis the difference observed in favour of the olaparib arm compared with the chemotherapy arm in TDT (HR: 0.20; 95% CI: 0.14, 0.29) was clinically meaningful. However, this result should be interpreted with caution because, despite the protocol instructing that treatment was to be

given until disease progression, in clinical practice, chemotherapy is frequently given for a fixed number of cycles or as tolerated by the patient.

- Efficacy outcomes of PFS2, OS, TFST, TSST, and TDT in the confirmed Myriad *gBRCAm* subset were consistent with the FAS at the time of the final OS analysis.
- The safety profile of olaparib at the time of the final OS analysis was consistent with the known safety profile for olaparib. No new safety findings were observed.
- The olaparib safety and tolerability profile observed in this study was generally consistent with that observed in previous studies of olaparib monotherapy and is supportive of long-term use of olaparib 300 mg bd tablet in this setting.
- The Coronavirus Disease 2019 pandemic is not judged to have had a meaningful impact on the overall quality of the study, including the conduct, data, and interpretation of results.