AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281)
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A Randomized, Double-blinded, Placebo Controlled, Multicentre Phase III Study to Assess the Efficacy and Safety of Olaparib (AZD2281) in Combination with Paclitaxel, Compared to Placebo in Combination with Paclitaxel, in Asian Patients with Advanced Gastric Cancer (Including the Gastro-oesophageal Junction) who have Progressed Following First-line Therapy (GOLD)

Study dates: First subject enrolled: 03 September 2013
Last subject last visit: 28 March 2016 (data cut-off)

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.

Study centre(s)

The study was open for enrolment at 58 study centres: China (27 study centres), Japan (14 study centres), Korea (12 study centres) and Taiwan (5 study centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by OS in all patients, and the subgroup of patients whose tumours tested negative for ATM protein by IHC, with advanced gastric cancer (including GEJ) who had progressed following first-line therapy.	OS: the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.
Secondary	Efficacy	To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by PFS and ORR including the time to response and the duration of the response, in all patients and a subgroup of patients whose tumours tested negative for ATM protein with advanced gastric cancer (including GEJ) who had progressed following first-line therapy.	PFS: the time from randomisation until the date of objective radiological disease progression according to 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. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST assessment. ORR: the number of patients with a BOR of CR or PR divided by the number of patients in the FAS with measurable disease at baseline. Only patients with PR and measurable disease at enrolment could have achieved an objective response of CR or PR; other permissible categories of BOR were

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Objective			Variable
Priority	**Type**	**Description**	**Description**
			NE, PD and stable disease. The BOR was calculated based on the overall visit responses from each RECIST assessment. DoR: the time from the date of first documented response (ie, the latest of the dates contributing towards the first visit response of PR or CR) until the date of documented progression or death in the absence of disease progression. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. If a patient did not progress following a response, then their DoR used the PFS censoring date as the date at which that patient was censored for DoR. Time to response: the time from randomisation to the first onset of a confirmed objective tumour response.
Secondary	Safety, efficacy and pharmacokinetics	To investigate plasma exposure to olaparib in a subgroup of olaparib-dosed patients in the presence of paclitaxel and assess the impact of previous gastric surgery on that exposure.	Determination of the PK parameters C_{max}, t_{max}, t_{last}, AUC_{0-t} and AUC_{0-12} for olaparib following a single 100 mg dose in the presence of paclitaxel.

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To assess the effects of olaparib when given in combination with paclitaxel compared to paclitaxel in combination with placebo on the time to deterioration of HRQoL as assessed by the EORTC QLQ-C30 global HRQoL scale in all patients and the subgroup of patients whose tumours tested negative for ATM protein.	Time to deterioration of HRQoL: the time from randomisation to a clinically important deterioration in the global HRQoL score or death (by any cause) in the absence of a clinically meaningful symptom deterioration, provided death occurred within 2 EORTC assessment visits of the last EORTC assessment where the global HRQoL score could be evaluated, and regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to deterioration in HRQoL. EORTC QLQ-C30: A 30-question scale designed for all cancer types that measures HRQoL. STO22: A 22-question scale developed specifically for patients with gastric cancer.
Safety	Safety	To investigate the safety and tolerability of olaparib when given in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who had progressed following first-line therapy.	AEs, SAEs, DAEs, OAEs, laboratory results, vital signs and ECGs.
Exploratory	Safety	To explore potential biomarkers (such as, but not limited to, mutational status) in archival tumour, and in optional plasma/serum samples, which may influence the development of cancer and/or response to study treatment[a].	Tumour/plasma/serum samples, as applicable.

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacogenetics	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer[a].	Genetic samples stored for future use.
Exploratory	Health economics	To explore changes in health utility status in all patients and the subgroup of patients whose tumours tested negative for ATM protein receiving olaparib plus paclitaxel or placebo in combination with paclitaxel.	EQ-5D-5L: a standardised measure of health status providing a simple, generic measure of health for clinical and economic appraisal.
Exploratory	Patient Reported Outcomes	To explore the impact of treatment and disease state on symptoms and HRQoL as measured by the EORTC QLQ-C30 + STO22 disease-related multi-item symptom scales and multi-item functional scales in all patients and in the subgroup of patients whose tumours tested negative for ATM protein.	EORTC QLQ-C30: A 30-question scale designed for all cancer types that measures HRQoL. STO22: A 22-question scale developed specifically for patients with gastric cancer.
Exploratory	Health economics	To investigate the impact of olaparib plus paclitaxel and placebo in combination with paclitaxel on gastric cancer management resource use[a].	Resource use outcome variables included frequency of palliative interventions, reason for hospitalisation, length of stay, reasons for the intervention, time to intervention, and length of any time spent in the ICU.
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 adjusted for the impact of subsequent PARP inhibitor trial or treatment.

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Efficacy	To investigate further the impact of a complete absence of measured ATM protein in archival tumour on efficacy of study treatment.	Collection of archival or newly collected FFPE tumour samples. ATM null status determined by IHC on mandatory archival tumour samples.

[a] This objective will be reported outside of this Clinical Study Report.

Abbreviations: AE, adverse event; ATM, ataxia telangiectasia mutated; AUC_{0-t}, area under the plasma concentration-time curve from zero to time t; AUC_{0-12}, area under the plasma concentration-time curve from zero to 12 hours; BOR, best objective response; C_{max}, maximum plasma concentration; CR, complete response; DAE, discontinuation of study drug due to an adverse event; DoR, duration of response; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5 dimensions, 5-level version; FAS, full analysis set; FFPE, formalin fixed paraffin embedded; GEJ, gastro-oesophageal junction; HRQoL, heath-related quality of life; ICU, intensive care unit; IHC, immunohistochemistry; NE, not evaluable; OAE, other significant adverse event; ORR, objective response rate; OS, overall survival; PARP, polyadenosine 5'-diphosphoribose (poly-[ADP-ribose]) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; QLQ-C30, Quality of Questionnaire Core 30 item module; RECIST 1.1, Response Evaluation Criteria in Solid Tumors modified Version 1.1; SAE, serious adverse event; STO22, Gastric Module; t_{last}, time to last measurable plasma concentration; t_{max}, time to reach maximum plasma concentration.

Study design

This Phase III, randomised, double-blinded, multi-centre study assessed whether olaparib in combination with paclitaxel could improve overall survival (OS) in patients with advanced gastric cancer (including gastro-oesophageal junction [GEJ]) whose tumours had progressed following first-line therapy (ie, second-line gastric cancer patients). The study compared olaparib in combination with paclitaxel with placebo in combination with paclitaxel in the overall study population and in an ataxia telangiectasia mutated (ATM) protein negative population, where the benefit of olaparib may be greater. The ATM status of each patient was assessed was after randomisation and identified prior to data cut-off (DCO) and unblinding.

Target subject population and sample size

For inclusion in the study, patients were required to have a confirmed diagnosis of advanced gastric adenocarcinoma (including GEJ adenocarcinoma) that had progressed following first-line therapy. Male or female Asian patients ≥18 years of age (≥20 years for Japanese patients) were required to provide a tumour sample (from either a resection or biopsy). Patients who had received previous adjuvant/neoadjuvant chemotherapy were allowed to participate in the study if this treatment was completed more than 6 months prior to starting the first-line therapy. All patients were required to have an Eastern Cooperative Oncology Group performance status of ≤1, a life expectancy of ≥16 weeks from the proposed first dose date and at least 1 lesion (measurable/non-measurable) that could be accurately assessed by computed tomography or magnetic resonance imaging at baseline and follow up visits.

Overall survival was the primary endpoint of this study that comprised 2 primary populations: all randomly assigned patients and the subgroup of patients whose tumours tested negative for ATM protein. The study was sized on a hazard ratio (HR) of 0.7, as observed in a previous study for the weighted analysis of OS, in the overall study population. This assumed a 90% power and a 2.5% alpha with 1:1 randomisation, which required 391 deaths and a HR of 0.8 or lower to achieve statistical significance ($p \leq 0.025$) in the overall study population.

A minimum of 70 patients whose tumours were ATM negative were to be randomised in total. The ATM negative subgroup was sized on a HR of 0.35 assuming a ≥90% power and a 2.5% alpha, which required 49 deaths; a HR of 0.53 or lower would achieve statistical significance ($p \leq 0.025$) in the ATM negative subgroup.

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

Olaparib (AZD2281) or matching placebo was administered orally as 100 mg tablets twice daily (bd), continuously, with paclitaxel administered as an intravenous infusion over 1 hour at 80 mg/m^2 weekly, on Days 1, 8 and 15 of a 28-day cycle.

The olaparib or matching placebo dose was to be increased to 300 mg bd when given as monotherapy.

CCI [redacted]

Duration of treatment

Patients were to continue to receive olaparib or matching placebo in combination with paclitaxel until they demonstrated objective disease progression (determined by Response Evaluation Criteria in Solid Tumors [RECIST] modified Version 1.1 [RECIST 1.1]) or met any other discontinuation criteria.

In the event a patient discontinued paclitaxel due to any reasons (such as an AE) other than objective disease progression, the patient was to continue to receive olaparib or matching placebo as monotherapy until objective disease progression (determined by RECIST 1.1) was demonstrated, or other discontinuation criteria were met. The olaparib or matching placebo dose was to be increased to 300 mg bd as monotherapy, with no maximum duration of treatment.

It was permitted that patients continue with olaparib or matching placebo as monotherapy beyond objective disease progression (determined by RECIST 1.1) at the discretion of the investigator if they were clinically benefiting from the treatment and they did not meet any other discontinuation criteria. This was to be determined in agreement with the AstraZeneca Study Physician.

Statistical methods

There were 2 primary populations in the study: the full analysis set (FAS) and the ATM negative subgroup. As there were 2 primary populations, the Hochberg approach was used to adjust for multiple statistical testing of OS across the 2 populations to maintain the overall type I error rate of 5%. All endpoints were analysed in the FAS and in the ATM negative subgroup unless otherwise stated. The treatment comparison was olaparib in combination with paclitaxel versus placebo in combination with paclitaxel. Unless otherwise stated, results of all statistical analysis are presented using a 97.5% confidence interval (CI) and 2-sided p-value.

Overall survival, the primary analysis, was performed using a Cox proportional hazards model adjusted for ATM status, country, and gastrectomy status at baseline. Sensitivity analyses of the primary endpoint were performed using an unadjusted log-rank test.

The secondary efficacy variables were progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), time of the initial response and time to response and health-related quality of life (HRQoL) (as assessed by the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Questionnaire Core 30 item module [QLQ-C30] and Gastric Module [STO22]).

Progression-free survival data were analysed at the time of the OS analysis using the same methodology and model as the primary analysis of OS. Sensitivity analyses were performed using an unadjusted log-rank test and to assess the possible evaluation-time bias and attrition bias.

The ORR, based on the investigator's assessment of RECIST, was analysed using logistic regression adjusted for the following covariates: ATM status, country and gastrectomy status at baseline.

Time to deterioration of HRQoL was analysed using the same methodology and model as described for the primary analysis of OS. A sensitivity analysis was performed to assess the impact of attrition bias.

Supportive exploratory analyses were performed for EORTC symptom scores and EuroQol 5 dimensions, 5-level version, and health economics.

Assessments of safety were based on the safety population. Safety and tolerability was assessed in terms of adverse events (AEs) (including serious AEs [SAEs]), deaths, laboratory data, vital signs, treatment exposure, dose intensity and electrocardiogram (ECG) results. Safety data were summarised and listed only; no formal statistical analyses were performed.

The maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to time t and area under the plasma concentration-time curve from zero to 12 hours (AUC_{0-12}) were summarised by gastrectomy status and presented graphically. No formal statistical analysis was performed.

Subject population

A total of 525 patients were randomised to the study and the FAS; 263 patients were randomised to the olaparib in combination with paclitaxel (OP) arm and 262 patients were randomised to the placebo in combination with paclitaxel (PP) arm. The patients were representative of a target population of Asian patients with metastatic gastric cancer whose tumours arose wholly within the stomach and whose disease had progressed following first-line therapy with fluoropyrimidine/platinum chemotherapy regimen.

There were 94 randomised patients whose archival tumour samples were retrospectively tested for ATM status and identified as ATM protein negative prior to DCO and unblinding of treatment: 48 patients were randomised to the OP arm and 46 patients were randomised to the PP arm.

Demographic and baseline characteristics were generally well balanced between treatment arm in both the overall study population and ATM negative population.

The pre-specified covariates of ATM status, gastrectomy status and country were generally well balanced between treatment arms in both the overall study population and ATM negative population.

Summary of efficacy results

The Hochberg alpha-spend rules were followed and resulted in a significance level of 0.025 required to claim success in the overall study population and ATM negative population. There was a numerical, but not statistically significant, improvement in OS observed in favour of the OP arm compared with the PP arm in both the overall study population (68.8% vs 76.3% of patients died, respectively; HR 0.79; 97.5% CI 0.63, 1.00; p=0.0262) and the ATM negative population (60.4% vs 76.1% of patients died, respectively; HR 0.73; 97.5% CI 0.40, 1.34; p=0.2458).

The Kaplan-Meier (KM) median OS was longer in both treatment arms in the ATM negative population (12.0 months in the OP arm and 10.0 months in the PP arm) compared with the overall study population (8.8 months in the OP arm and 6.9 months in the PP arm).

Despite a numerical benefit for the OP arm, the GOLD study did not meet its primary objective of demonstrating a statistically significant improvement in OS in either the overall study population or the ATM negative population in patients with advanced gastric cancer receiving second-line treatment with olaparib in combination with paclitaxel compared with placebo in combination with paclitaxel.

There was a numerical, but not statistically significant, improvement in PFS observed in favour of the OP arm compared with the PP arm in both the overall study population (82.1% vs 88.9% of patients progressed, respectively; HR 0.84; 97.5% CI 0.67, 1.04; p=0.0645) and ATM negative population (77.1% vs 84.8% of patients progressed, respectively; HR 0.74; 97.5% CI 0.42, 1.29; p=0.2199).

The KM median PFS was longer in both treatment arms in the ATM negative population (5.3 months in the OP arm and 3.7 months in the PP arm) compared with the overall study population (3.7 months in the OP arm and 3.2 months in the PP arm).

There was a numerical, but not statistically significant, improvement in the adjusted response rate observed in favour of the OP arm compared with the PP arm in both the overall study population (adjusted response rate: 24.0% vs 15.8% of patient responded, respectively; odds ratio 1.69; 97.5% CI 0.92, 3.17; p=0.0548) and ATM negative population (adjusted response rate: 37.5% vs 16.1% of patients responded, respectively; odds ratio 4.24; 97.5% CI 0.95, 23.23; p=0.0309).

The median time to onset of response from randomisation was similar in both treatment arms in the overall study population (57.0 days in both the OP arm and PP arm) and the ATM negative population (57.5 days in the OP arm and 57.0 days in the PP arm). However, the KM median DoR from onset was longer in the OP arm compared with the PP arm in both the overall study population (OP arm: 166.0 days and PP arm: 64.0 days) and the ATM negative population (OP arm: 171.0 days; PP arm: 108.0 days).

There was a numerical, but not statistically significant, advantage in median time to global HRQoL deterioration observed in favour of the OP arm compared with the PP arm in the overall study population (3.4 months vs 2.4 months, respectively; HR 0.82; 97.5% CI 0.64, 1.05; p=0.0716) and ATM negative population (3.7 months vs 1.9 months, respectively; HR 0.63; 97.5% CI 0.34, 1.16; p=0.0927).

The OS and PFS subgroup analyses showed that there was a suggestion of a greater treatment benefit with olaparib in combination with paclitaxel for OS and PFS in some subgroups (particularly in male patients and those who had full or partial gastrectomy). Of note, OS subgroup analyses demonstrated that, while potentially prognostic, ATM negative status was not predictive of a survival advantage with olaparib in combination with paclitaxel.

Summary of pharmacokinetic results

The pharmacokinetic (PK) results showed that the olaparib plasma concentration-time profiles in combination with paclitaxel for patients with gastric surgery were characterised by a rapid absorption phase (median t_{max} 0.50 and 1.00 hours for the full and partial gastrectomy groups, respectively), whereas absorption was more steady for patients with no gastric surgery (median t_{max} 3.51 hours), with a wider individual range from shortest to longest time to peak compared to the groups with surgery. Concentration-time profiles showing double peaks were observed for some patients in all the groups.

The geometric mean (Gmean) C_{max} was lower by approximately 13.0% and 21.6%, respectively, for the full and partial gastrectomy groups than that for the no gastric surgery group. Similarly, the Gmean AUC_{0-12} was lower by approximately 47.0% and 25.6%, respectively, for the full and partial gastrectomy groups than that for the no gastric surgery group.

High inter-subject variability in exposure was observed, with geometric coefficient of variation values of 210.2% and 75.21% for C_{max} and 59.82% and 60.58% for AUC_{0-12} for the partial and no gastric surgery groups, respectively, with individual C_{max} and AUC_{0-12} values overlapping across the groups.

The efficacy results showing that gastrectomy status is predictive of a greater treatment benefit with olaparib in combination with paclitaxel in patients with full or partial gastrectomy cannot be explained by the PK results.

Summary of pharmacogenetic results

Pharmacogenetic samples were collected that will be analysed and reported separately. The results of the genetic study are not part of the CSR.

Summary of safety results

Overall, olaparib 100 mg bd tablet in combination with weekly paclitaxel 80 mg/m^2 was well tolerated, whether followed by olaparib 300 mg bd tablet as monotherapy or not. Olaparib in combination with paclitaxel compared with placebo in combination with paclitaxel resulted in a slightly increased incidence and/or severity of some known effects of either of the treatment components; however, in general, these effects could be managed by dose change, interruption and discontinuation of study treatment. No new unexpected safety signals were observed for olaparib 100 mg bd tablet in combination with weekly paclitaxel 80 mg/m^2 or olaparib 300 mg bd tablet as monotherapy during this study.

The median total treatment duration of olaparib or placebo was longer in the OP arm (111.0 days and 73.5 days, respectively) compared with the PP arm (72.0 days and 59.0 days, respectively). Likewise, the median total treatment duration of paclitaxel was longer in the OP arm (111.0 days) compared with the PP arm (82.0 days).

In the combination phase, the median relative dose intensity (RDI) and percentage intended dose (PID) of olaparib or placebo were slightly lower in the OP arm (RDI: 80.75%, PID: 82.95%) compared with the PP arm (RDI: 88.33%, PID: 90.42%). However, the median RDI and PID of paclitaxel were similar in the OP arm (RDI: 81.06%, PID: 81.32%) and PP arm (RDI: 85.62%, PID: 85.99%).

Almost all patients had at least 1 AE during the study (260 [99.2%] patients in the OP arm and 254 [98.1%] patients in the PP arm). In the OP arm, the most common AEs (reported in >20% of patients) by preferred term (PT) were: neutropenia, alopecia, anaemia, decreased appetite, nausea, leukopenia, diarrhoea, neutrophil count decreased and white blood cell count decreased. In the PP arm, the most common AEs (reported in >20% of patients) by PT were: alopecia, neutropenia, decreased appetite, anaemia, nausea, leukopenia, fatigue and diarrhoea. Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher were reported in a higher percentage of patients in the OP arm (204 [77.9%] patients) compared with the PP arm (160 [61.8%] patients).

There were numerically fewer deaths in the OP arm (181 [68.8%] patients) compared with the PP arm (200 [76.3%] patients). The majority of the deaths were considered related to the disease under investigation only (166 [63.1%] patients in the OP arm and 193 [73.7%] patients in the PP arm). There were 5 more patients who had AEs with an outcome of death in the OP arm (11 [4.2%] patients) compared with the PP arm (6 [2.3%] patients).

Serious AEs were reported in a higher percentage of patients in the OP arm (92 [35.1%] patients) compared with the PP arm (65 [25.1%] patients). A small percentage of patients in both treatment arms had SAEs that were considered by the investigator to be causally related to olaparib or placebo (19 [7.3%] patients in the OP arm and 11 [4.2%] patients in the PP arm), or paclitaxel (30 [11.5%] patients in the OP arm and 18 [6.9%] patients in PP arm).

There were 41 (15.6%) patients in the OP arm compared with 25 (9.7%) patients in the PP arm who had AEs leading to discontinuation of olaparib or placebo.

A relatively small percentage of patients had a maximum on-treatment CTCAE grade of 3 or 4 in the evaluated haematology and clinical chemistry parameters in both treatment arms. No clinically important changes in vital signs, ECG parameters or physical examination were observed during the study across the overall study population in either the OP arm or PP arm.

Conclusion(s)

- The 525 patients who were randomised onto this study were representative of a target population of Asian patients with metastatic gastric cancer whose tumours arose wholly within the stomach and whose disease had progressed following first-line therapy with fluoropyrimidine/platinum chemotherapy regimen.

- The study was well conducted, with a relatively small percentage of patients with at least 1 important protocol deviation.

- Despite a numerical benefit for the OP arm, the GOLD study did not meet its primary objective of demonstrating a statistically significant improvement in OS in either the overall study population or the ATM negative population.

- There was a numerical, but not statistically significant, improvement/advantage in PFS, ORR and time to deterioration in HRQoL observed in favour of the OP arm compared with the PP arm in both the overall study population and ATM negative population.

- Subgroup analyses of OS by ATM status (positive and negative) demonstrated that, while potentially prognostic, ATM negative tumour status was not predictive of a survival advantage with olaparib in combination with paclitaxel.

- There was a trend for a greater treatment benefit with olaparib in combination with paclitaxel in patients with full or partial gastrectomy for both OS and PFS in the FAS; there was also a suggestion of a greater treatment benefit with olaparib in combination with paclitaxel in male patients for both OS and PFS in the FAS.

- In both the overall study population and ATM negative population, the median time to onset of response from randomisation was similar in both treatment arms; however, the KM median DoR from onset was longer in the OP arm compared with the PP arm.

- Overall, olaparib 100 mg bd tablet in combination with weekly paclitaxel 80 mg/m^2 had a similar impact on HRQoL compared to placebo in combination with paclitaxel.

- Exposure to olaparib in combination with paclitaxel appeared to be lower in patients with gastric surgery, although the difference may not be statistically significant or clinically important because of the high inter-patient variability in the data.

- Overall, olaparib 100 mg bd tablet in combination with weekly paclitaxel 80 mg/m^2 was well tolerated, whether followed by olaparib 300 mg bd tablet as monotherapy or not.

- Olaparib in combination with paclitaxel compared with placebo in combination with paclitaxel resulted in a slightly increased incidence and/or severity of some known effects of either of the treatment components; however, in general, these effects could be managed by dose change, interruption and discontinuation of study treatment.

- No new unexpected safety signals were observed for olaparib 100 mg bd tablet in combination with weekly paclitaxel 80 mg/m^2 or for olaparib 300 mg bd tablet as monotherapy during this study.