Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281 KU-0059436)
Study Code	D0810C00020
Edition Number	1
Date	3 November 2010

Phase II, Open Label, Non-Randomized Study of AZD2281 in the Treatment of Patients with Known *BRCA* or Recurrent High Grade Serous/Undifferentiated Tubo-Ovarian Carcinoma and in Known *BRCA* or Triple Negative Breast Cancer to Determine Response Rate and Correlative Markers of Response

Study dates:	First patient enrolled: 8 July 2008 Data cut-off: 26 March 2010
Phase of development:	Therapeutic Exploratory (II)

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

Study centres

Patients were enrolled at 6 centres in Canada.

Publications

Gelmon KA, Hirte HW, Robidoux A, et al. Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer. J Clin Oncol 2010; 28(7S):3002 (abstr).

Objectives

The primary objective of this study was to determine the single agent olaparib's objective response rate (ORR) as evaluated according to RECIST guidelines in known *BRCA* or high grade serous/undifferentiated ovarian cancer and known *BRCA* or triple negative breast cancer including enrichment for tumours with *BRCA* mutations.

The secondary objectives of the study were:

- Identification of markers of olaparib efficacy through analysis of tumour material.
- To investigate progression free survival (PFS) in patients treated with olaparib
- To assess the safety and tolerability profile of olaparib when administered orally to patients with recurrent breast and ovarian cancer in both *BRCA* inherited mutation carriers and non-carriers.

Note that the first secondary objective listed includes a further secondary objective from the original CSP (these were combined by CSP amendment 4). This secondary objective is not addressed in this CSR. These data will be combined with data from other studies and presented separately.

Study design

This was a Phase II, open label, non-randomized correlative study of olaparib as a single agent given twice daily (bd) to patients with recurrent breast and ovarian cancer. The study enrolled both *BRCA* inherited mutation carriers and non-carriers. Patients with either triple negative breast cancer (TNBC) or serous ovarian cancer who had previously tested negative for the *BRCA* mutation were enrolled in the 'unknown *BRCA* mutation status' arms of the study. Patients were enrolled into 4 arms as follows: 1) TNBC with unknown *BRCA* mutation status; 2) Known *BRCA* mutation positive breast cancer; 3) High grade serous/undifferentiated tubo-ovarian carcinoma with unknown *BRCA* mutation status; 4) Known *BRCA* mutation positive ovarian cancer. All patients received olaparib 400 mg bd until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Patients with unknown *BRCA* status at entry had to provide a DNA sample for *BRCA* mutation analysis, which was performed at Myriad Genetics.

Target patient population and sample size

Ten patients were planned to be enrolled into each of the known *BRCA* mutation positive arms (in practice, 11 breast cancer patients and 10 ovarian cancer patients were recruited). For the unknown *BRCA* mutation status arms an optimal 2-stage Simon design was used. Fifteen patients with unknown *BRCA* mutation status were enrolled to each of the TNBC and high grade serous/undifferentiated ovarian groups in 'stage 1'. One or more responses were required in these 15 patients to progress to 'stage 2' (in which further patients were to be recruited) otherwise accrual was to be stopped. In the TNBC group, a further 20 patients were to be recruited in stage 2 while in the high grade serous/undifferentiated ovarian group a further 40 patients were to be recruited in stage 2. *Note that the number of additional patients to be recruited to the high grade serous/undifferentiated ovarian group in stage 2 was increased from 20 to 40 patients by CSP amendment 4.*

Investigational product: dosage, mode of administration and batch numbers´

Micronised olaparib was supplied by Patheon Pharmaceuticals Inc as an oral 50 mg capsule, with Gelucire 44/14 (Lauroylmacrogylcerides) as excipient (solubiliser). Batch numbers were: 3064515R, 3065255R and 3070200R.

Duration of treatment

The treatment period was divided into cycles of 28 days, and patients were to be treated and followed up until there was no apparent clinical benefit or the patient was withdrawn from the study.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Best objective RECIST response (BoR); disease control rate (DCR = Complete response [CR] + Partial response [PR] + Stable disease [SD]); duration of response; best % change in tumour size; objective response based on CA-125 levels; best % change in CA-125 levels; progression free survival (PFS) by RECIST; PFS by CA-125; PFS by RECIST and CA-125 combined; ECOG performance status. Note that variables based on CA-125 levels were for ovarian cancer patients only.

Criteria for evaluation - safety (main variables)

Adverse events; laboratory tests; physical examination; ECGs, vital signs.

Statistical methods

This is a non-comparative study and no formal hypothesis testing has been performed. Data are presented using summary statistics.

Within this report, data are summarised primarily by confirmed *BRCA* mutation status and tumour type determined from the study data and not the groups defined for study entry. Of the 55 ovarian cancer patients recruited with unknown *BRCA* mutation status 7 were found to be *BRCA* positive (5 with serous cancer, 2 with non-serous cancer). Of the 10 ovarian cancer

patients recruited to the known *BRCA* mutation positive arm, 8 had serous and 2 had non-serous cancer.

Of the 15 breast cancer patients recruited with unknown *BRCA* mutation status, 1 was found to be *BRCA* positive; all 15 patients had TNBC. Of the 11 breast cancer patients recruited to the known *BRCA* mutation positive arm, 4 had TNBC, 5 had non-TNBC; the remaining 2 patients (Patients E0100027 and E0104015) were reclassified as *BRCA* negative (with TNBC) because these patients had mutations identified as 'genetic variants of uncertain significance' according to the Myriad classification system. Both reclassifications were made before database lock.

One main analysis set (defined in the SAP) has been used, the Safety analysis set, which includes all patients who received at least one dose of olaparib. All efficacy analyses have been based on the Safety analysis set but depending on the efficacy variables, different evaluable sets were defined as shown in Table S1.

Table S1 Summary of efficacy and pharmacodynamic variables and analysis sets

Evaluable set	Definition
Evaluable for RECIST Response	A subset of the Safety analysis set that includes all patients with evaluable (ie, at least one measurable [target] lesion) RECIST data at baseline.
Evaluable for Duration of Response	A subset of the Evaluable For RECIST Response set that includes all patients with best objective tumour response of either CR or PR
Evaluable for CA-125 Response	A subset of the Safety analysis set that includes all patients who had CA-125 at least 2 x ULN measured within 2 weeks prior to starting treatment
Evaluable For Response	A subset of the Safety analysis set that includes all patients who belong to either of Evaluable For RECIST Response or Evaluable For CA-125 Response

Subject population

Fifteen patients with unknown *BRCA* status were enrolled into the high grade serous/undifferentiated ovarian group during the first stage of the trial and because there were 1 or more responses in this group recruitment was expanded to include a further 40 patients, as per the Simon design. In contrast, there were no responses among the 15 patients with unknown *BRCA* status who were enrolled into the triple negative breast cancer group and so recruitment was stopped, as per the Simon design.

The patient population comprised 91 women with histologically or cytologically confirmed ovarian (n=65) or breast cancer (n=26). The 65 ovarian cancer patients comprised 58 serous ovarian and 7 non-serous ovarian patients; 13/58 serous ovarian patients and 4/7 non-serous ovarian patients were *BRCA* mutation carriers. Of the 26 breast cancer patients 21 had the "triple negative" phenotype and 5 of these 21 patients were *BRCA* mutation carriers; the 5 non-triple negative breast cancer patients were also *BRCA* mutation carriers.

The majority (90.6%) of patients with ovarian cancer were white with a mean age of 59.4 years (range 39 to 84 years). The majority (69.2%) of patients with breast cancer were white with a mean age of 48.2 years (range 24 to 80 years). The patients were heavily pre-treated and 37 patients with ovarian cancer and 19 patients with breast cancer had had three or more prior chemotherapy treatments.

Summary of efficacy results

Primary variable: Best objective response (BoR)

The objective response rate for patients with ovarian cancer is summarised in Table S2 and for patients with breast cancer in Table S3.

Table S2 Summary of objective response rate for patients with ovarian cancer: Evaluable for RECIST response set

BRCA status	Cancer type	N	Number of responses	ORR (%)	95% CI [a]
Positive	Non-serous	4	3	75.00	30.06, 95.44
Positive	Serous	13	4	30.77	12.68, 57.63
Positive	Any	17	7	41.18	21.6, 64.0
Negative	Non-serous	3	0	0	0.00, 56.15
Negative	Serous	43	11	25.58	14.93, 40.24
Negative	Any	46	11	23.91	13.9, 37.9
Total	Any	63	18	28.57	18.90, 40.70

ORR Objective response rate; CI Confidence Interval
[a] CI Confidence Interval - calculated using the Wilson score method

The effect of olaparib in a non-selected population of serous ovarian cancer patients (ie, regardless of *BRCA* status), can be determined from the 54 patients recruited into the original high grade serous ovarian *BRCA* mutation unknown cohort (ignoring subsequent *BRCA* status test results). The confirmed best objective RECIST response (BoR) in this cohort was 14/53 26% (95% CI, 16% to 40%) (Evaluable for RECIST response set).

Table S3 Summary of objective response rate for patients with breast cancer: Evaluable for RECIST response set

BRCA status	Cancer type	N	Number of responses	ORR (%)	95% CI [a]
Positive	Non-TN	4	0	0	0.00, 48.99
Positive	TN	4	0	0	0.00, 48.99
Positive	Any	8	0	0	0, 32.4
Negative	TN	15	0	0	0.00, 20.39
Total		23	0	0	0.00, 14.31

ORR Objective response rate; TN Triple negative
[a] CI Confidence Interval - calculated using the Wilson score method

Secondary efficacy variables: disease control rate, duration of response, best % change in tumour size; objective response based on CA-125 levels; best % change in CA-125 levels; progression free survival (PFS) by RECIST; PFS by CA-125; PFS by RECIST and CA-125 combined:

Overall disease control rate (CR + PR + SD) at 16 weeks was 48% (95% CI 37% to 60%) for ovarian cancer patients and 15% (95% CI 6% to 34%) for breast cancer patients.

The median duration of response was 277 days for ovarian cancer patients. No responses were seen in patients with breast cancer and so duration of response was not calculable.

The median best % change from baseline in tumour size was a 14.2% reduction in the ovarian cancer patients and a 10.1% increase in the breast cancer patients.

Median (95% CI) PFS as determined by RECIST criteria was 219 days (95% CI 110 to 273 days) for ovarian cancer patients. Median PFS for the breast cancer patients overall was 54 days (95% CI 51 to 106 days).

Overall, 54 patients with ovarian cancer were evaluable for CA-125 response of whom 13 (24.1%) had a complete response and 4 (7.4%) had a partial response. The overall response rate was 31% (95% CI 21% to 45%). The median best change from baseline in CA-125 was a 38.5% reduction.

Overall, 23/64 (35.9%) ovarian cancer patients had either a RECIST or a CA-125 response. Median PFS for the ovarian cancer patients overall, determined by either RECIST or CA-125 response, was 108 days (95% CI 55 to 220 days).

Summary of pharmacokinetic, pharmacodynamic and pharmacogenetic results

Not applicable.

Summary of safety results

Overall median exposure to study treatment was 157 days (range 11 to 595 days) for the ovarian cancer patients and 56 days (range 20 to 288 days) for the breast cancer patients.

The number of ovarian cancer patients who had at least 1 AE in any category during the course of the study is presented in Table S4. Corresponding data for breast cancer patients is presented in Table S5.

Table S4 Summary of number (%) of ovarian cancer patients who had at least 1 AE in any category: Safety analysis set

	Number (%) of patients [a]				
	BRCA		Non-*BRCA*		
	Non-serous (n=4)	Serous (n=13)	Non-serous (n=3)	Serous (n=44)	Total (n=64)
Any AE	4 (100.0)	13 (100.0)	3 (100.0)	44 (100.0)	64 (100.0)
Any AE of CTC grade 3 or higher	2 (50.0)	8 (61.5)	2 (66.7)	11 (25.0)	23 (35.9)
Any AE with outcome = death	0	0	0	1 (2.3)	1 (1.6)
Any SAE (including death)	0	4 (30.8)	0	6 (13.6)	10 (15.6)
Any AE leading to discontinuation of treatment	0	0	0	5 (11.4)	5 (7.8)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Table S5 Summary of number (%) of breast cancer patients who had at least 1 AE in any category: Safety analysis set

	Number (%) of patients [a]			
	BRCA		Non-*BRCA*	
	Non-TN (n=5)	TN (n=5)	TN (n=16)	Total (n=26)
Any AE	5 (100.0)	5 (100.0)	15 (93.8)	25 (96.2)
Any AE of CTC grade 3 or higher	1 (20.0)	3 (60.0)	4 (25.0)	8 (30.8)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	0	2 (40.0)	2 (12.5)	4 (15.4)
Any AE leading to discontinuation of treatment (DAE)	0	0	1 (6.3)	1 (3.8)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

AEs reported with olaparib were generally consistent with the known safety profile as described in the Investigator's Brochure. AEs occurring in ≥25% of ovarian cancer patients overall were fatigue (45 patients, 70.3%), nausea (42 patients, 65.6%), vomiting (25 patients, 39.1%), decreased appetite (23 patients, 35.9%) and abdominal distension (16 patients, 25.0%).

AEs occurring in ≥25% of breast cancer patients overall were nausea (16 patients, 61.5%), fatigue (13 patients, 50.0%), vomiting (9 patients, 34.6%) and decreased appetite (7 patients, 26.9%).

A total of 23/64 (35.9%) ovarian cancer patients and 8/26 (30.8%) breast cancer patients had at least 1 AE of CTC grade ≥3. AEs of CTC grade ≥3 occurring in ≥2 ovarian cancer patients

were abdominal pain, diarrhoea, fatigue and haemoglobin decreased. AEs of CTC grade ≥3 occurring in ≥2 breast cancer patients were anaemia, gamm-GT decreased and dyspnoea.

There were 5 deaths in the study. Two ovarian cancer patients and 2 breast cancer patients died due to disease progression and one ovarian cancer patient died due to an AE (chronic respiratory failure). The AE with a fatal outcome started 95 days after first dose of olaparib. No action was taken with respect to study drug and the patient died from the event after 149 days treatment with olaparib 400 mg bd. The investigator considered the event to be unrelated to study drug and causes of death were recorded as chronic respiratory failure and metastatic ovarian cancer.

Overall, 10/64 (15.6 %) ovarian cancer patients experienced 10 SAEs and 4/26 (15.4 %) breast cancer patients experienced 7 SAEs. SAEs that occurred in ovarian cancer patients comprised thrombocytopenia, left ventricular dysfunction, gastrointestinal pain, haematemesis, haemoglobin decreased, hypoglycaemia, back pain, chronic respiratory failure, dyspnoea and hernia repair. SAEs that occurred in breast cancer patients comprised: anaemia, pleural infection, dehydration, dyspnoea, pneumonitis, pneumothorax and pulmonary embolism.

Overall 5/64 (7.8%) ovarian cancer patients discontinued olaparib due to AEs of abdominal distension (1), diarrhoea (2), vomiting (1) and peripheral oedema (1). Overall 1/26 (3.8%) breast cancer patient discontinued olaparib due to AEs of dyspnoea and pneumonitis.

Overall, 23/64 (35.9%) ovarian cancer patients and 4/26 (15.4%) breast cancer patients had a dose modification due to an AE. With the exception of rash, the AEs that led to dose interruptions or reductions were generally events known to be associated with olaparib (eg, nausea, vomiting, diarrhoea, fatigue and haematological disturbances.

There were no clinically important changes from baseline in any of the haematology parameters following treatment with olaparib, although there were trends towards a decrease in hemoglobin and red blood cells and increases in MCV.

No clinically significant changes in vital signs were observed and no clinically important trends in physical findings were noted in the study.

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