Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
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A Randomised, Double-Blinded, Multicentre Phase II Study to Assess the Efficacy of Olaparib (AZD2281, KU-0059436) in Combination with Paclitaxel versus Paclitaxel in Patients with Recurrent or Metastatic Gastric Cancer who Progress Following First-Line Therapy

Study dates: First subject enrolled: 02 February 2010
Last subject last visit: 11 May 2012

Phase of development: Therapeutic exploratory (II)

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

Study centres

A total of 13 centres from South Korea participated in this study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives reported in the Clinical Study Report are summarised in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives [a]	Outcome variables	Type
Primary	**Primary**	
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by PFS, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	PFS	Efficacy
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by PFS in patients with recurrent and metastatic gastric cancer whose tumours are defined as HRD by way of loss of expression of ATM protein ("ATM-negative patients") who progress following first-line therapy.	PFS	Efficacy
Secondary	**Secondary**	
To determine the safety and tolerability of olaparib when given in combination with paclitaxel in patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	Frequency and severity of AEs, SAEs, Laboratory data, vital signs, ECG, and physical examination	Safety
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by OS, RR and percentage change in tumour size at Week 8, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	OS, RR[b], Percentage change in tumour size at Week 8	Efficacy
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by OS, RR and percentage change in tumour size at Week 8 in ATM-negative patients with recurrent and metastatic gastric cancer who progress following first-line therapy	OS, RR, Percentage change in tumour size at Week 8	Efficacy
To conduct a preliminary assessment of the effects of olaparib when given in combination with paclitaxel on the time of deterioration of disease related symptom and HRQoL as assessed by the EORTC QLQ-C30 + -STO22 questionnaires.	STODYS (dysphagia), STOEAT (eating restriction), STOPAIN (stomach pain), STOFX (reflux), STOANX (anxiety) sub-scales, Global QoL sub-scale	PRO

a There were 3 exploratory objectives in this study which will be reported separately from this report.
b Additional endpoints of Best objective response and Duration of response were summarised and not formally analysed.
AE Adverse Event; ATM Ataxia-Telangiectasia Mutation; EORTC European Organisation for Research and Treatment of Cancer; HRD Homologous Recombination Deficient; HRQoL Health Related Quality of Life; OS Overall Survival; PFS Progression Free Survival; PRO Patient Reported Outcome; RR Response Rate; SAE Serious Adverse Event.

Study design

This was a Phase II randomised, double-blind study of olaparib+paclitaxel versus matching placebo+paclitaxel in patients with recurrent and metastatic gastric cancer who had progressed following first-line chemotherapy. The study consisted of combination phase (olaparib+paclitaxel/placebo+paclitaxel) and maintenance phase (patients continuing on olaparib/placebo until objective progression or as long as in the investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria, after stopping paclitaxel).

Olaparib was administered in combination with paclitaxel at a dose of 100 mg bd, tablet formulation. Patients were administered paclitaxel 80 mg/m^2 intravenous, weekly on Days 1, 8, and 15 of a 4−week schedule and it was expected that patients would receive between 6 to 10 cycles of paclitaxel. Following completion of the last cycle of chemotherapy, the olaparib or matching placebo dose was increased to 200 mg bd.

Target subject population and sample size

The target population consisted of patients of ≥18 years of age with recurrent or metastatic gastric cancer that had progressed following first-line therapy. The patients had to have a confirmed Ataxia-Telangiectasia Mutation (ATM) status, Eastern Co-operative Oncology Group (ECOG) performance status ≤2, normal organ and bone marrow function, and life expectancy ≥16 weeks.

A total of 120 patients were planned to be randomised in this study. The study was enriched to include a higher proportion of ATM negative patients than occur naturally in the patient population. Due to the ATM negative status being less prevalent, recruitment of the ATM positive patients was faster than the recruitment of ATM negative patients. After required ATM positive patients were recruited, recruitment of the ATM positive patients was closed and recruitment of the ATM negative patients continued until the required number had been enrolled. In total, 124 patients were randomised in the study (62 in the OP arm and 62 in the PP arm) and all patients were included in Full Analysis Set (FAS).

This trial was sized using 1-sided 10% significance level, as it was a Phase II study looking for a signal of improved efficacy.

Investigational product (IP) and comparator: Dosage, mode of administration, and batch numbers

The details of IP and any other study treatment are provided in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Olaparib	25 mg tablet (4 tablets) 100 mg tablet (1 tablet)	AstraZeneca	Not Applicable	25 mg tablet: 8300.1/1A, 8300.2/1A 100 mg tablet: 8300.3/1A, 8300.6/1A, 8300.7/1A, 8300.8/1A, 8300.10/1A, 8300.19/1A
Placebo to match olaparib	Tablet	AstraZeneca	Not Applicable	25 mg tablet: 8300.1/1B, 8300.2/1B 100 mg tablet: 8300.3/1B, 8300.6/1B, 8300.7/1B, 8300.8/1B, 8300.10/1B 8300.19/1B
Paclitaxel	80 mg/m^2 Intravenous	Bristol-Myers Squibb SRL.	Not Applicable.	9J49286, 0B58524, 0E58858, 0K58956, 0L61313, 1B00197, 1D00313, 1E00448, 1G00085

Duration of treatment

There was no maximum duration of treatment with olaparib or matching placebo. Patients were expected to receive 6 to 10 cycles of olaparib+paclitaxel or matching placebo+paclitaxel in the combination phase before entering the maintenance phase. After the combination treatment was stopped, patients continued with olaparib or matching placebo as long as in the investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

Statistical methods

All analyses were performed under the direction of Biostatistics group, AstraZeneca. All calculations were performed with the SAS® software version 9.1.3. A comprehensive statistical analysis plan (SAP) was prepared before unblinding of the data.

The null hypothesis for all efficacy analyses was that there was no difference in treatment effects between olaparib in combination with paclitaxel compared with paclitaxel alone. A 1-sided 10% significance level test was used to assess the statistical significance of the treatment group differences in the efficacy outcome variables. No adjustments for multiplicity were made in sizing the study but this was taken into account when interpreting the data.

There were 2 populations of interest in the analyses in this study; the overall population containing all randomised patients and the ATM negative population containing only the randomised patients whose ATM status was negative. Analyses of Progression Free Survival (PFS), Overall Survival (OS), Objective Response Rate (ORR), and change in tumour size at Week 8 have been performed in both populations.

The analysis sets used in the analysis were:

- **Full analysis set (FAS)**: Included all randomised patients following the principle of intention-to-treat and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or protocol violations.
- **Safety analysis set**: Included all patients who received either olaparib or matching placebo and compared treatment groups on the basis of actual treatment received.
- **Evaluable for Response (EFR)**: A subset of the FAS that included patients with target lesions measured at baseline.

Efficacy variables:

Progression Free Survival: PFS was analysed using a Cox proportional hazards model. In the overall population, the model allowed the effect for treatment and included terms for gastrectomy (full, partial, none) and ATM status (positive, negative). In the ATM negative population, the model included terms for treatment and gastrectomy (full, partial and none).

Overall Survival: OS was analysed using the same methodology as PFS.

For both PFS and OS, in the overall and the ATM negative population, the Hazard Ratio (HR) for treatment (olaparib+paclitaxel: matching placebo+with paclitaxel) was estimated together with 2-sided 80% and 95% Confidence Intervals (CI) (a HR <1 favours the olaparib arm).

Objective Response Rate: ORR was analysed using a logistic regression model. The model allowed for the effect of treatment and included terms for covariates as described for PFS.

Percentage change in Tumour size at Week 8: The effect of olaparib in combination with paclitaxel on the percentage change in tumour size from baseline to Week 8 was estimated using an Analysis of Covariance (ANCOVA) model. In the overall population, the model included terms for treatment group and covariates for gastrectomy (full, partial and none), ATM status, and baseline tumour size. In the ATM negative population, the model included terms for treatment group and covariates for gastrectomy (full, partial and none) and baseline tumour size.

Health Related Quality of Life (HRQoL) and disease related symptoms: The mean changes in score from baseline were presented graphically. For each score, the QoL response over time and the best QoL response were summarised, and the number and percentage of patients in each category were presented.

Safety variables: Safety data from consent until 30 days following the last dose of olaparib or matching placebo are included in the summaries. Safety data is summarised by initial treatment received in the overall population. No formal hypothesis testing was conducted on the safety data generated from this study.

Subject population

In the results section, the olaparib+paclitaxel and placebo+paclitaxel arms are referred to as OP and PP arms, respectively.

A total of 266 patients were enrolled in the study from 13 centres in South Korea. Of these, 124 patients were randomised (62 in the OP arm and 62 in the PP arm) to receive study treatment.

Of the 124 randomised patients, 61 (98.4%) patients received olaparib and paclitaxel in the OP arm and 62 (100%) patients received placebo and paclitaxel in the PP arm.
One (1.6%) patient in the OP arm did not receive either olaparib or paclitaxel, as the patient was randomised in error and was subsequently withdrawn.

At the time of analysis, 57 (93.4%) patients discontinued olaparib and 58 (95.1%) patients discontinued paclitaxel in the OP arm; while 60 (96.8%) patients discontinued placebo and 61 (98.4%) patients discontinued paclitaxel in the PP arm. 'Condition under investigation worsened' was the most common reason for discontinuation of olaparib/placebo/paclitaxel in both treatment arms.

At the time of data cut-off (last patient last visit [11 May 2012]), there were 4 (6.5%) patients in the OP arm and 2 (3.2%) patients in the PP arm who were ongoing in the study. Of these, 3 patients were receiving olaparib+paclitaxel and 1 patient was receiving olaparib from the OP arm; while 1 patient was receiving placebo+paclitaxel and 1 patient was receiving placebo in the PP arm

Fifty eight (93.5%) patients in the OP arm and 60 (96.8%) patients in PP arm terminated the study. Death was the most common reason for termination from study in both treatment arms (33 [53.2%] in the OP arm and 48 [77.4%] in the PP arm). Eleven (17.7%) patients in the OP arm and 7 (11.3%) patients in the PP arm entered the maintenance phase in the study.

All randomised patients (124) were included in FAS. The safety analysis set included 123 patients and the evaluable for response set included 100 patients. One patient randomised in the OP arm did not receive study treatment and was excluded from the safety analysis set.

Demographic and baseline characteristics were generally well balanced between the treatment arms and were representative of an advanced gastric cancer population.

In the study, all patients were Asian and the mean age was 59.2 years in the overall population and 60.5 years in the ATM negative population. There were more male patients, compared to female patients (93 [75%] vs 31 [25%] in the overall population and 49 [77.8%] vs 14 [22.2%]) in the ATM negative population).

Summary of efficacy results

Progression free survival: The effect on PFS was not statistically significant between the treatment arms for either the overall population or the ATM negative population. In the

overall population, the median PFS was 3.91 months in the OP arm and 3.55 months in the PP arm with HR 0.80; 80% CI 0.62, 1.03; 1-sided p-value=0.131. In the ATM negative population, the median PFS was 5.29 months in the OP arm and 3.68 months in the PP arm with HR=0.74; 80% CI 0.51, 1.08; 1-sided p-value=0.157. There were 110/124 (88.7%) progression events in the overall population and 54/63 (85.7%) progression events in the ATM negative population.

The results of sensitivity analyses were consistent with the primary analyses. There was a trend for patients with full or partial gastrectomy to have a longer PFS compared with patients with no gastrectomy.

Overall survival: A statistically significant and clinically meaningful OS benefit was demonstrated for olaparib in combination with paclitaxel in second-line gastric cancer patients in the overall population and the ATM negative population. In the overall population, the median OS was 13.1 months in the OP arm and 8.3 months in the PP arm with HR 0.56; 80% CI 0.41, 0.75; 1-sided p-value=0.005. In the ATM negative population, the median OS was not calculated for the OP arm as the Kaplan Meier median was not met due to lack of events. The median OS was 8.2 months in the PP arm (HR=0.35; 80% CI 0.22, 0.56; 1-sided p-value=0.002). There were 81/124 deaths in the overall population and 35/63 deaths in the ATM negative population.

Objective response rate: There was no statistically significant difference between the treatment arms in terms of objective response rate, for either the overall population or the ATM negative population. In the overall population, the response rate was 26.4% for the OP arm and 19.1% for the PP arm (odds ratio 1.65; 80% CI 0.86, 3.23; 1-sided p-value=0.162). In the ATM-negative population, the response rate was 34.6% for the OP arm and 26.1% for the PP arm (odds ratio 1.76; 80% CI 0.76, 4.21; 1-sided p-value=0.195).

Percentage change in tumour size at Week 8: There was no statistically significant difference between the treatment arms in terms of the percentage change in tumour size at Week 8, for either the overall population or the ATM negative population. In the overall population, the LS Mean percentage change in tumour size was -7.7% for the OP arm and 0.2% for the PP arm (1-sided p-value=0.121). In the ATM-negative population, the LS Mean percentage change in tumour size was -8.2% for the OP arm and -5.7% for the PP arm (1-sided p-value=0.386).

Although not statistically significant, PFS, ORR, and percentage change in the tumour size at Week 8 results were numerically in favour of olaparib.

Patient reported outcome: A detrimental impact on QoL, HRQoL, and symptoms was not observed in the OP arm compared to the PP arm.

No meaningful differences were observed between the arms with regards to “improved”, “no change”, and “worsened” responses in the QoL scores of ‘fatigue’, ‘nausea and vomiting’, ‘dysphagia’, ‘eating restriction’, ‘stomach pain’, ‘reflux’, and ‘anxiety’. However, numerically higher proportion of patients in the OP arm, compared to the PP arm, reported

best response of 'improved' for Global QoL score (32 [52.46%] in the OP arm and 20 [33.33%] in the PP arm) and Pain (28 [45.9%] in the OP arm and 21 [35%] in the PP arm).

There were no significant differences between the treatment arms with respect to time to deterioration.

Summary of safety results

The overall treatment duration was higher in the OP arm compared to the PP arm. The median duration (actual treatment duration) was 82 days for olaparib treatment and 63.5 days for placebo treatment in the combination phase, reflecting median PFS. The mean daily dose received for total duration over the course of the trial in combination phase was 173.1 mg olaparib and 179.3 mg placebo.

The median duration of paclitaxel treatment was 119 days in the OP arm and 112 days in the PP arm. The majority of patients on both treatment arms (41 [67.2%] in the OP arm and 32 [51.6%] in the PP arm) received at least 4 cycles of treatment with a small number of patients on both treatment arms receiving ≥9 cycles of treatment (7 [11.5%] in the OP arm and 7 [11.3%] in the PP arm). A higher number of patients in the OP arm (45 [73.8%]) compared to the PP arm (33 [53.2%]) completed ≥3 cycles of paclitaxel.

A summary of number of patients who had at least 1 Adverse Event (AE) in any category is presented in Table S3. The safety results have been reported for overall phase (combination+maintenance phase). All patients who were included in the safety analysis set experienced at least 1 AE (61 [100%] patients in the OP arm and 62 [100%] patients in the PP arm).

Table S3 Summary of number (%) of patients who had at least one AE in any category (Safety analysis set)

	Number (%) of patients[a]											
	Combination Phase				Maintenance Phase				Overall			
	Olaparib/ Paclitaxel (N=61)		Placebo/ Paclitaxel (N=62)		Olaparib/ Paclitaxel (N=11)		Placebo/ Paclitaxel (N=7)		Olaparib/ Paclitaxel (N=61)		Placebo/ Paclitaxel (N=62)	
AE category												
Any AE	61	(100.0)	62	(100.0)	8	(72.7)	7	(100.0)	61	(100.0)	62	(100.0)
Any AE causally related to olaparib/placebo[b]	14	(23.0)	11	(17.7)	3	(27.3)	0		16	(26.2)	11	(17.7)
Any AE causally related to paclitaxel[b]	60	(98.4)	59	(95.2)	1	(9.1)	0		60	(98.4)	59	(95.2)
Any AE causally related to both olaparib/placebo and paclitaxel	60	(98.4)	60	(96.8)	4	(36.4)	0		60	(98.4)	60	(96.8)

Table S3 Summary of number (%) of patients who had at least one AE in any category (Safety analysis set)

	Number (%) of patients[a]											
	Combination Phase				Maintenance Phase				Overall			
	Olaparib/ Paclitaxel (N=61)		Placebo/ Paclitaxel (N=62)		Olaparib/ Paclitaxel (N=11)		Placebo/ Paclitaxel (N=7)		Olaparib/ Paclitaxel (N=61)		Placebo/ Paclitaxel (N=62)	
AE category												
Any AE of CTCAE grade 3 or higher	46	(75.4)	45	(72.6)	2	(18.2)	4	(57.1)	46	(75.4)	46	(74.2)
Any AE of CTCAE grade 3 or higher causally related to olaparib/placebo	1	(1.6)	2	(3.2)	2	(18.2)	0		3	(4.9)	2	(3.2)
Any AE of CTCAE grade 3 or higher causally related to paclitaxel [b]	6	(9.8)	6	(9.7)	0		0		6	(9.8)	6	(9.7)
Any AE with outcome=death	0		1	(1.6)	0		0		0		1	(1.6)
Any SAE(including events with outcome=death)	16	(26.2)	23	(37.1)	1	(9.1)	1	(14.3)	17	(27.9)	23	(37.1)
Any SAE casually related to olaparib/placebo	0		0		0		0		0		0	
Any SAE casually related to paclitaxel [b]	7	(11.5)	12	(19.4)	0		0		7	(11.5)	12	(19.4)
Any AE leading to discontinuation of olaparib/placebo	1	(1.6)	5	(8.1)	0		0		1	(1.6)	5	(8.1)
Any AE leading to discontinuation causally related to olaparib/placebo	0		0		0		0		0		0	
Any AE leading to discontinuation causally related to paclitaxel [b]	1	(1.6)	3	(4.8)	0		0		1	(1.6)	3	(4.8)

[a] Patients with multiple events in the same category are counted only once in that category.
b As assessed by the investigator.
Adverse Events are summarised in the phase in which they started.
Combination phase adverse events have a date of onset between the date of first dose and the end of the final cycle of paclitaxel for patients who progress to the maintenance phase, or between the date of first dose and 30 days after the discontinuation date for patients who discontinue the study or do not progress to the maintenance phase.
Maintenance phase adverse events have a date of onset between the day after the end of the final cycle of paclitaxel and 30 days after the last dose of olaparib (or placebo).
Overall phase=combination phase+maintenance phase.

Overall, AEs were most commonly reported from the System Organ Class (SOC) of Blood and lymphatic disorders and Gastrointestinal disorders in both treatment arms. The incidence of AEs from the following SOCs was higher in the OP arm, compared to the PP arm: Blood and lymphatic disorder (50 [82%] patients in the OP arm and 46 [74.2%] patients in the PP arm), Gastrointestinal disorders (50 [82%] patients in the OP arm and 44 [71%] patients in the PP arm), and Nervous system disorder (34 [55.7%] patients in the OP arm and 28 [45.2%] patients in the PP arm).

The incidence of AEs across following SOCs was lower in the OP arm compared to the PP arm: General disorder and administration site conditions (37 [60.7%] in the OP arm and 46 [74.2%] in the PP arm), Infections and infestations (17 [27.9%] in the OP arm and 23 [37.1%] in the PP arm), and Musculoskeletal and connective tissue disorders (14 [23%] in the OP arm and 32 [51.6%] in the PP arm).

Neutropenia was the most common AE observed in this study in both treatment arms, with a higher incidence in the OP arm, compared to the PP arm (46 [75.4%] patients in the OP arm and 40 [64.5%] patients in the PP arm). A higher number of patients in the OP arm (30 [49.2%]) had peripheral neuropathy (including preferred terms peripheral neuropathy and peripheral sensory neuropathy), compared with the PP arm (23 [37.1%]). The incidence and severity of nausea and vomiting was higher in the PP arm, compared to the OP arm (nausea: 21 [34.4%] patients in the OP arm and 26 [41.9%] patients in the PP arm; vomiting: 10 [16.4%] patients in the OP arm and 14 [22.6%] patients in the PP arm). Anaemia was reported by similar number of patients in both treatment arms (11 [18%] in the OP arm and 12 [19.4%] in the PP arm).

The most common AEs causally related to olaparib, as assessed by investigator, were rash (4 [6.6%] patients) and pruritus (3 [4.9%] patients). The most common AEs causally related to placebo, as assessed by investigator, were rash (3 [4.8%] patients) and diarrhoea (3 [4.8%] patients). The most common AEs causally related to paclitaxel, as assessed by investigator, were neutropenia (46 [75.4%] patients in the OP arm and 39 [62.9%] patients in the PP arm) and alopecia (28 [45.9%] patients in the OP arm and 29 [46.8%] patients in the PP arm).

Overall, the number of patients with at least 1 AE of Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥3 was similar across both treatment arms (46 [75.4%] patients in OP arm and 46 [74.2%] patients in PP arm). The most common AEs with CTCAE Grade ≥3 in both the treatment arms were neutropenia (34 [55.7%] patients in the OP arm and 24 [38.7%] patients in the PP arm) and anaemia (7 [11.5%] patients in the OP arm and 7 [11.3%] patients in the PP arm). The incidence of neutropenia was higher in the OP arm compared to the PP arm.

A higher number of deaths were observed in the PP arm compared to the OP arm (32 [52.5%] deaths in the OP arm and 48 [77.4%] deaths in the PP arm). All the deaths, except 1 (Patient E6001001), were related to disease under investigation. Patient E6001001 from the PP arm had an AE of cerebral infarction which resulted in death.

A lower number of patients in the OP arm, compared to the PP arm, reported serious adverse event (17 [27.9%] in the OP arm and 23 [37.1%] in the PP arm) and discontinuation of IP due to AE (1 [1.6%] in the OP arm and 5 [8.1%] in the PP arm).

The proportion of patients reporting AEs leading to dose modification and dose interruption was similar in both treatment arms. The incidence of AEs leading to dose reduction was higher in the OP arm, compared to the PP arm. Neutropenia was the most common AE leading to dose modification, dose interruption, and dose reduction in both treatment arms.

There were no major changes in the haematology values except neutrophils absolute count, lymphocytes absolute count, haemoglobin, and white blood cells. The proportion of patients reporting CTCAE Grade 3 or 4 changes in neutrophil values were higher in the OP arm compared to the PP arm. The proportion of patients reporting CTCAE Grade 3 or 4 changes in haemoglobin values were slightly higher in the PP arm, compared to the OP arm. The proportion of patients with CTCAE Grade 3 or 4 changes in lymphocytes absolute values were slightly higher in the PP arm compared to the OP arm. The proportion of patients with CTC Grade 3 or 4 changes in white blood cell values were higher in the OP arm compared to the PP arm.

There were higher number of patients in the PP arm compared to the OP arm who had CTCAE Grade 3 or 4 changes for ALT, ALP, and total bilirubin. Six patients (1 in OP arm and 5 in PP arm) had liver parameters which met potential Hy's law; however all these patients had confirmed alternative explanation that would explain ALT or AST and total bilirubin elevation. A higher number of patients in the OP arm compared to the PP arm had CTCAE Grade 3 or 4 changes for lipase. Few patients in either treatment arm had shifts from negative or normal urine blood, protein or glucose at baseline to 3+ or >3+ values during the study. There was only 1 patient in the OP arm, who had normal ECG assessment at baseline but reported abnormal clinically significant ECG assessment during follow-up.

There were no unexpected changes noted in vital signs or physical examination safety parameters in the study.