AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281; KU 0059436)
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A Phase II, Open-Label, Randomised, Comparative, Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients with Platinum Sensitive Advanced Serous Ovarian Cancer

Study dates:	First subject enrolled: 12 February 2010 Last subject randomised: 30 July 2010 Primary analysis data cut-off: 10 October 2011
Phase of development:	Therapeutic exploratory (II)

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

Study centre(s)

Patients were enrolled and randomised at 43 sites in 12 countries (Australia, Belgium, Canada, Czech Republic, Germany, Italy, Japan, the Netherlands, Panama, Spain, the UK and the USA). This study was ongoing at the data cut-off for the clinical study report (CSR) (10 October 2011).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The purpose of this synopsis is to report the results of the primary and secondary objectives.

Table S1 Objectives and outcome variables

Objective			Outcome Variable Description
Priority	**Type**	**Description**	
Primary	Efficacy	To compare the efficacy of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone.	PFS (based on independent central review).
Secondary	Efficacy	To compare the efficacy of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone.	OS, percentage change in total tumour size, ORR, ovarian cancer response rate, CA-125 response rate.
	Safety	To compare the safety and tolerability of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone.	AEs, vital signs, ECGs, physical exam, haematology and clinical chemistry.
	PK	To investigate the possible PK interaction among olaparib, paclitaxel and carboplatin in Japanese patients, by assessing the plasma concentration profiles of olaparib alone or in combination with paclitaxel and carboplatin and the plasma concentration profiles of paclitaxel and free carboplatin alone or in combination with olaparib.	Plasma concentrations and the following PK parameters from the Japanese patients enrolled in the study: olaparib: C_{max}, t_{max}, $t_{½}$, $AUC_{(0-12)}$, $AUC_{(0-t)}$. paclitaxel: C_{max}, t_{max}, $t_{½}$, AUC. carboplatin (based on free drug): C_{max}, t_{max}, $t_{½}$, AUC. Ratios of exposure (C_{max}, $AUC_{(0-12)}$, $AUC_{(0-t)}$ or AUC) in combination versus monotherapy.

Table S1 Objectives and outcome variables

Objective			Outcome Variable Description
Priority	**Type**	**Description**	
Exploratory[a]	Biomarker	To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses.	Candidate predictive biomarkers for olaparib efficacy.

[a] This exploratory objective is not reported in this synopsis or the CSR.

AE Adverse event; AUC Area under the plasma concentration-time curve from time zero to infinity; $AUC_{(0-12)}$ AUC from time zero to 12 hours after drug administration; $AUC_{(0-t)}$ AUC from time zero to the last sampling point where the plasma concentration is quantifiable; CA-125 Cancer antigen-125; C_{max} Maximum plasma concentration following drug administration; ECG Electrocardiogram; ORR Ovarian response rate; OS Overall survival; PFS Progression free survival; PK Pharmacokinetics; $t_{½}$ Half-life; t_{max} Time to reach maximum concentration following drug administration.

Study design

This was a Phase II, open-label, randomised, comparative, multi-centre study. Patients were randomised to 1 of 2 treatment arms, each of which comprised 2 phases:

> **Arm A** ("O/C4/P" arm): combination phase - olaparib in combination with paclitaxel and carboplatin (area under the plasma concentration time curve from time zero to infinity [AUC] 4) for at least 4 cycles; maintenance phase - olaparib monotherapy.
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> **Arm B** ("C6/P" arm): combination phase - paclitaxel and carboplatin (AUC 6) for 6 cycles; post-completion (maintenance phase) - no treatment was administered.

Target subject population and sample size

Patients were females aged >18 years with histologically or cytologically diagnosed serous ovarian cancer. They were to have received ≤3 previous platinum-containing regimens and were to be progression free, in the opinion of the investigator, for at least 6 months following completion of their last platinum-containing regimen. In addition, patients were to have at least 1 lesion that could be accurately measured at baseline and which was suitable for accurate repeated measurements.

Patients receiving any systemic anticancer chemotherapy or radiotherapy (except palliative) within 2 weeks from the last dose prior to study treatment were excluded from the study. Hypersensitivity to pre-medications required for treatment with carboplatin and paclitaxel was also an exclusion criterion.

It was planned to enrol approximately 150 evaluable patients into 2 treatment arms (1:1 ratio).

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

Olaparib (AZD2281; KU0059436) 50 mg capsules were manufactured by Patheon Pharmaceuticals Inc. on behalf of AstraZeneca. Nine batches of olaparib were used in this study: individual batch numbers are included in the CSR. Paclitaxel and carboplatin are commercially available and were supplied locally.

The doses administered in each arm of the study were as follows:

> **O/C4/P arm:** combination phase - olaparib 200 mg twice daily [bd] Days 1 to 10 of a 21-day cycle, in combination with paclitaxel intravenous (iv) (175 mg/m^2 Day 1 of a 21-day cycle) and carboplatin iv (AUC 4 Day 1 of a 21-day cycle) for at least 4 cycles; maintenance phase - olaparib monotherapy 400 mg bd continuous dosing, Days 1 to 21.
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> **C6/P arm:** combination phase - paclitaxel iv (175 mg/m^2 Day 1 of a 21 day cycle) and carboplatin iv (AUC 6 Day 1 of a 21 day cycle) for 6 cycles; maintenance phase - no treatment was administered.

Duration of treatment

Patients in the O/C4/P arm were to receive at least four 21-day cycles of treatment in the combination phase prior to entering the maintenance phase. They could stay in the maintenance phase until progression or until other discontinuation criteria were met.

Patients in the C6/P arm were to receive 6 cycles of treatment in the combination phase prior to entering the maintenance phase (no treatment). Although they did not receive any study treatment during the maintenance phase they continued to be followed for survival. They could stay in the maintenance phase until progression or until other discontinuation criteria were met.

Statistical methods

The primary outcome variable, progression-free survival (PFS), was based on the independent central review of the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 data, blinded to randomised treatment. The treatment arms were compared using a stratified log-rank test with strata defined for number of prior platinum-containing treatment lines (1 or >1) and time to disease progression following previous platinum-containing therapy (>6 to ≤12 months versus >12 months). Kaplan-Meier plots of PFS were presented by treatment arm in the CSR.

The analysis of overall survival (OS) planned to use the same stratified log-rank test as described for the primary PFS analysis; however, this analysis was not performed because there were too few survival events. Kaplan-Meier plots of OS were presented by treatment arm in the CSR.

The percentage change in tumour size at Week 9 and Week 18 scheduled site tumour assessments was calculated for each patient based on the change in sum of target lesion longest diameters from baseline. The effect of olaparib on change in tumour size was estimated from an analysis of covariance model at Week 9 and Week 18, including covariates for baseline tumour size, number of prior platinum therapies (1 or >1) and time to progression on previous platinum-containing therapy (<6 to ≤12 months or >12 months).

For the objective response rate (ORR), ovarian cancer response rate and cancer antigen-125; (CA-125) response rate, the proportion of responding patients was analysed by logistic regression, adjusting for the number of prior platinum therapies (1 or >1) and the time to progression on prior therapy (<6 to ≤12 months or >12 months). The effect of treatment was estimated using the adjusted odds ratio and its corresponding 1-sided 80% and 2-sided 95% Confidence Intervals (CIs).

Subgroup analyses for PFS and change in tumour size were performed: number of prior platinum treatment lines (1 or >1); time to disease progression following previous platinum-containing therapy (>6 to ≤12 months versus >12 months); breast cancer gene (BRCA) mutation status (BRCA positive/BRCA negative/Unknown).

The safety analyses consisted of assessment of the safety and exposure profiles in terms of adverse events (AEs)/serious AEs (SAEs), laboratory data, vital signs and electrocardiograms (ECGs) that were collected for all patients. There was no formal analysis of safety endpoints.

Subject population

In total, 173 patients were enrolled from 43 sites in 12 countries. Of these, 162 were randomised to receive treatment: 81 to each treatment arm. Of the 81 patients who entered the O/C4/P arm, 66 went on to the maintenance phase. Of the 81 patients who entered the C6/P arm, 55 entered the maintenance phase.

The data cut-off date for this primary analysis was 10 October 2011 and at that time 123 patients were ongoing in the study ie, they were still receiving study treatment or were being followed up for PFS or survival (67 from the O/C4/P arm and 56 from the C6/P arm). Of the 67 patients from the O/C4/P arm ongoing in the study, 23 were receiving olaparib treatment.

All 162 randomised patients were included in the full analysis set (FAS). All 81 patients in the O/C4/P arm and 75 of the 81 patients in the C6/P arm were included in the Safety Analysis Set; 6 patients in the C6/P arm were excluded from the Safety Analysis Set because they did not receive at least 1 dose of study treatment. In addition to these 6 patients who did not take any study treatment, 4 patients in the C6/P arm withdrew from the study after receiving 1 cycle of C6/P. Because all 10 of these patients had no follow-up RECIST assessments an unplanned exploratory analysis population (the EAS: used for response type variables) was defined that excluded these 10 patients. The EAS consisted of 81 patients in the O/C4/P arm and 71 patients in the C6/P arm. As this was an exploratory population, results from the

analyses based on this population are not presented in this synopsis but are described in the CSR.

Summary of efficacy results

Progression free survival

The study met its primary endpoint. There was a statistically significant improvement in PFS (independent central review) in the O/C4/P arm compared with the C6/P arm. The hazard ratio was 0.51 (95% CI: 0.34 to 0.77; p=0.0012), indicating a 49% reduction in risk of disease progression over the study period. Median PFS was 12.2 months for the O/C4/P arm versus 9.6 months for the C6/P arm. The improvement in PFS appeared to be driven by a separation in the Kaplan-Meier curves after approximately 7 months. Very few events (2 patients in O/C4/P arm and 3 in C6/P arm) occurred during the chemotherapy phase of the study. The number of patients with progression events was slightly lower in the O/C4/P arm: 47/81 patients (58.0%) versus 55/81 patients (67.9%) in the C6/P arm.

Subgroup analyses of platinum sensitivity and number of previous platinum therapies for PFS (independent central review) were consistent with results from the primary analysis of PFS. The subgroup analysis for BRCA was not performed due to an insufficient number of patients with known BRCA status.

Overall survival

There were insufficient events to perform a statistical analysis for OS or to calculate median OS. Twelve patients (14.8%) in the O/C4/P arm and 11 patients (13.6%) in the C6/P arm had died.

Change in tumour size

There was no statistically significant difference between treatment arms in percentage change in tumour size at Week 9 or Week 18. For Week 9, the LS Mean percentage change in tumour size was -38.4% for O/C4/P and -39.1% for C6/P (95% CI: -10.1 to 11.5; p=0.8979). For Week 18, the LS Mean percentage change in tumour size was -53.7% for O/C4/P and -52.5% for C6/P (95% CI: -12.8 to 10.5; p=0.8467). Subgroup analyses of percentage change in tumour size at Week 9 and Week 18 were consistent across subgroups.

Objective response rate, ovarian cancer response rate and CA-125 response rate

The results described below are based on the FAS.

Objective response rates were similar on both treatment arms: there was no statistically significant difference between treatment arms for ORR based on independent central review of RECIST. Objective responses were achieved for 52/81 patients (64.2%) in the O/C4/P arm and 47/81 patients (58.0%) in the C6/P arm (odds ratio 1.30, 95% CI: 0.68 to 2.51, p=0.4238). The majority of these responses were during randomised treatment; however, 6 responses in the C6/P arm were after starting subsequent therapy for cancer.

The ovarian cancer response rates from RECIST response and/or CA-125 response were similar on both treatment arms (64/81 patients [79%] O/C4/P, 56/81 patients [69%] C6/P). The odds ratio for ovarian cancer response rate was 1.69 (95% CI: 0.82 to 3.58) and the p-value was 0.1586.

CA-125 response rate was evaluated in 59 patients in the O/C4/P arm and 50 patients in the C6/P arm. CA-125 response rates were similar on both treatment arms: 51/59 patients (86.4%) in the O/C4/P arm and 37/50 patients (74.0%) in the C6/P arm (odds ratio 2.19, 95% CI: 0.81 to 6.24, p=0.1239).

Summary of pharmacokinetic results

Pharmacokinetic data from 6 patients from Japan who received olaparib indicated that co-administration with C4/P appeared to have little or no effect on single dose exposure to olaparib and also that co-administration with olaparib appeared to have had no effect on exposure to free carboplatin or paclitaxel.

Summary of safety results

Exposure

Exposure to olaparib during the combination phase was in line with what was intended in the protocol; mean total duration of olaparib treatment was 111.6 days (based on a 21-day treatment cycle) and mean actual duration of olaparib treatment was 52.7 days (based on a 10-day dosing period within the 21-day cycle [ie, maximum of 60 days]). The mean total duration of exposure to carboplatin was similar in both treatment arms during the combination phase (122.9 days in the O/C4/P arm and 115.6 days in the C6/P arm), although it should be noted that each treatment arm had a different AUC dose of carboplatin. The calculated mean AUC dose of carboplatin administered per cycle in the combination phase was 3.752 mg.min/mL in the O/C4/P arm and 5.646 mg.min/mL in the C6/P arm. The mean total duration of exposure to paclitaxel was generally similar in both treatment arms during the combination phase: 122.9 days in the O/C4/P arm and 115.6 days in the C6/P arm.

The calculated mean total duration of olaparib treatment during the maintenance phase was 234.5 days. The mean actual duration of treatment for olaparib was 227.7 days.

Adverse events

In the combination phase, all patients in the O/C4/P arm and the majority of patients in the C6/P arm experienced at least 1 AE. In the maintenance phase, a greater number of patients in the olaparib arm compared with the no treatment arm experienced at least 1 AE (Table S2). No fatal AEs were reported in either arm in the combination phase or the monotherapy phase of the study.

Table S2 Summary of number (%) of patients who had at least one AE in any category: Safety Analysis Set

AE category[a]	Combination phase[b]		Maintenance phase[c]	
	O/C4/P n=81	C6/P n=75	Olaparib (Post-O/C4/P) n=66	No treatment (Post-C6/P) n=55
Any AE	81 (100.0)	73 (97.3)	64 (97.0)	41 (74.5)
Any AE causally related to olaparib[d]	76 (93.8)	NA	51 (77.3)	NA
Any AE of CTCAE Grade 3 or higher	53 (65.4)	43 (57.3)	19 (28.8)	9 (16.4)
Any AE of CTCAE Grade 3 or higher, causally related to olaparib[d]	37 (45.7)	NA	11 (16.7)	NA
Any AE of CTCAE Grade 3 or higher, causally related to olaparib and either carboplatin or paclitaxel	36 (44.4)	NA	2 (3.0)	NA
Any AE with outcome = death	0	0	0	0
Any SAE	12 (14.8)	16 (21.3)	6 (9.1)	4 (7.3)
Any SAE causally related to olaparib only[d]	6 (7.4)	NA	2 (3.0)	NA
Any SAE, causally related to olaparib and either carboplatin and or paclitaxel[d]	6 (7.4)	NA	0	NA
Any AE leading to discontinuation of study treatment	15 (18.5)	12 (16.0)	5 (7.6)	NA
Any AE leading to discontinuation of olaparib	5 (6.2)	NA	5 (7.6)	NA
Any AE leading to discontinuation of study treatment, causally related to olaparib[d]	4 (4.9)	NA	2 (3.0)	NA

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Combination phase denominators are from the Safety Analysis Set.
[c] Maintenance phase denominators are from the Maintenance Safety Analysis Set.
[d] As assessed by the investigator.
AE Adverse event; CTCAE Common Terminology Criteria (CTC) for Adverse Events; NA Not applicable; SAE Serious adverse event.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

In the combination phase, the most common AEs in both the O/C4/P and C6/P arms were alopecia, nausea and fatigue. The following events occurred more frequently, with a difference of >10%, in the O/C4/P arm compared with the C6/P arm: alopecia (74.1% versus

58.7%), nausea (69.1% versus 57.3%), diarrhoea (42.0% versus 26.7%), headache (33.3% versus 9.3%) and dyspepsia (25.9% versus 12.0%). Most AEs reported were of mild or moderate intensity (ie, Common Terminology Criteria [CTC] for Adverse Events [CTCAE] Grade 1 or 2; approximately 90% in each arm), with the exception of neutropenia. The frequency of neutropenia AEs (all grades) was greater in the O/C4/P arm compared with the C6/P arm (39 patients [48.1%] versus 29 patients [38.7%]); these were predominantly AEs of CTCAE Grade 3 or higher (34 patients [42.0%] versus 25 patients [33.3%]). Slightly more patients in the O/C4/P arm had AEs of CTCAE Grade 3 or higher compared with the C6/P arm (53 patients [65.4%] versus 43 patients [57.3%]; 148 versus 130 events).

In the maintenance phase, the most common AEs (>15% incidence) in the olaparib arm were nausea (50.0%), vomiting (28.8%), fatigue (19.7%), cough (16.7%), decreased appetite (16.7%), nasopharyngitis (common cold [16.7%]) and diarrhoea (15.2%). The majority of these AEs were mild to moderate in intensity (CTCAE Grade 1 or 2, approximately 95% in each arm), with very few AEs of CTCAE Grade 3 or higher. The following events occurred more frequently, with a difference of >10%, in the olaparib arm compared with the no treatment arm: nausea (50.0% versus 5.5%), vomiting (28.8% versus 7.3%), fatigue (19.7% versus 9.1%), decreased appetite (16.7% versus 1.8%), nasopharyngitis (common cold [16.7%] versus 5.5%]), headache (12.1% versus 1.8%) and constipation (10.6% versus zero). A greater number of patients in the olaparib arm compared with the no treatment arm experienced AEs of CTCAE Grade 3 or higher (19 patients [28.8%] versus 9 patients [16.4%]; 25 events versus 11 events). There were a greater number of CTCAE Grade 3 or higher haematological AEs such as anaemia (5 patients [7.6%] versus 1 patient [1.8%]) and neutropenia (3 patients [4.5%] versus 0 patients) in the olaparib arm compared with the no treatment arm.

Serious adverse events

In the combination phase, 12 patients (14.8%) in the O/C4/P arm experienced 14 SAEs and 16 patients (21.3%) in the C6/P arm experienced 20 SAEs. Only febrile neutropenia (3 patients O/C4/P arm, 1 patient C6/P arm), neutropenia (3 patients O/C4/P arm, 1 patient C6/P arm), drug hypersensitivity (2 patients in each treatment arm), abdominal pain (2 patients in C6/P arm) and anaemia (2 patients in C6/P arm) occurred in more than 1 patient.

In the maintenance phase, no SAEs were reported by more than 1 patient. Six patients (9.1%) in the olaparib arm had 7 SAEs (upper abdominal pain and vomiting [same patient], cytomegalovirus infection, femoral neck fracture, pleural effusion, small intestinal obstruction and myelodysplastic syndrome). An additional patient in the olaparib arm reported myelodysplastic syndrome after database lock. Four (7.3%) patients in the no treatment arm had 5 SAEs (hepatitis acute, cervical vertebral fracture, pleural effusion, entropion and eyelid ptosis [same patient]).

Adverse events leading to discontinuation

In the combination phase, 15 patients (18.5%, 20 events) and 12 patients (16.0%, 12 events) had AEs leading to discontinuation in the O/C4/P and C6/P arms, respectively. In the

O/C4/P arm, the only events occurring in more than 1 patient were drug hypersensitivity (4 patients [4.9%]), anaemia, neutropenia and thrombocytopenia (each in 2 patients [2.5%]). In the C6/P arm, the only event occurring in more than 1 patient was drug hypersensitivity (7 patients [9.3%]). More patients in the O/C4/P arm had haematological toxicity leading to discontinuation than in the C6/P arm.

Overall, few patients (5 patients [7.6%]) discontinued olaparib maintenance monotherapy due to AEs (anaemia, ascites, dysphagia, haemoptysis and myelodysplastic syndrome).

Laboratory data

With the exception of neutrophils, few CTCAE Grade 3 or 4 haematological or clinical chemistry parameter changes were observed during the combination phase of the study. CTCAE Grade 3 or 4 neutrophil changes were observed in both treatment arms. In the maintenance phase, the majority of haematological parameter changes were mild or moderate (CTCAE Grade 1 or 2) and were consistent with the known safety profile for olaparib. Few CTCAE Grade 3 or 4 clinical chemistry parameter changes were observed during the maintenance phase.