Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00022
Edition Number	1
Date	29 July 2009

A Phase I, Open Label, Dual Centre Study To Assess The Safety And Tolerability Of AZD2281 In Combination With Bevacizumab (Avastin®) In Patients With Advanced Solid Tumours

Study dates: First patient enrolled: 13 June 2008
Last patient last visit: 25 March 2009

Phase of development: Clinical pharmacology (I)

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

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centres

This study was a dual centre study conducted in the United Kingdom.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to determine the safety and tolerability of twice daily (bd) oral doses of olaparib (also known as AZD2281, KU-0059436) when administered in combination with bevacizumab to patients with advanced solid tumours by assessment of adverse events (AEs), vital signs, electrocardiograms (ECG), clinical chemistry, haematology, urinalysis and physical examination.

The secondary objective was to compare exposure to olaparib when given alone and in combination with bevacizumab, by assessment of appropriate derived pharmacokinetic (PK) parameters.

Study design

Successive cohorts of 4 to 6 patients received increasing doses of olaparib (100, 200 and 400 mg bd) continuously in combination with intravenous (iv) bevacizumab at a fixed dose of 10 mg/kg given every 14 days (1 cycle). A safety review of the data was performed at the end of each cycle of bevacizumab to determine if any dose-limiting toxicity (DLT) would prevent escalation to the next dose of olaparib. Dosing with bevacizumab started on Day 8 and continued for a minimum of 2 cycles. To be evaluable for PK assessment and potential dose escalation, patients had to complete at least 1 cycle of bevacizumab, and have a full PK profile for olaparib taken both in the monotherapy setting (on Day 4) and on the day of first administration of bevacizumab.

Target patient population and sample size

Up to 18 patients with histologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent, with a life expectancy of at least 12 weeks and Eastern Co-operative Oncology Group (ECOG) Performance status 0 to 2.

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

Olaparib 50 mg capsules given orally bd at doses of 100, 200 and 400 mg.

Batch numbers: FH45686, FH45687, FH45690, FH45695, FH48443, FH48444, FH48445, FH48447.

Bevacizumab 10 mg/kg given by iv infusion over 60 or 90 minutes, every 14 days.

Batch numbers: 100 mg vials (4 mL) - FH45807, FH49244.

Batch numbers: 400 mg vials (16 mL) - FH46065, FH49245.

Note: The batch numbers cited are packaging reference numbers. At the time of database lock, olaparib and bevacizumab were still being packaged and supplied for this study and a list of batch numbers was not available. Batch numbers will be supplied in a separate batch report when study treatment supply has been completed.

Duration of treatment

A minimum of two 14-day cycles of bevacizumab. Patients could continue combinational study treatment[a] indefinitely until they met a withdrawal criterion if, in the investigator's opinion, they were receiving some benefit.

Criteria for evaluation - pharmacokinetics (main variables)

Maximum and minimum plasma concentrations at steady state ($C_{max,ss}$, and $C_{min,ss}$), time to C_{max} (t_{max}) and area under the plasma concentration-time curve during the dosing interval at steady state (AUC_{ss}).

Criteria for evaluation - safety (main variables)

AEs, vital signs, ECG, haematology, clinical chemistry, urinalysis, physical examination.

Statistical methods

There was no formal statistical analysis of PK variables or of safety and tolerability data. Data have been listed and summarised.

Patient population

Twelve patients (4 in each treatment group) with a mean age 49.7 years (range 22 to 71 years) were enrolled and received study treatment (olaparib and bevacizumab). Most patients (11/12) were White and 10/12 were female. Three patients were still receiving their initial treatment (olaparib and bevacizumab) at data cut-off (Last patient last visit: 25 March 2009). No patients experienced dose-limiting toxicity and so each dose of olaparib was received by 4 patients. Three patients were excluded from the PK analyses due to protocol deviations.

Summary of pharmacokinetic results

A summary of the PK parameters of olaparib for 200 and 400 mg bd, alone and in combination with bevacizumab, is presented in Table S1.

For both the 200 mg and 400 mg bd groups, the geometric mean (Gmean) AUC_{ss}, in combination with bevacizumab, were similar to that when given alone (26.57 ng.h/mL

[a] Unless otherwise specified, study treatment refers to both olaparib and bevacizumab administered as part of the schedule.

compared to 25.79 ng.h/mL for the 200 mg bd group, and 50.33 ng.h/mL compared to 58.08 ng.h/mL for the 400 mg bd group), with similar inter-patient variability (%CVs). Similar results were observed for the Gmean $C_{max,ss}$. The mean ratios of olaparib AUC_{ss} and $C_{ss,max}$ (olaparib in combination with bevacizumab to olaparib alone) for both the 200 mg bd and 400 mg bd groups were both near to 1.0, at 1.030 and 0.867 for AUC_{ss} and 1.105 and 0.889 for $C_{max,ss}$, respectively. Of the 7 assessable patients, 4 patients had AUC_{ss} values in combination with bevacizumab that were within 10% of those values for olaparib alone, and 3 patients had values that were within 20%. These results were reflected in the data for the individual ratios of $C_{max,ss}$. For the 2 patients administered 100 mg olaparib bd that had $C_{max,ss}$ data, 1 patient had a $C_{max,ss}$ value in combination with bevacizumab that was within 15% of that for olaparib alone. The other patient showed approximately an apparent 40% decrease.

Table S1 Pharmacokinetic parameters of olaparib: PK analysis set

PK parameter, units	Summary statistics	Olaparib dose (mg bd)			
		200 alone	200 + bevacizumab	400 alone	400 + bevacizumab
n		3	3	4	4
$C_{ss,min}$, µg/mL	Gmean (CV%)	0.544 (191.2)	0.612 (158.6)	1.602 (46.05)	1.254 (43.94)
$C_{ss,max}$, µg/mL	Gmean (CV%)	4.739 (35.56)	5.237 (49.04)	9.078 (27.18)	8.067 (17.15)
t_{max}, h	median (range)	NC	NC	NC	NC
AUC_{ss}, µ.h/mL	Gmean (CV%)	25.79 (70.02)	26.57 (78.12)	58.08 (29.37)	50.33 (23.05)
AUC_{ss} ratio[a]	Mean (range)	N/A	1.030 (11.96)	N/A	0.867 (6.082)
$C_{ss,max}$ ratio[b]	Mean (range)	N/A	1.105 (22.06)	N/A	0.889 (12.21)

[a] Ratio of AUC_{ss} = AUC_{ss} for olaparib in combination with bevacizumab to AUC_{ss} for olaparib alone.
[b] Ratio of $C_{ss,max}$ = $C_{ss,max}$ for olaparib in combination with bevacizumab to $C_{ss,max}$ for olaparib alone.
AUC_{ss} Area under the plasma concentration-time curve during any dosing interval at steady state; bd Twice daily; $C_{max,ss}$ Maximum plasma (peak) concentration in plasma during dosing interval; $C_{min,ss}$ Minimum plasma (trough) concentration in plasma during dosing interval; CV Coefficient of variation; Gmean Geometric mean; N/A Not assessable; PK Pharmacokinetics; t_{max} Time to reach peak or maximum concentration or maximum response following drug administration.

Summary of safety results

Table S2 presents an overview of AEs reported in this study. There were no deaths in the study. In total, 8 serious adverse events (SAEs) were reported (in 4 patients) and none were considered by the investigator to be causally related to olaparib. Nine patients were withdrawn from study treatment, mostly (6/9 patients) due to worsening of the condition under investigation. Three patients discontinued study treatment due to AEs. There were

3 patients (1 patient in each dose group) who had AEs of Common Terminology Criteria (CTC) grade ≥3 (9 events in 3 patients) and none of these were considered by the investigator to be related to olaparib.

Table S2 Number (%) of patients who had at least one adverse event in any category overall: Safety analysis set

Category	Number (%) of patients[a]			
	Olaparib			
	100 mg bd (n=4)	200 mg bd (n=4)	400 mg bd (n=4)	All patients (n=12)
Any AE	4 (100.0)	4 (100.0)	4 (100.0)	12 (100.0)
Any AE causally related to olaparib[b]	2 (50.0)	3 (75.0)	4 (100.0)	9 (75.0)
Any AE of CTC grade ≥3	1 (25.0)	1 (25.0)	1 (25.0)	3 (25.0)
Any AE of CTC grade ≥3 causally related to olaparib[b]	0	0	0	0
Any AE with outcome = death	0	0	0	0
Any AE leading to discontinuation of study treatment	1 (25.0)[c]	1 (25.0)[d]	1 (25.0)[e]	3 (25.0)
Any AE leading to discontinuation of study treatment causally-related to olaparib[b]	0	0	0	0
Any SAE (including outcome = death)	1 (25.0)	1 (25.0)	2 (50.0)	4 (33.3)
Any SAE causally related to olaparib	0	0	0	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the Investigator.
[c] One patient in the 100 mg bd group had **both** olaparib **and** bevacizumab permanently stopped due to a CTC grade 4 SAE of small intestinal obstruction. This patient also had a CTC grade 3 SAE of intestinal perforation for which bevacizumab treatment was permanently discontinued.
[d] One patient in the 200 mg bd group had **both** olaparib **and** bevacizumab permanently stopped due to a CTC grade 3 SAE of metastatic pain.
[e] One patient in the 400 mg bd group had olaparib treatment **only** discontinued due to AEs of CTC grade 2 diarrhoea, CTC grade 2 nausea and CTC grade 1 fatigue. At the time that olaparib treatment was permanently discontinued due to AEs, bevacizumab treatment had already been permanently discontinued due to investigator decision.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
AE Adverse event; bd Twice daily; CTC Common Terminology Criteria; SAE Serious adverse event.

The most commonly reported AEs (reported in 3 or more patients overall) were nausea (reported in 7 patients overall), fatigue (6 patients), headache (5 patients), and constipation, diarrhoea, and epistaxis (each reported in 4 patients overall). Overall, nausea (reported in 5 patients) and fatigue (reported in 4 patients) were the most frequently reported AEs considered by the investigator to be causally related to olaparib. The majority of these events were CTC grade 1 (mild) or 2 (moderate).

There were no clinically important changes noted in any of the clinical laboratory safety parameters, with no individual abnormalities that raised any safety concerns. No clinically significant abnormalities in the haematological, clinical chemistry or urinalysis parameters of any patient over time were reported as an AE in this study. Some physical observations were reported as AEs but, other than these, there were no clinically important physical observations, ECGs or changes in vital signs seen in the study.