AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281 KU-0059436)
Study Code	D0810C00006 (KU36-93)
Edition Number	1
Date	25 March 2010

A Phase I, Open-label, Study of the Safety and Tolerability of KU-0059436 and Topotecan in the Treatment of Patients with Advanced Solid Tumours

Study dates:	First patient enrolled:	17 July 2007
	Last patient completed:	16 December 2008
Phase of development:	Clinical pharmacology (I)	

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

Reason for early study termination

The maximum tolerated dose (MTD) of KU-0059436 (hereafter referred to as olaparib) was determined to be continuous 100 mg bd in combination with 1.0 mg/m^2/day topotecan for three days per cycle. This is an approximately 60% reduction of the cumulative topotecan dose of 1.5 mg/m^2/day for five days in a three weekly cycle, suggested in the label for the treatment of ovarian cancer, and a sub-optimal dose of olaparib. Despite these sub-optimal doses, the bone marrow related toxicities observed in this study were higher than would be expected from topotecan monotherapy at this dose level. A decision was taken not to progress development of the combination and recruitment was stopped.

Study centres

Three centres in the United Kingdom participated in this study.

Publications

None at the time of writing this report.

Objectives

Primary

To investigate the safety and tolerability and establish the MTD of olaparib when administered orally in combination with topotecan to patients with advanced solid tumours.

Secondary

- To identify the Dose Limiting Toxicity (DLT) of the combination of olaparib and topotecan
- To characterize the onset, duration, intensity, predictability and reversibility of the toxicities of the combination of topotecan and olaparib
- To determine the plasma pharmacokinetic profile of olaparib, administered alone and in combination with topotecan
- To determine the plasma pharmacokinetic profile of topotecan, administered alone and in combination with olaparib
- To investigate the pharmacokinetic-pharmacodynamic profile of olaparib in surrogate and tumour tissues when given in combination with topotecan
- To enable a preliminary assessment of the anti-tumour activity of olaparib when given in combination with topotecan
- To select a dose of olaparib for future studies in combination with topotecan.

Exploratory

- To investigate exploratory biomarkers in whole blood, serum and tumour biopsies (option to evaluate on-treatment and/or historical samples) to ascertain if there are any which differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of disease.

Study design

This was an open-label, multi-centre, phase I study of olaparib when administered orally in combination with topotecan to patients with advanced solid tumours, consisting of 2 parts: A dose-escalation part to establish the maximum tolerated dose (MTD) of the selected combination, and a dose-expansion part to further establish the safety and tolerability of the combination treatment.

Target population and sample size

Male or female patients with histologically or cytologically diagnosed advanced solid tumours for whom no suitable effective therapy exists, with adequate bone marrow, renal and hepatic function, and a life expectancy of at least 12 weeks. It was expected that up to 36 patients would be enrolled in the dose escalation part of the study and a maximum of 12 patients in the dose expansion part. The overall size of the study was not expected to exceed 48 patients.

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). Olaparib was given orally at doses of 50 to 200mg bd. Batch numbers were: PLR/07/434/A/B/C, PLR/07/434/A/B/D, PLR/07/434/A/B/G, PLR/07/434/A/B/J, PLR/07/434/A/B, PLR/07/434/A/C, PLR/07/434/A/D, PLR/07/434/A/E, PLR/07/434/A/F, PLR/07/434/A/G, PLR/07/434/A/H, PLR/07/434/A/J, PLR/07/434/A/N

Commercially available topotecan (Hycamtin®) from GlaxoSmithKline was supplied as an intravenous infusion (final concentration 25-50 µg/mL) and doses of 0.5 to 1.0mg/m^2/day were given by intravenous infusion for three days per cycle.

Duration of treatment

Each cycle of treatment lasted 21 days. Patients could receive up to 6 cycles of treatment. Patients with at least stable disease could continue olaparib on a compassionate supply basis at the discretion of the investigator.

Criteria for evaluation – efficacy (main variables)

Although tumour response was not the primary endpoint of this study, patients with measurable disease were assessed by Response Evaluation Criteria In Solid Tumours (RECIST) criteria.

Criteria for evaluation – safety (main variables)

Safety data, including laboratory parameters and adverse events, were collected for all patients in order to determine the toxicity, reversibility of toxicity and DLT of orally administered olaparib and intravenous topotecan administered in combination.

Statistical methods

Due to the non-comparative nature of the study design, no formal analysis was conducted.

Subject population

Due to premature study termination, 21 patients participated in the study of whom 19 received treatment. The 19 patients comprised 5 females (26%) and 14 males (74%) with a mean age of 56.4 years. All patients had received prior chemotherapy and only 3 patients received only one prior chemotherapy regimen.

Results

Dose liming toxicities were observed in 3 patients: Patient 02-02-0010 (cohort 2: 0.5 mg/m^2/day for three days plus 100 mg bd olaparib) had a treatment delay of more than 2 weeks due to thrombocytopenia; Patient 01-04-0019 (cohort 4: 1.0 mg/m^2/day for three days plus 200 mg bd olaparib) had grade 4 neutropenia lasting more than 5 days, febrile neutropenia and other CTCAE grade 3/4 non-haematological toxicities; Patient 01-04-0021 (cohort 4: 1.0 mg/m^2/day for three days plus 200 mg bd olaparib) had febrile neutropenia.

Summary of efficacy results

Best objective response in the study was summarised overall and not at cohort level, because with such small number of patients in each cohort, there would have been a possibility of over-interpreting any percentage response rates.

Six of 19 patients (32%) had a best objective response of stable disease (of at least 6 weeks) and 7 patients (37%) had a best objective response of progression. The remaining 6 patients were not evaluable. Of the 8 patients (42%) who had progressive disease or died during the study, the median progression-free survival was 41.5 days.

Summary of safety results

An overview of adverse events (AEs) by category and dose is presented in Table S1.

Table S1 Overall adverse event summary (safety population)

AE category [a]	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Overall	
	Number of events, n (%)	Number of patients, n (%)	Number of events, n (%)	Number of patients, n (%)	Number of events, n (%)	Number of patients, n (%)	Number of events, n (%)	Number of patients, n (%)	Number of events, n (%)	Number of patients, n (%)
Any AEs	63 (21.4%)	3 (15.8%)	52 (17.7%)	7 (36.8%)	109 (37.1%)	6 (31.6%)	70 (23.8%)	3 (15.8%)	294 (100%)	19 (100%)
AEs leading to death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
SAEs not leading to death	2 (14.3%)	2 (22.2%)	2 (14.3%)	1 (11.1%)	5 (35.7%)	3 (33.3%)	5 (35.7%)	3 (33.3%)	14 (100%)	9 (100%)
Discontinuations due to AEs	0 (0%)	0 (0%)	3 (75.0%)	2 (66.7%)	0 (0%)	0 (0%)	1 (25.0%)	1 (33.3%)	4 (100%)	3 (100%)
Study treatment related AEs [b]	26 (15.2%)	3 (18.8%)	25 (14.6%)	4 (25.0%)	73 (42.7%)	6 (37.5%)	47 (27.5%)	3 (18.8%)	171 (100%)	16 (100%)

Percents are distribution of AEs between cohorts.

[a] Patient could have AEs in >1 category.

[b] If, in the opinion of the investigator, there was a reasonable possibility that the AE was causally related to study treatment.

Treatment combinations: Cohort 1: topotecan 0.5 mg/m²/d x 3, olaparib 50 mg bd; Cohort 2: topotecan 0.5 mg/m²/d x 3, olaparib 100 mg bd; Cohort 3: topotecan 1.0 mg/m²/d x 3, olaparib 100 mg bd. Cohort 4: topotecan 1.0mg/m^2/d x 3, olaparib 200mg bd.

AE = adverse event; SAE = serious adverse event

So

Of 294 AEs in 19 patients, 1 was a serious adverse event (SAE) of pneumonia leading to death in (Cohort 4; Patient Number 01-04-0020). Otherwise, 14 SAEs occurred in 9 patients across the 4 cohorts. This excludes the one on-study death due to disease progression (Patient Number 02-01-0003), per protocol data capture requirements. Three patients were reported as discontinued due to an adverse event: 2 patients in Cohort 2 (Patient Numbers 01-02-0005 for the SAEs nausea and vomiting and 02-02-0010 for the AE hyperbilirubinaemia) and 1 patient in cohort 4 (patient number 01-04-0020) for the SAE of neutropenic sepsis, this patient was subsequently reported as discontinued due to disease progression by the investigator. A total of 171 treatment-related AEs occurred in 16 patients across the 4 cohorts.

There was a clear dose effect for both topotecan and olaparib with regard to neutropenia. No patients in the cohorts treated with 0.5 mg/m^2/day x 3 topotecan had grade 3 or 4 neutropenia whereas 5 of the 6 patients treated with 1.0 mg/m^2/day x 3 topotecan in combination with 100 mg bd olaparib had grade 3 or 4 neutropenia and all patients treated with 1.0 mg/m2/day x 3 topotecan in combination with 200 mg bd olaparib had grade 4 neutropenia. There is also a suggestion of a dose effect of both topotecan and olaparib on lymphocytes and platelets.

There were no notable changes in clinical chemistry.