AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281 KU-0059436)
Study Code	D0810C00008 (KU36-44)
Edition Number	1
Date	9 July 2009

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 breast cancer.

Study dates: First patient enrolled: 15 June 2007
Data cut-off: 27 February 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 16 centres in 6 countries: Australia (2), Germany (3), Spain (1), Sweden (1), UK (3) 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) in terms of objective tumour response rate when administered orally to patients with advanced BRCA1- or BRCA2-associated breast cancer.

The secondary objectives of the study were:

- To assess the efficacy of olaparib in terms of clinical benefit rate (complete response [CR] and PD and SD) at various timepoints and time to disease progression (TTP) when administered orally to patients with advanced BRCA1- or BRCA2-associated breast cancer.
- To investigate the pharmacodynamic profile of olaparib peripheral blood mononuclear cells (PBMCs).
- To assess the safety & tolerability profile of olaparib when administered orally to patients with advanced BRCA1- or BRCA2-associated breast cancer.
- To determine exposure to olaparib following oral administration to patients with advanced BRCA1- or BRCA2-associated breast 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

Originally, up to 40 patients were to be dosed in the 400 mg bd group. A second dose group (100 mg bd) was added by protocol amendment 1 and up to 24 patients were to be dosed in this group. Following protocol amendments 2 and 3, up to 27 patients were to be dosed in each dose 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 excipients (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/08/591, 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 was withdrawn from 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); maximum 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 54 women with advanced BRCA1- or BRCA2-associated breast 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). These patients had been exposed to a median of three or four prior lines of chemotherapy. Overall, 29 patients successfully completed the full study schedule up to and including cycle 6 and 8 patients were ongoing at the data cut-off for the CSR (27 February 2009).

Four patients (3 in the 100 mg bd group, 1 in the 400 mg bd group) had major protocol deviations and were excluded from the PP analysis set.

The majority (94.4%) of patients were white with a mean age of 44.7 years (range 28 to 72 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, 23 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 11/26 (42.3%) at 400 mg bd and 6/24 (25.0%) at 100 mg bd (Table S1). The corresponding data for the ITT analysis set were 11/27 (40.7%) at 400 mg bd and 6/27 (22.2%) 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=24	400 mg bd N=26	Total n=50
Total	24 (100.0)	26 (100.0)	50 (100.0)
Objective response (CR/PR)	6 (25.0)	11 (42.3)	17 (34.0)
Complete response (CR)	0	1 (3.8)	1 (2.0)
Partial response (PR)	6 (25.0)	10 (38.5)	16 (32.0)
Stable disease (SD)	11 (45.8)	11 (42.3)	22 (44.0)
Progressive disease	7 (29.2)	4 (15.4)	11 (22.0)
Not evaluable	0	0	0

In the 400 mg bd group 9/18 (50.0%) patients with BRCA1 mutations and 2/8 (25.0%) patients with BRCA2 mutations, had an objective response. In the 100 mg bd group 3/14 (21.4%) patients with BRCA1 mutations and 3/10 (30.0%) 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 (84.6% vs 62.5%). SD = stable disease for ≥8 weeks ± 1 week visit window.

The median duration of response was 144.0 days (range 92 to 393 days) for the 400 mg bd group and 140.5 days (range 55 to 175 days) for the 100 mg bd group.

The median best % change (reduction) from baseline in tumour size was –29.43% in the 400 mg bd group and –10.14% in the 100 mg bd group.

Median (95% CI) PFS was 193.5 (140-226) days (6.5 months) in the 400 mg bd group and 122.0 (91-167) days (4.1 months) in the 100 mg bd group.

At cycle 7 day 1 (ie after completing 6 cycles of treatment) ECOG performance status was available for 11 patients in the 100 mg bd group and 15 patients in the 400 mg bd group. In the 100 mg bd group 1 patient had improved, 7 were unchanged and 3 had worsened. In the 400 mg bd group 6 patients had improved, 8 were unchanged and only 1 had worsened.

Complete response + partial response + stable disease was associated with improvements in all components of the FACT-B questionnaire 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 147 days (range 27 to 318 days) for the 100 mg bd group and 199 days (range 23 to 450 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

	Number (%) of patients [a]		
	100 mg bd	400 mg bd	Total
AE category	n=27	n=27	n=54
Any AE	27 (100.0)	27 (100.0)	54 (100.0)
Any AE of CTC grade 3 or higher	9 (33.3)	11 (40.7)	20 (37.0)
Any AE with outcome = death	0	0	0
Any AE leading to discontinuation of treatment (DAE)	2 (7.4)	0	2 (3.7)
Any SAE (including events with outcome = death)	5 (18.5)	9 (33.3)	14 (25.9)

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 patients across the two dose cohorts were fatigue (36 patients, 66.7%), nausea (31 patients, 57.4%), headache (16 patients, 29.6%), vomiting (16 patients, 29.6%), and constipation (14 patients, 25.9%). 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 anaemia, nausea, vomiting, fatigue and pleural effusion.

There were no AEs with an outcome of death in the study. SAEs that occurred in more than one patient included anaemia/haemoglobin decreased (3 patients), nausea (3 patients), vomiting (2 patients) and dyspnoea (2 patients). Anaemia, nausea and vomiting are known to be associated with olaparib treatment and the dyspnoea events (which both occurred in the 100 mg bd group) may have been related to the underlying disease.

Only one patient (in the 100 mg bd group) had an AEs that led to discontinuation of olaparib and this was a SAE (convulsion).

Overall, 43/54 (79.6%) patients had no dose interruptions or dose reductions due to AEs. Eight patients in the 400 mg bd group and 2 patients in the 100 mg bd group had a dose interruption due to AEs. Nine patients in the 400 mg bd group and 1 patient in the 100 mg bd group had a dose reduction due to AEs. Note that the patient in the 100 mg bd group who had a dose reduction had previously escalated to 400 mg bd following protocol amendment 3.

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.