Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00012
Edition Number	1

A Phase II, Open-Label, Randomised, Comparative, International Multicentre Study to Compare the Safety and Efficacy of Two Different Doses of AZD2281 Given Orally Twice Daily Versus Intravenous Liposomal Doxorubicin Given Monthly in Patients With Advanced BRCA1- or BRCA2-Associated Ovarian Cancer Who Have Failed Previous Platinum-Based Chemotherapy

Study dates:	First subject enrolled: 30 July 2008 Last patient enrolled (for initial treatment): 3 March 2009
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)

This was an international multicentre study conducted in 25 centres in 9 countries: Australia (3), Belgium (1), Germany (1), Israel (3), Poland (1), Spain (2), Sweden (1), the UK (5) and the USA (8).

Publications

Kaye S, Kaufman B, Lubinski J, Matulonis U, Gourley C, Karlan B, et al. Phase II study of the oral PARP inhibitor olaparib (AZD2281) versus liposomal doxorubicin in ovarian cancer patients with BRCA1 and/or BRCA2 Mutations. Ann Oncology 2010;21(Suppl 8):Abstract 9710.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the efficacy of 2 different dose levels of olaparib versus liposomal doxorubicin in patients with advanced BRCA1- or BRCA2 associated ovarian cancer.	PFS	Efficacy
Secondary	**Secondary**	
To compare the efficacy of 2 different dose levels of olaparib versus liposomal doxorubicin in patients with advanced BRCA1- or BRCA2 associated ovarian cancer.	ORR, disease control rate, overall duration of response, tumour size, CA-125 levels, patients with RECIST confirmed response and/or a CA-125 response (in the absence of progression), OS	Efficacy
To compare the safety and tolerability profile of 2 different dose levels of olaparib versus liposomal doxorubicin in the study population.	AEs, vital signs, ECG, physical exam, haematology and clinical chemistry, concomitant medications.	Safety
To determine olaparib exposure at the 2 different dose levels following oral administration [Only a patient listing of olaparib plasma concentration will be reported in this CSR].	Blood samples collected from all patients receiving olaparib for PK analysis.	PK
To conduct a preliminary assessment of HRQoL as measured by the FACT-O questionnaire.	FACT-O questionnaire (TOI; Total FACT-O Score; FOSI Endpoint).	HRQoL

AE Adverse event; BRCA Breast cancer gene; CA cancer antigen; CSR Clinical study report; ECG Electrocardiogram; FACT-O Functional Assessment of Cancer Therapy – Ovarian Cancer; FOSI FACT-O symptom index; ORR Objective response rate; OS Overall survival; PFS Progression free survival; PK Pharmacokinetic; PRO Patient-reported outcomes; HRQoL Health related Quality of life; TOI Trial Outcome Index.

Study design

This was a Phase II, open-label, randomised, comparative, multicentre study to compare the safety and efficacy of 2 different doses of olaparib with intravenous liposomal doxorubicin in the treatment of patients with advanced breast cancer gene (BRCA) 1- or BRCA2-associated ovarian cancer who have failed previous platinum-based chemotherapy. Patients were randomised (1:1:1) to receive either olaparib 200 mg twice daily (bd) orally, olaparib 400 mg bd orally, or liposomal doxorubicin 50 mg/m^2 intravenously (iv).

Target subject population and sample size

It was intended to enrol up to 90 patients (30 patients per treatment group) with histologically or cytologically-confirmed advanced BRCA1- or BRCA2-associated ovarian cancer who had failed previous platinum-based chemotherapy, with an estimated life expectancy of at least 16 weeks and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2.

The primary analysis on which the study was powered was based on progression free survival (PFS). The analysis was to be performed when a total 57 PFS events had occurred. If the true hazard ratio (HR) for the combined olaparib groups relative to the liposomal doxorubicin group was equal to 0.55 (corresponding to a 82% increase in median PFS from 4 to 7.3 months) and the overall Type I error rate was 10% (1-sided), there was approximately 80% power to demonstrate a promising difference in favour of olaparib (ie, $p<0.1$, 1-sided). An observed HR of 0.7 or less was required to achieve this level of significance.

Statistical significance, in favour of olaparib, was declared if the observed p value was <0.02 (1-sided). This level of significance corresponded to an observed HR of 0.56. An additional 0.5% Type I error (1-sided) was used to compare each olaparib dose separately with liposomal doxorubicin (highest dose was compared first using a closed test procedure) in case the combined comparison was not statistically significant. An observed HR of 0.44 was needed to conclude statistical significance for a given pairwise comparison. The overall Type I error for declaring statistical significance, in favour of olaparib, was no more than 2.5% (1-sided).

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

Micronised olaparib was supplied by Pharmaceutical and Analytical Research and Development (PAR&D), AstraZeneca as an oral 50 mg capsule with Gelucire 44/14 (Lauroyl macroglycerides) as an excipient (solubiliser). Olaparib was dosed at 200 mg or 400 mg bd orally. The following batch numbers of olaparib were used: 53506107, 3065255R, 3070200R and 3072918R.

Liposomal doxorubicin was supplied by either by the investigator's pharmacy or via AstraZeneca according to local and national requirements as either:

- translucent, red liposomal dispersion in 10 mL (20 mg doxorubicin hydrochloride [HCl] at 2 mg/mL) or 30 mL (50 mg doxorubicin HCl at 2 mg/mL) glass vials, or

- translucent, red suspension in 10 mL (20 mg pegylated liposomal doxorubicin HCl) or 25 mL (50 mg pegylated doxorubicin HCl) glass vials.

Liposomal doxorubicin was administered iv at 50 mg/m^2 at initial rate of 1 mg/min every 4 weeks.

Duration of treatment

Patients receiving olaparib were treated until they had radiologically-confirmed progressive disease (PD) or were withdrawn from treatment for another reason. Once patients on olaparib had been withdrawn from treatment, other treatment options were at the discretion of the investigator. Patients on liposomal doxorubicin were treated until they had radiologically-confirmed PD, they were withdrawn from treatment for another reason, or the lifetime maximum cumulative dose of anthracyclines was reached according to local practices and treatment guidelines. Once patients on liposomal doxorubicin had centrally confirmed objective radiological progression, they were given the opportunity to begin treatment with olaparib (400 mg bd dose level) if eligible to do so. Patients who stopped liposomal doxorubicin for other reasons waited until centrally confirmed objective radiological progression before crossover to olaparib. Alternatively, they could have been withdrawn from liposomal doxorubicin and assigned to other treatment options at the discretion of the investigator.

If patients were withdrawn from initially randomised treatment for reasons other than objective progression, they continued to be followed for radiologically confirmed PD according to the study schedule, unless consent was withdrawn. Patients who discontinued study treatment and had radiologically-confirmed PD, were continued to be followed for survival.

Once a total planned 57 PFS events had been confirmed for the primary analysis, ongoing patients continued to receive study treatment until they met any discontinuation criteria. For patients on liposomal doxorubicin, the option to crossover to olaparib (400 mg bd dose level) was still allowed. Any crossover patients were followed for full safety assessments for 57 days. All patients (patients still on study treatment and patients withdrawn from study treatment) were followed for survival.

Statistical methods

PFS was analysed using a Cox proportional hazards model with factors for treatment (olaparib compared with liposome doxorubicin), BRCA (1 or 2), and platinum sensitivity (sensitive=1 or resistant/refractory=0) in accordance with the stratification used at randomisation. The effect of treatment was based on combining the 2 olaparib groups and comparing to the liposomal doxorubicin group. The combined effect was estimated by the adjusted HR together with its corresponding 80% and 95% confidence intervals (CIs). If the observed p-value for the combined olaparib groups was <0.02 (1 sided) then the result was to be regarded as statistically significant and each olaparib dose was to be compared separately with liposomal doxorubicin (highest dose was to be compared first using a closed test procedure) at the 0.02 (1-sided) significance level. If the combined comparison was not

statistically significant, each olaparib dose was compared separately with liposomal doxorubicin (highest dose first using a closed test procedure). An observed p-value of <0.005 (1-sided) was to be regarded as statistically significant for a given pair-wise comparison (following the rules of the closed testing sequence). The overall Type I error for declaring statistical significance, in favour of olaparib, was to be no more than 2.5% (1-sided). Kaplan-Meier plots of PFS were presented by treatment group (1 plot with olaparib groups combined and a second plot displaying the different doses).

Summary statistics were presented for each secondary efficacy variable by treatment group (including olaparib groups combined). In addition, objective response rate (ORR) was compared between olaparib (separately and combined) and liposomal doxorubicin using logistic regression. Corresponding odds ratios (olaparib to liposomal doxorubicin) were estimated along with the associated 80% and 95% CIs. For duration of objective response, a Kaplan-Meier estimate of the median duration for those patients who responded was presented. For change in tumour size, treatment groups were compared using analysis of covariance with factors as for the primary analysis of PFS. Adjusted mean differences between the treatment groups and corresponding 80% and 95% CIs were calculated. Waterfall plots were also produced. For cancer antigen (CA)-125 values, the time from randomisation to a 50%, or greater, and increase in CA-125 were compared between the treatment groups using a Cox proportional hazards model with factors as for PFS. The number (%) of patients reporting a Response Evaluation Criteria in Solid Tumours (RECIST) confirmed response and/or a CA-125 response (in the absence of progression) were also tabulated. At the time of the final PFS analysis, a Kaplan Meier plot of overall survival (OS) was presented by treatment group (including olaparib groups combined). At the final analysis of survival, an adjusted HR with corresponding 80% and 95% CI was estimated from a Cox proportional hazards model with factors for treatment (olaparib groups combined) and the stratification factors used at randomisation.

Appropriate summaries of laboratory data/vital signs and adverse events (AEs)/serious adverse events (SAEs) were produced. Pharmacokinetic (PK) data analysis was performed using non-linear mixed effects modelling (only a patient listing of olaparib plasma concentration is reported in the clinical study report [CSR]). Change from baseline in Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) was summarised by treatment group. Patients' health-related quality of life (HRQoL) data at baseline and Cycle 3 was described and tabulated for the treatment groups (2 different doses of olaparib, combined olaparib doses and liposomal doxorubicin) using numerical (standardised) score data for the trial outcome index (TOI), FACT-O symptom index (FOSI), total FACT-O, individual subscales (physical well being [PWB], social well being [SWB], emotional well being [EWB], functional well being [FWB] and additional concerns) and 1 item within the FACT-O instrument entitled "I am bothered by side effects of treatment" in terms of mean, median, standard deviation, minimum, maximum scores and the number of patients in each treatment group. The proportion of patients 'Improved' and the proportion "Worsened" were compared using logistic regression with factors as for the analysis of PFS. Patients with non-evaluable scores at the Cycle 3 assessment were assigned to the "Worsened" category" in the analysis.

The association between quality of life (QoL) and RECIST response was assessed through an appropriate cross tabulation of the 2 datasets.

Subject population

Of the 97 patients randomised into the study, all olaparib patients (32 in each group) and 32 liposomal doxorubicin patients received study treatment. One patient who was randomised to the liposomal doxorubicin group voluntarily discontinued from the study before receiving study treatment. The patients in this study had advanced BRCA1- or BRCA2-associated ovarian cancer.

At data cut-off for PFS analysis (15 September 2009), 10 (31.3%), 12 (37.5%), and 7 (21.9%) patients in the olaparib 200 mg bd group, olaparib 400 mg bd group, and the liposomal doxorubicin group, respectively, were still receiving their initial study treatment. A total of 22 (68.8%), 20 (62.5%), 25 (78.1%) patients in the olaparib 200 mg bd group, olaparib 400 mg bd group, and the liposomal doxorubicin group, respectively, discontinued treatment prematurely.

At the time of the PFS analysis, a total of 14 patients had crossed over from the liposomal doxorubicin group to the olaparib 400 mg bd group.

The majority (98%) of patients were white with a mean age of 55 years (range 35 to 81 years). Approximately 30% of the study population were Ashkenazi Jewish and 2% were Sephardic Jewish. There were no notable differences in demographic characteristics between the treatment groups. Baseline characteristics were also generally well balanced between the treatment groups.

Summary of efficacy results

Primary efficacy variable: Progression free survival

The statistical analysis of investigator-assessed PFS showed no statistically-significant difference between olaparib monotherapy and liposomal doxorubicin (HR 0.88, 80% CI 0.62 to 1.28, p=0.6604). Olaparib 400 mg was numerically superior to olaparib 200 mg bd (versus liposomal doxorubicin [olaparib 400 mg bd: HR 0.86, 80% CI 0.56 to 1.30, olaparib 200 mg bd: HR 0.91, 80% CI 0.60 to 1.39]), but neither was statistically significantly different to liposomal doxorubicin.

Table S2 Summary of progression free survival analysis (RECIST investigator assessment): FAS

	Olaparib 200 mg bd n=32	Olaparib 400 mg bd n=32	Olaparib 200 mg + 400 mg bd n=64	Liposomal doxorubicin n=33
n (%) of events	19 (59.4)	20 (62.5)	39 (60.9)	20 (60.6)
Median PFS, months[a]	6.5	8.8	-	7.1
80% CI for median	5.6, 8.0	6.3, 9.2	-	5.5, 7.8
95% CI for median	5.5, 10.1	5.4, 9.2	-	3.7, 10.7
Treatment effect[b]				
Hazard ratio	0.91	0.86	0.88	
80% CI	0.60, 1.39	0.56, 1.30	0.62, 1.28	
95% CI	0.48, 1.74	0.45, 1.62	0.51, 1.56	
2-sided p-value[c]	0.7794	0.6316	0.6604	

Note: The analysis was performed using a Cox proportional hazards model with factors for treatment, BRCA status and platinum sensitivity. A hazard ratio < 1 favoured olaparib.

[a] Kaplan-Meier estimate.

[b] Pair-wise comparison versus liposomal doxorubicin.

[c] Statistical significance level was 4% (2-sided) for olaparib 200 mg + 400 mg bd versus liposomal doxorubicin comparison. Statistical significance level for the olaparib 200 mg and 400 mg bd comparisons with liposomal doxorubicin was 4% (2-sided) following a closed testing procedure.

bd Twice daily; CI Confidence interval; FAS Full analysis set; PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.

Secondary efficacy variables: Objective response rate, disease control rate, duration of response, tumour size, CA-125 levels, overall survival, and quality of life

Results of the key secondary efficacy variables are presented in Table S3. There was no statistically significant difference between either olaparib group and the liposomal doxorubicin group for any of the parameters. Treatment with olaparib 400 mg bd was generally numerically superior to treatment with olaparib 200 mg bd but there was no marked difference in efficacy.

Table S3 Summary of key secondary efficacy variables: FAS

	Olaparib 200 mg bd n=32	Olaparib 400 mg bd n=32	Olaparib 200 mg + 400 mg bd n=64	Liposomal doxorubicin n=33
ORR, n (%) of responses[a]	8 (25.0)	10 (31.3)	18 (28.1)	6 (18.2)
DCR at 4 months[b], n (%)	21 (65.6)	21 (65.6)	42 (65.6)	19 (57.6)
Median duration of response (months)[c, d]	5.95	6.80	6.24	5.49
Median best percentage change from baseline in target lesion size (range), cm	-15.90 (-75.30 to 31.48)	-24.60 (-100.00 to 51.10)	-23.15 (-100.00 to 51.10)	-14.30 (-87.50 to 32.40)
RECIST response	8 (25.0)	12 (37.5)	20 (31.3)	9 (27.3)
CA-125 response	11 (34.4)	18 (56.3)	29 (45.3)	11 (33.3)
Confirmed RECIST response and/or CA-125 response[e]	12 (37.5)	19 (59.4)	31 (48.4)	13 (39.4)
Final Overall Survival				
n (%) of deaths	9 (28.1)	11 (34.4)	20 (31.3)	13 (39.4)
Treatment effect[f]				
Hazard ratio	0.66	1.01	0.82	-
80% CI	0.37, 1.15	0.59, 1.71	0.52, 1.31	-
95% CI	0.27, 1.55	0.44, 2.27	0.41, 1.70	-
2-sided p-value	0.3417	0.9877	0.5781	-

[a] No patients had a best objective response of CR. A total of 24 patients had a best objective response of PR
[b] Confirmed complete response (CR) and confirmed partial response (PR) and stable disease (SD) >4 months.
[c] Responding patients only.
[d] Based on the Kaplan-Meier estimate.
[e] CA-125 response in the absence of RECIST progression.
[f] Pairwise comparison versus liposomal doxorubicin.

bd Twice daily; CA Cancer antigen; CI Confidence interval; DCR Disease control rate; FAS Full analysis set; ORR Objective response rate; PFS Progression free survival; RECIST Response Evaluation Criteria in Solid Tumours.

No statistically significant difference was observed with respect to improvements in HRQoL from baseline to Cycle 3 from the 2 patient-reported outcomes endpoints of TOI and FOSI, or for worsening rates for the 3 patient-reported endpoints. However, for the Total FACT-O endpoint, the improvement in HRQoL in the olaparib 400 mg bd group was statistically significant versus liposomal doxorubicin (OR: 7.23, 80% CI: [2.00, 40.71], p= 0.0392). Analysis of secondary tumour response by HRQoL response rates did not generate data that could be meaningfully interpreted due to very small numbers of patients.

Summary of pharmacokinetic, pharmacodynamic and pharmacogenetic results

These data are not included in this CSR but will be combined with data from other studies and presented separately.

Summary of safety results

The overall median exposure to study treatment was 209.0 days, 218.0 days and 178.0 days in the olaparib 200 mg bd, olaparib 400 mg bd and liposomal doxorubicin groups, respectively. Overall median dose intensity was 99.35% (range 49.41 to 100.00%), 93.53% (range 53.20 to 100.00%) and 82.03% (range 33.08 to 105.25%) in the olaparib 200 mg bd, olaparib 400 mg bd and liposomal doxorubicin groups, respectively.

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S4.

Table S4 Summary of number (%) of patients who had at least one adverse event in any category: Safety analysis set

AE category[a]	Number (%) of patients		
	Olaparib 200 mg bd	Olaparib 400 mg bd	Liposomal doxorubicin
	n=32	n=32	n=32
Any AE	32 (100.0)	32 (100.0)	31 (96.9)
Any AE causally related	26 (81.3)	29 (90.6)	31 (96.9)
Any AE of CTCAE grade 3 or higher	12 (37.5)	12 (37.5)	23 (71.9)
Any AE of CTCAE grade 3 or higher, causally related[b]	7 (21.9)	9 (28.1)	20 (62.5)
Any AE with outcome = death	2 (6.3)	0	0
Any AE with outcome = death, causally related[b]	2 (6.3)	0	0
Any SAE (including events with outcome = death)	5 (15.6)	6 (18.8)	4 (12.5)
Any SAE (including events with outcome = death), causally related[b]	4 (12.5)	0	2 (6.3)
Any AE leading to discontinuation of study treatment	2 (6.3)	1 (3.1)	3 (9.4)
Any causally related[b] AE leading to discontinuation of study treatment	2 (6.3)	1 (3.1)	3 (9.4)

[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] As assessed by the investigator.
Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study medication.
AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; SAE Serious adverse event.

AEs occurring in ≥25% of patients overall (across the 3 treatment groups) were nausea (62 patients, 64.6%), fatigue (49 patients, 51.0%), vomiting (37 patients, 38.5%), abdominal pain (32 patients, 33.3%), diarrhoea (28 patients, 29.2%), constipation (26 patients, 27.1%), and headache (24 patients, 25.0%). In the olaparib 200 mg bd group, nausea (19 patients, 59.4%), and fatigue (13 patients, 40.6%) were the most commonly reported AEs (ie, occurring in ≥40% of patients in the treatment group); in the olaparib 400 mg bd group, nausea (25 patients, 78.1%), fatigue (21 patients, 65.6%), and vomiting (16 patients, 50.0%) were the

most commonly reported AEs; in the liposomal doxorubicin group, palmar-plantar erythrodysaesthesia syndrome (20 patients, 62.5%), stomatitis (19 patients, 59.4%), nausea (18 patients, 56.3%), fatigue (15 patients, 46.9%), and rash (14 patients, 43.8%) were the most commonly reported AEs. Nausea and fatigue were the most frequently reported AEs considered by the investigator to be causally-related to olaparib 200 mg bd. Nausea, fatigue, and vomiting were the most frequently reported AEs considered to be causally-related to olaparib 400 mg bd. Stomatitis, palmar-plantar erythrodysaesthesia syndrome, nausea, fatigue, and rash were the most frequently reported AEs considered by the investigator to be causally-related to liposomal doxorubicin. Most AEs were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2. A higher percentage of patients in the liposomal doxorubicin group had AEs of CTCAE grade ≥3 compared with the olaparib groups. At the episode level, the number of CTCAE grade ≥3 AEs was also higher in the liposomal doxorubicin group compared with the olaparib groups. AEs of CTCAE grade ≥3 occurring in ≥3 patients in any treatment group were anaemia (reported in 4 patients in the olaparib 400 mg bd group), fatigue (reported by 3 patients in the olaparib 400 mg bd group and 3 patients in the liposomal doxorubicin group), rash (reported by 3 patients in the liposomal doxorubicin group), and palmar-plantar erythrodysaesthesia syndrome (reported by 12 patients in the liposomal doxorubicin group).

Of the 96 patients who received study medication, 16 patients died during the study; 4 (12.5%), 7 (21.9%), and 5 (15.6%) in the olaparib 200 mg bd, olaparib 400 mg bd and liposomal doxorubicin groups, respectively. In the investigator's opinion, the majority (14/16 [87.5%]) of these patients died due to progression of their ovarian cancer. One patient (in the olaparib 200 mg bd group) was considered by the investigator to have died as a consequence of an AE alone (myelodysplastic syndrome). One patient (olaparib 200 mg bd group) died due to disease progression and an AE (cerebrovascular accident).

Fatigue (reported in 1 patient in the olaparib 200 mg bd group and 1 patient in the liposomal doxorubicin group), cerebrovascular accident (reported in 2 patients in the olaparib 200 mg bd group), intestinal obstruction (reported in 1 patient in the olaparib 200 mg bd group and 1 patient in the olaparib 400 mg group) and myelodysplastic syndrome (reported in 3 patients, 2 in the olaparib 200 mg bd group and 1 in the liposomal doxorubicin group) were the only SAEs reported in >1 patient.

Six patients had study treatment permanently discontinued due to AEs. In the olaparib 200 mg bd group, 1 patient had an AE of cerebrovascular accident, 1 patient had an AE of neutropenia and 1 patient had an AE of myelodysplastic syndrome; in the olaparib 400 mg bd group, 1 patient had an AE of nausea and an AE of vomiting; in the liposomal doxorubicin group, 2 patients had an AE of palmar-plantar erythrodysaesthesia syndrome and 1 patient had an AE of drug hypersensitivity and an AE of palmar-plantar erythrodysaesthesia syndrome. All of these AEs leading to permanent discontinuation of study treatment were considered by the investigator to be related to study treatment.

Four (12.5%), 17 (53.1%), and 18 (56.3%) patients in the olaparib 200 mg bd, olaparib 400 mg bd and liposomal doxorubicin groups, respectively, had an AE leading to dose modification.

There were no unexpected changes noted in any of the clinical laboratory, vital signs or physical examination safety parameters in the olaparib or liposomal doxorubicin treatment groups, and no individual abnormalities raised any new safety concerns.

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