AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281 KU-0059436)
Study Code	D0810C00009 (KU36-58)
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A Phase II, Open-Label, Non-Comparative, International, Multicentre Study To Assess The Efficacy And Safety Of KU-0059436 Given Orally Twice Daily In Patients With Advanced BRCA1- Or BRCA2-Associated Ovarian Cancer

Study dates: First patient enrolled: 11 June 2007
Data cut-off: 17 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 centres

Patients were enrolled at 12 centres in 5 countries: Australia (3), Germany (1), Spain (1), Sweden (1) and the USA (6).

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the efficacy of olaparib (also known as AZD2281 or KU-0059436) at two dose levels in terms of objective tumour response rate when administered orally to patients with advanced BRCA1- or BRCA2-associated ovarian cancer.

The secondary objectives of the study were:

- To assess the efficacy of olaparib at two dose levels in terms of clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD]) at various timepoints and progression-free survival (PFS) when administered orally to patients with advanced BRCA1- or BRCA2-associated ovarian cancer.
- To investigate the pharmacodynamic profile of two different dose levels of olaparib in peripheral blood mononuclear cells (PBMCs).
- To assess the safety and tolerability profile of olaparib at two dose levels when administered orally to patients with advanced BRCA1- or BRCA2-associated ovarian cancer.
- To determine exposure to olaparib at two dose levels following oral administration to patients with advanced BRCA1- or BRCA2-associated ovarian cancer.

Study design

This was an international, multi-centre, proof-of-concept, single-arm, Phase II study. Two sequential patient cohorts received continuous oral olaparib in 28-day cycles initially at 400 mg bd and subsequently at 100 mg bd.

Target patient population and sample size

Up to 40 patients were to be dosed in the 400 mg bd group and up to 24 in the 100 mg bd group. As a measure of study precision and assuming a true response rate of 20%, 40 evaluable patients would ensure that the lower and upper limits of the 95% confidence interval were no further than 10% and 15%, respectively, from the observed response rate. Similarly, 20 evaluable patients would ensure that the limits were no further than 12% and 21% from the observed response rate.

Both BRCA1 and BRCA2 patients were recruited and it was planned that at least 10 patients of each type would be dosed in the 400 mg bd group and 6 of each type in the 100 mg bd group. The CSP allowed for recruitment to continue beyond the 64 patients planned until the minimum of each type (BRCA1 and BRCA2) was reached.

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

Micronised olaparib was supplied by Quay Pharma as an oral 50 mg capsule with Gelucire 44/14 (Lauroylmacrogylcerides) as excipient (solubiliser). Batch numbers were: PLR/07/430, PLR/07/431, PLR/07/432, PLR/07/433, PLR/07/506, PLR/07/507, PLR/07/508, PLR/07/509, PLR/07/532, PLR/07/533, PLR/07/534, PLR/07/535, PLR/07/559, PLR/08/634

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 discontinued the study.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Objective tumour response (ORR) (according to RECIST criteria); clinical benefit rate (CBR); progression free survival (PFS); best % change in tumour size; ECOG performance status; PARP inhibition (%) in PBMCs.

Criteria for evaluation - safety (main variables)

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

Statistical methods

This is a non-comparative study and no formal hypothesis testing has been performed. Estimates of parameters of clinical importance are presented together with their confidence intervals as appropriate and the results are presented by dose.

Three analysis sets defined in the Clinical Study Protocol (CSP) have been used: a safety analysis set, consisting of patients who received at least one dose of olaparib, an intention-to-treat (ITT) analysis set, consisting of patients with positive BRCA status, who received at least one dose of olaparib and a per-protocol (PP) analysis set consisting of patients with positive BRCA status, who received at least one dose of olaparib and who completed the trial schedule and medication regime without any major deviations to the CSP.

Subject population

The patient population participating in this study comprised 58 women with advanced BRCA1- or BRCA2-associated ovarian cancer (includes patients who are found to have loss-of-function mutations in the BRCA-1 or BRCA-2 genes as determined by the Myriad test). One patient (E0613003) was not allocated to treatment and so was excluded from all analysis sets. Of the remaining 57 patients, 24 successfully completed the full study schedule up to and including cycle 6 and 5 patients were ongoing at the data cut-off for the CSR (17 March 2009).

In addition to patient E0613003, a further 4 patients (2 in each treatment group) had major protocol deviations and were excluded from the PP analysis set.

The majority (93.0%) of patients were white with a mean age of 56.3 years (range 35 to 74 years). Although not randomised there were no notable differences in demographic and baseline characteristics between the dose cohorts.

Note that following implementation of protocol amendment 3, 6 patients in the 100 mg bd group dose escalated to 400 mg bd.

Summary of efficacy results

Primary variable: Objective tumour response (ORR)

In the PP analysis set, the confirmed RECIST ORR overall was 11/31 (35.5%) at 400 mg bd and 3/22 (13.6%) at 100 mg bd (Table S1). The corresponding data for the ITT analysis set were 11/33 (33.3%) at 400 mg bd and 3/24 (12.5%) at 100 mg bd.

Table S1 Summary of number (%) of patients with confirmed best RECIST response: PP analysis set

	Number (%) of patients		
	100 mg bd N=22	400 mg bd N=31	Total n=53
Total	22 (100.0)	31 (100.0)	53 (100.0)
Objective response (CR/PR)	3 (13.6)	11 (35.5)	14 (26.4)
Complete response (CR)	0 (0)	2 (6.5)	2 (3.8)
Partial response (PR)	3 (13.6)	9 (29.0)	12 (22.6)
Stable disease (SD)	7 (31.8)	11 (35.5)	18 (34.0)
Progressive disease	12 (54.5)	9 (29.0)	21 (39.6)

In the 400 mg bd group 5/19 (26.3%) patients with BRCA1 mutations and 6/12 (50.0%) patients with BRCA2 mutations, had an objective response. In the 100 mg bd group 3/17 (17.6%) patients with BRCA1 mutations and none of the 5 patients with BRCA2 mutations, had an objective response

Secondary efficacy variables: clinical benefit rate, duration of response, maximum change in tumour size, progression-free survival and patient-reported outcomes:

Overall clinical benefit rate (CR + PR + SD) was greater in the 400 mg bd group than in the 100 mg bd group (71.0% vs 45.5%). SD = stable disease for ≥8 weeks ± 1 week visit window.

The median duration of response was 290 days (range 126 to 506 days) for the 400 mg bd group and 269 days (range 169 to 288 days) for the 100 mg bd group. One out of 3 responses

in the 100 mg bd group and 3 out of 11 responses in the 400 mg bd group were ongoing at data cut-off.

The median best percentage change from baseline in the 400 mg bd group was a 29.0% reduction in tumour size compared to a 0% reduction in the 100 mg bd group.

Median (95% CI) PFS was 226.0 (105-338) days in the 400 mg bd group and 62.5 (56-113) days in the 100 mg bd group.

Complete response + partial response + stable disease was associated with improvements in all aspects of the FACT-O domains for both treatment groups.

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

Overall median exposure to study treatment was 85 days (range 12 to 491 days) for the 100 mg bd group and 231 days (range 34 to 604 days) for the 400 mg bd group.

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S2.

Table S2 Summary of number (%) of patients who had at least 1 AE in any category: Safety analysis set

Category	Number (%) of patients [a]					
	100 mg bd N=24		400 mg bd N=33		Total n=57	
Any AE	23	(95.8)	33	(100.0)	56	(98.2)
Any AE of CTC grade ≥3	14	(58.3)	17	(51.5)	31	(54.4)
Any AE with outcome = death	1	(4.2)	1	(3.0)	2	(3.5)
Any AE leading to discontinuation of treatment	1	(4.2)	4	(12.1)	5	(8.8)
Any SAE (including outcome = death)	7	(29.2)	12	(36.4)	19	(33.3)

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 occurring in ≥25% of patients across the two dose cohorts were nausea (36 patients, 63.2%), fatigue (30 patients, 52.6%), diarrhoea (19 patients, 33.3%), abdominal pain (including "lower abdominal pain" and "upper abdominal pain", 18 patients, 31.6%), and vomiting (17 patients, 29.8%). Most AEs were mild to moderate (CTC grade 1 or 2). AEs of CTC grade ≥3 occurring in ≥2 patients in either treatment group were, neutropenia, intestinal obstruction, nausea, vomiting, hypokalaemia and pulmonary embolism.

Two patients, one from each dose group died as a result of an AE. One patient in the 100 mg bd group experienced congestive heart failure (PT cardiac failure congestive) and respiratory failure (PT respiratory failure) 64 days after the first dose of olaparib. Study drug was stopped and the patient died on Day 68. One patient in the 400 mg bd group experienced a bowel perforation (PT intestinal perforation) 323 days after the first dose. Study drug was stopped and the patient died on Day 325. The investigators did not consider these events to be related to treatment with olaparib.

SAEs that occurred in more than one patient included intestinal obstruction (2 patients), large intestinal obstruction (2 patients), nausea (3 patients) and vomiting (3 patients). Nausea and vomiting are known to be associated with olaparib treatment and the intestinal obstruction events may have been related to the underlying disease.

Five patients (1 in the 100 mg bd group; 4 in the 400 mg bd group) had AEs that led to discontinuation of olaparib.

Overall, 41/57 (71.9%) patients had no dose interruptions or dose reductions due to adverse events. The remaining 16 patients had a dose interruption and 8 of these also had a dose reduction, due to adverse events.

Overall, the clinical laboratory findings are consistent with the known safety profile of olaparib, together with the advanced disease under investigation and pre-existing medical conditions. No new safety concerns were identified.

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