AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C0002 (KU36-92)
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A Phase I, Pharmacokinetic and Biological Evaluation of a Small Molecule Inhibitor of Poly ADP-Ribose Polymerase-1 (PARP-1), KU-0059436, in Patients with Advanced Tumours

Study dates: First patient enrolled: 11 July 2005
Data cut-off: 17 December 2008

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This was an open-label, dose-escalating, non-randomised, multi-centre phase I study of olaparib administered orally to patients with advanced solid tumours. The study was initially conducted UK (Amsterdam). For the expanded phase of the study, the additional centres (UK), (Belgium), and Poland) were added. The first patient was enrolled on 11 July 2005.

Publications

Objectives

The primary objective was:

- to determine the safety, tolerability, dose-limiting toxicity (DLT), PARP inhibitory dose range (PID) and maximum tolerated dose (MTD) of olaparib when administered orally to patients with advanced solid tumours.

The secondary objectives were:

- To determine the pharmacokinetic profile of oral olaparib.
- To investigate the pharmacokinetic-pharmacodynamic profile of olaparib in surrogate and tumour tissues.
- To enable a preliminary assessment of the anti-tumour activity of olaparib.
- To further evaluate the safety and efficacy of olaparib in an expanded cohort of BRCA enriched population, primarily ovarian cancer patients.

Study design

The study was designed to establish the PID and MTD of olaparib and to explore the safety, tolerability, PK and PD profiles and anti-tumour activity in the patient population. There were two distinct phases: a dose escalation phase (patients with advanced solid cancers) and a dose expansion phase using the recommended dose established in the escalation phase. The expansion was to include up to 60 patients with BRCA 1/2 mutations, with at least 20 evaluable ovarian cancer patients. Optional PK and PD assessments were to be performed on patients in all groups. All patients were assessed for safety. The starting dose was 10 mg olaparib, once daily.

Target patient population and sample size

This study included patients aged at least 18 years with histologically or cytologically confirmed malignant advanced solid tumour refractory to standard therapy or for which no suitable effective standard therapy exists and who have evaluable or measurable disease (as

defined by RECIST). Patients had to have adequate bone marrow, hepatic and renal function and have a performance status at entry of ECOG 0-2. The expansion phase of the study recruited patients with ovarian, breast or prostate cancer with a confirmed BRCA 1 or 2 mutation. The expected maximum number of patients was 100.

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

The IP is olaparib (ADZ2281, KU-0059436). No comparators or placebos were used. Fifty two batches of olaparib were used in this study. Individual batch numbers are included in the CSR.

Duration of treatment

Initially each cycle was 21 days' duration. This was increased to 28 days' duration via a protocol amendment. The protocol allowed patients to received up to 2 cycles, although provisions were made for patients to receive more than 2 cycles if the patient was deriving benefit from the treatment (in the investigator's opinion) and was tolerating the treatment without dose limiting toxicities.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

The primary efficacy variables were Overall Best Response (RECIST and RECIST/GCIG), Duration of Response, Duration of Stable Disease and Time to Disease Progression. Blood sampling for PK and PD analysis was performed and patients were also asked to consent to tumour biopsies and hair follicle collection (for PD analysis).

Criteria for evaluation - safety (main variables)

The main safety variables were dose limiting toxicities (to establish the MTD); adverse events, laboratory parameters and vital signs.

Statistical methods

No formal statistical analyses were carried out; descriptive statistical analyses were performed using SAS version 8.01 in accordance with the Statistical Analysis Plan, which was finalised before database lock. The primary analysis was performed following an initial data cut-off approximately 3 months after the last patient had the last protocol-specified visit (17 December 2008). The safety and tolerability profile of olaparib was assessed by adverse events, laboratory tests, physical examination and vital signs. No formal statistical analyses were performed on the safety variables. Analysis of the pharmacokinetic data was carried out using standard non-compartmental analysis techniques (NCA) via WINNONLIN (version 4.1). Pharmacokinetic/pharmacodynamic (PKPD) modelling of the plasma concentrations and PARP activity data obtained in the PBMC samples collected during the study was performed, using non-linear mixed effects modelling. In April 2014, in response to CHMP (Committee for Medicinal Products for Human Use) questions received as part of the review of the marketing authority application, the population PKPD analysis was repeated. This updated clinical study synopsis reflects the results of the updated population PKPD analysis.

Subject population

Overall, 98 patients were enrolled on the study and received study treatment. At the time of data cut-off (17 December 2008), 11 patients with BRCA 1/2 mutations were still receiving treatment and 87 patients had discontinued the study for the following reasons: 71 patients due to disease progression, 5 patients refused further treatment, 4 patients due to unacceptable toxicity, 3 patients due to intercurrent illness, 3 patients due to the investigator's decision, and for one patient, death was the reason for discontinuation. Overall, despite the study not being randomised, the distribution of patients in the escalation cohorts was well balanced by sex, age, tumour heterogeneity and performance status. After the dose escalation phase was complete, the study expanded to enrol BRCA 1/2 mutated patients, primarily patients with ovarian cancer. Thus the sex ratio was heavily weighted to a female population in the expansion phase.

Summary of efficacy results

- An overall RECIST response rate of 14.3% (14 in 98 patients) was observed in this study with responses noted at olaparib dose levels of 100 mg bd 14d/21d and above.

- All observed RECIST responses occurred in patients with confirmed genetic BRCA mutations or a strong familial history of cancer.

- The response rate in ovarian cancer patients with BRCA 1/2 mutations was notably high with 24.5% (12 of 49) by RECIST and 36.7% (18 of 49) by either RECIST or GCIG criteria. The number of BRCA1/2 patients with other tumour types was too low to assess the response rate in these populations.

- The median time to disease progression (including symptomatic progression or death on study due to disease progression) in ovarian BRCA 1/2 was determined as 115 days.

- In the whole ITT population of 98 patients, clinically significant stable disease determined as SD for 12 weeks or more was also noted in 19 patients. Most (14) were BRCA 1/2 mutation carriers (9 ovarian cancer BRCA 1/2 patients, 3 breast BRCA 1/2 patients and 2 prostate BRCA 1/2 patients). The other 5 patients had normal (1) or unknown (4) BRCA status.

- RECIST and/or GCIG criteria responses were seen in all initial platinum sensitivity sub-groups (ie refractory, resistant and sensitive).

Summary of pharmacokinetic results

Following single and multiple doses from 10 mg to 600 mg, olaparib was found

- To be orally bioavailable and rapidly absorbed

- To have a terminal elimination half-life of approximately 5 to 7 hours after a single dose and 7 to 12 hours at steady state
- Show less than proportional increase in exposure with increasing dose at doses above 100 mg
- To show no marked increase in exposure at steady state over a single dose
- To show no marked time dependency in exposure from single dose to steady state.

Summary of pharmacodynamic results

- In 10 of the 11 patients who provided tumour biopsy samples, (Patient 001-01-0022 was excluded from the summaries) the % inhibition of PARP-1 activity ranged from 7 % to 99 % (mean = 68 % ± 25 SD) and showed no apparent relationship with dose.
- The PID range was determined to be at olaparib doses above 40 mg od (although lower doses were not tested in this study).
- The mean olaparib plasma concentration required for 50 % inhibition of PARP-1 activity (IC_{50}) in PBMCs was estimated as 281 ng/mL. The level of PARP-1 inhibition achieved following dosing with olaparib was typically 50 – 60 %.
- The PBMC PARP-1 inhibition dose response curve appeared to be flat with moderate interindividual variability at the dose levels investigated (10 to 600 mg), the maximum drug effect appeared to have been achieved at olaparib doses ≥ 40 mg. For an approximate 65-fold AUC range, the maximum % PARP-1 inhibition increased only approximately 20 %.
- The data obtained for γH2AX foci induction in hair follicles was consistent with the PARP-1 inhibition data in PBMC samples and showed a rapid onset of effect after dosing, an effect that was sustained on continuous dosing and no apparent relationship between the magnitude of effect and the dose administered.

Summary of pharmacogenetic results

The results of the genetic study are not part of this clinical study report.

Summary of safety results

Table 1 Summary of number (%) of patients who had at least one TEAE in any category: Safety population

	Initial Dose Level (mg 28 days)					
Treatment-emergent AEs[a]	**<100 bd [e]**	**100 bd**	**200 bd**	**400 bd**	**600 bd**	**Overall[d]**
Number of patients[b]	**22**	**5**	**58**	**8**	**5**	**98**
Any TEAE	22 (100.0%)	5 (100.0%)	58 (100.0%)	8 (100.0%)	5 (100.0%)	98 (100.0%)
TEAE of CTCAE grade[c] 3, 4 or 5	11 (50.0%)	4 (80.0%)	31 (53.4%)	7 (87.5%)	5 (100.0%)	58 (59.2%)
TEAE with fatal outcome	2 (9.1%)	0	6 (10.3%)	1 (12.5%)	1 (20.0%)	10 (10.2%)
TEAE leading to discontinuation of treatment	4 (18.2%)	1 (20.0%)	11 (19.0%)	4 (50.0%)	1 (20.0%)	21 (21.4%)
SAE (including events with fatal outcome)	5 (22.7%)	3 (60.0%)	24 (41.4%)	7 (87.5%)	3 (60.0%)	42 (42.9%)

a Patients with multiple events in a category were counted only once in that category. Patients with events in more than one category were counted once in each category. Includes TEAEs and AEs occurring post-treatment during the 30 day f/u AEs that occurred after the first dose of study medication or within 30 day post-treatment period.
b Number of patients used as denominator to calculate percentages
c CTCAE Grade or Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening or disabling, 5=Fatal.
d All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE).
e Note: <100 bd includes the following doses (mg): 10 od, 20 od, 40 od, 80 od, 60 bd and 100 bd 14 days.

Olaparib was administered over a median 30-fold range in the dose cohorts in this study. This was conducted in a series of pre-determined steps across a broad range of doses (10 mg od to 600 mg bd) and across a varied patient population with solid tumours. The BRCA-mutated patients in the expansion phase population were equally exposed to olaparib as other populations and demonstrated a similar tolerability profile. Below the dose limiting toxicity level no specific precaution or restriction regarding exposure applies to any patient population.

Two dose limiting toxicities were encountered at the 600 mg bd dose level (CTCAE grade 4 thrombocytopenia and CTCAE grade 3 somnolence) and therefore 400 mg bd was considered to be the maximum tolerated dose (MTD). Based on the safety data from this study, no specific precautions or restrictions regarding dosing of patients with advanced solid tumours were identified, other than the determination of the maximum tolerated dose (400 mg bd) which was the primary objective of the study. Oral administration of olaparib was generally well tolerated by the majority of patients with various solid tumours at doses up to and including 400 mg twice daily, as monotherapy, although, as expected, all patients on olaparib experienced at least one adverse event. Most of the AEs were mild to moderate (CTCAE grade 1 or 2) in intensity at doses up to 400 mg bd. Many of the AEs reported are frequently

seen in patients with advanced tumours due to their underlying disease, comorbidity and concomitant medications.

TEAEs occurring in >than or = to 30% of patients overall were nausea (57 patients, 58.2%); fatigue (52 patients, 53.1%); vomiting (45 patients, 45.9%); tachycardia (36 patients, 36.7%); and anorexia (30 patients, 30.6%). Nausea, vomiting and fatigue are adverse events considered to be associated with administration of olaparib.

Most of the AEs were mild to moderate in intensity. The percentage of patients with CTCAE grade ≥3 events attributed to the study medication by the investigator was 23.5% (23 patients), and increased with increasing dose. The percentage of patients with AEs leading to discontinuation of treatment was 21.4% (21 patients), with only 5.1% (5 patients) discontinuing treatment due to events that the investigator attributed to study drug.

There were only 4 dose reductions for adverse events in the entire population of 98 patients treated; all were at the 200 to 600 mg bd dose levels.

In total, 44 deaths were recorded, none was considered drug-related and the majority occurred more than 30 days following the last study drug administration. Ten deaths were reported as a serious adverse event; these included 6 cases of disease progression and 4 TEAEs which occurred within the SAE reporting period (ie during the study or within 30 days following the last dose).

This study was carefully and closely monitored throughout and emerging adverse events which are considered associated with olaparib treatment have already been reported in the Investigators' Brochure. No additional or late-emerging adverse events have emerged with continued use in a target population of ovarian cancer patients.

Administration of olaparib has been associated with cases of: laboratory findings and/or clinical diagnoses of: Anaemia, generally mild to moderate (CTCAE grade 1 or 2), Neutropenia, predominately mild to moderate (CTCAE grade 1 or 2), Thrombocytopenia generally mild to moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4), Nausea and Vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment, and Fatigue, generally intermittent and of mild to moderate intensity (CTCAE grade 1 or 2).

Nausea and vomiting was common in this study, and was attributed to olaparib in 41% and 21% of patients, respectively. However, cases were mostly mild to moderate in intensity, and, when required, were managed with anti-nauseants and anti-emetics, while the patient continued on therapy. Overall, only 9.2% of patients required these interventions. One patient had a dose reduction for severe drug-related nausea and vomiting and was then discontinued when the symptoms recurred on rechallenge. Drug-related CTCAE grade 1 vomiting contributed to another patient's discontinuation for symptomatic deterioration. Three patients required dose interruptions for both nausea and vomiting, two patients required interruptions for vomiting alone and one patient for nausea alone.

Treatment-emergent, drug-related fatigue occurred in 36 patients, in one case was reported as an SAE. Fatigue is a common and ongoing problem in patients with advanced cancer and many patients already had fatigue at study entry. There is some evidence that the incidence of drug-related fatigue increased with the drug dose.

No safety concerns have been identified for the haematology or biochemistry results in this study. The majority of patients experienced no changes from baseline in CTC grade for platelets, WBC, ANC, prothrombin time or aPTT, and only four patients required platelet support, and one patient Pegfilgrastim. Of the small number of minor changes observed within the study, no dose response correlation was seen and co-existing clinical conditions, treatment, or prior cytotoxic regimens could account for these changes. The decreases in neutrophil and platelet counts were generally mild to moderate. Changes in MCV will continue to be monitored in future studies.

Anaemia is commonly observed in cancer patients and was also common in this study. Of the 98 patients who were treated in the study, 39 already had CTCAE grade 1 anaemia at baseline, and 5 had CTCAE grade 2. During the study, 59 patients became more anaemic. In 12 cases a causal relationship with olaparib was assigned. The most severe changes occurred in 9 patients who were in the normal range or had grade 1 anaemia at baseline and who dropped to grade 3, and in one patient who had grade 4 anaemia in cycle 11, down from the normal range at baseline. This patient also had grade 4 thrombocytopenia and grade 4 neutropenia at the same time. The pancytopenia was likely to have been caused by earlier palliative radiotherapy.

Twenty-five patients received some preparation of blood (red blood cells), often multiple times, for example on 6 separate occasions for one patient. In all but two cases blood transfusion was for treatment of CTCAE grade 2 or worse anaemia, occurring at any time in the treatment cycles. However, about one third of the patients with CTCAE grade 2 anaemia did not receive specific treatment for anaemia. Preclinical studies have shown that anaemia can emerge at high dose levels of the drug. Overall, the changes in haemoglobin were generally mild to moderate in intensity, and were managed by transfusion when necessary. Anaemia was not a limiting factor for the administration of olaparib.

Overall, few biochemical disturbances emerged during the study. Except for albumin, fewer than 10% of patients had disturbances for each of the parameters measured. The majority of patients experienced no changes from baseline in CTC grade for serum sodium, potassium, calcium, or phosphate. Of the small number of CTCAE grade $\geq$3 changes observed, no trends to abnormalities with higher or longer dosing were seen. Olaparib does not appear to be associated with alterations in the electrolytes. Where present, underlying conditions like diabetes, poor nutrition, and often advanced cancer, off an alternative explanation for the changes observed. Overall, no evidence of drug-related hepatotoxicity emerged in this study. The impact of olaparib on amylase and lipase is unclear and will be monitored in further studies with olaparib.

There are no trends to abnormal values in vital signs, including heart rate, during long term administration. Tachycardia was reported commonly, this was mild to moderate and asymptomatic and required no treatment and was not supported by increasing changes in pulse rate with increased dose or prolonged exposure. There is no evidence to suggest that olaparib affects body temperature, respiration rate, or weight.