AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2281 (Olaparib)
Study Code	D0810C00021
Edition Number	1
Date	14 March 2013

A Phase I, Open Label, Multi-Centre Study of AZD2281 Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours

Study dates:	First patient enrolled: 12 November 2008
	Last patient last visit: 8 June 2011
Phase of development:	Clinical pharmacology (I)

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

Study centres

Four centres, in 2 countries, participated in this study: 1 centre in Spain and 3 centres in the United States of America.

Publications

Balmaña J, Tung NM, Isakoff SJ, Graña B, Ryan PD, Rafi R, et al. Phase I, open-label study of olaparib plus cisplatin in patients with advanced solid tumors. 2012 Annual Meeting of the American Society of Clinical Oncology; 2012 Jun 1-5; Chicago, IL.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective	Outcome Variable	Type (Priority)
The primary objective was to determine the safety and tolerability of twice-daily oral doses of AZD2281 (olaparib) when administered in combination with cisplatin to patients with advanced solid tumours.	Adverse Events (AEs) Electrocardiogram (ECG) Physical examination Haematology Clinical chemistry Urinalysis Vital signs Audiometric testing	Safety (Primary)
To compare exposure to olaparib when given alone and in combination with cisplatin. (Only in patients receiving continuous dosing of olaparib)	The PK parameters of C_{max}, $t_{max,}$ and AUC_{0-t} for olaparib: Visit 2 (alone) and Visit 3 (in combination with cisplatin) from plasma concentration-time profiles. Where possible: Visit 3:Visit 2 ratios of C_{max} and AUC_{0-t} (t_{last}) were calculated)	Pharmacokinetic (Secondary)
To make a preliminary assessment of the anti-tumour activity of olaparib when given in combination with cisplatin, by measuring overall response rate.	Objective Response Rate (ORR) Onset and duration of objective response Percentage change in tumour size	Efficacy (Secondary)
To obtain an optional blood sample for DNA extraction for future pharmacogenetic analysis and other potential correlative markers of the activity of olaparib and drugs taken in combination with olaparib (ie, cisplatin).	(This will not form part of the CSR.)	Pharmacogenetic (Exploratory)

AUC_{0-t} Area under the plasma concentration-time curve during any dosing interval at steady state; C_{max} Maximum plasma (peak) concentration in plasma during dosing interval; CSR clinical study report; DNA Deoxyribonucleic acid; PK pharmacokinetic; t_{max} Time to reach peak or maximum concentration or maximum response following drug administration.

Study design

This was a Phase I non-randomised, open-label, dose-finding study, to determine the maximum tolerated dose (MTD) of olaparib that can be combined with cisplatin in patients with advanced solid tumours. Each cohort comprised a minimum of 3 evaluable patients. If 1 of the initial 3 patients experienced a dose-limiting toxicity (DLT), the cohort was to be

expanded to at least 6 patients. Once the desired dose or MTD of the combination therapy had been determined (or the highest dose level had been explored), the cohort was to be expanded in order to ensure that there were 6 evaluable patients who had completed 4 cycles of treatment. In the event that the continuous dosing regimens were not tolerated, intermittent dosing regimens were to be explored. In the event that cisplatin was permanently discontinued on the basis of cisplatin-related toxicity, treatment with olaparib alone was permitted.

Target subject population and sample size

The target patient population included male and female patients ≥18 years of age with advanced solid tumours (histologically confirmed metastatic cancer) not amenable to surgery or radiation therapy with curative intent for whom no standard (or approved) therapy was available. Patients were required to have adequate bone marrow, hepatic, and renal function, and a performance status (PS) score ≤2 with life expectancy of at least 12 weeks. The total number of patients was based on the desire to obtain adequate safety and tolerability data whilst exposing as few patients as possible to the study treatment and procedures. It was expected that a total of 60 patients would be enrolled.

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

The investigational product was olaparib, manufactured by Patheon Inc. on behalf of AstraZeneca, batch number 3084949R. Olaparib is a white to off-white crystalline solid with a molecular weight of 434 Da. The molecular formula is $C_{24}H_{23}FN_4O_3$. Micronised olaparib was supplied as an oral 50-mg capsule with Gelucire 44/14 (Laurolylmacroglycerides) as excipients (solubiliser). Capsules were Vcaps® Hydoroxypropyl Methylcellulose Capsugel®, which were not banded or enteric coated. Olaparib was to be taken twice daily either continuously or intermittently. Cisplatin (commercially available locally) was to be prepared in accordance with local prescribing guidelines and administered intravenously 75 mg/m^2 or 60 mg/m^2 or 50 mg/m^2 every 3 weeks after the first morning dose of olaparib for each cycle.

Duration of treatment

Olaparib was to commence at 50 mg bid in Cohort 1, then increase to 100 mg and 200 mg bid. Dose escalation of olaparib was to stop if DLT of the drug combination occurred. If 1 patient in a cohort of 3 evaluable patients experienced a DLT during the first cycle that was considered related to combination therapy, the cohort was to be expanded to at least 6 patients. The MTD was defined as the prior dose level below the drug combination that causes DLT, in at least 2 patients in a cohort of up to 6 patients. The dose escalation was to continue until the MTD was established; however, the highest dose to be explored was not to exceed 400 mg bid. Patients were expected to receive 4 to 6 cycles of combination treatment (21 days/cycle).

Statistical methods

No formal statistical analyses were performed on safety (primary objective), pharmacokinetic (PK), and efficacy data. All data were summarised descriptively and with plots. Where

appropriate, confidence intervals were presented as measures of study precision. For efficacy, categorisation of response rate was based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

Subject population

Of the 59 patients enrolled from 4 centres in 2 countries, 54 patients were assigned to treatment, and all these patients received at least 1 dose of study treatment. Patients received up to 10 cycles of combination treatment and then went on to receive olaparib monotherapy for as long as they continued to gain benefit. Twenty-nine (53.7%) patients received olaparib monotherapy following discontinuation of cisplatin. At the time of data cut-off (1 February 2012, when all patients had completed combination treatment, and all patients who were continuing to receive olaparib had been followed for a minimum of 3 months of monotherapy), 10 patients remained in the study; all these patients were on olaparib and all had discontinued cisplatin. Of the 44 (81.5%) patients who had discontinued from the study, 39 patients [72.2%) discontinued due to worsening of disease under investigation, 4 [7.4%] patients due to AEs, and 1 (1.9%) patient due to other reason. Majority of the patients were White (53 [98.1%] patients) with more female patients (52 [96.3%]) than male patients (2 [3.7%]). The median age was 47 years (range 27 to 74 years), with 26 (48.1%) patients in the age group of ≥35 to <50 years and 19 (35.2%) patients in the age group ≥50 to <65 years. Majority of patients had breast cancer (42 [77.8%] patients). PS ranged from 0 to 1 at baseline. Demographic and patient characteristics of study population were representative of the intended target population of cancer patients with histologically confirmed advanced solid tumours, not amenable to surgery or radiation therapy and were well balanced between cohorts. All patients used concomitant measures during the study. The concomitant measures used had no impact upon safety or study endpoints including the analysis of PK samples and were of the type and frequency expected for supportive care and interventions given to patients during chemotherapy. There were no protocol deviations affecting the interpretation of the results of the study. The dose escalation strategy and its relationship to study recruitment is summarised in Table S2.

Table S2 Dose escalation strategy and relationship to study recruitment

Cohort	Cisplatin (mg/m^2)	Olaparib dose	n	Tolerability evaluation
1	75	50 mg bid	3	No DLTs were noted in Cycle 1 and decision to escalate to olaparib 100 mg bid was made.
2	75	100 mg bid	3	No DLTs were noted in Cycle 1 and decision to escalate to olaparib 200 mg bid was made.

Table S2 Dose escalation strategy and relationship to study recruitment

Cohort	Cisplatin (mg/m^2)	Olaparib dose	n	Tolerability evaluation
3	75	200 mg bid	6	One of the first 3 patients experienced a DLT (2-week dose delay following Cycle 1 due to Grade 3 neutropenia), and the cohort was expanded to 6 patients. After 6 patients, this was determined to be a non-tolerated dose, and expansion proceeded in the 100 mg bid cohort.
2 Expansion	75	100 mg bid	10	Only 3 of 10 patients were able to receive more than 4 cycles of therapy. These observed toxicities prompted a subsequent decision to investigate whether an interrupted schedule of olaparib administration was better tolerated.
4	75	100 mg bid on Days 1-10 out of 21	14	Initially 12 patients were to be recruited, but 2 more patients were added (1 patient to replace a non-evaluable patient and 1 patient because this patient consented at the same time as the other replacement patient). The majority of the patients (8/12 patients [67%]) did not receive their Cycle 2 regimen on time and/or at the intended dose due to toxicities associated with marrow suppression. The decision made to reduce duration of olaparib dosing to Days 1-5 out of 21, and to start with 4 patients in subsequent cohorts.
5	75	50 mg bid on Days 1-5 out of 21	6	One of the initial 4 patients experienced a DLT (Grade 3 lipase elevation with associated Grade 2 amylase elevation in Cycle 1 causally related to cisplatin), so this cohort was expanded to 6 patients. Decision made to reduce the cisplatin dose.
6	60	50 mg bid on Days 1-5 out of 21	12	After an initial 4 patients were recruited, available data was reviewed and it was determined that this combination was well tolerated, and the cohort was expanded to 12 patients.

bid twice a day; DLT Dose-limiting toxicity

Summary of efficacy results

This study was not powered to make efficacy comparisons between regimens or patient types. A preliminary assessment of the anti-tumour activity of olaparib when given in combination with cisplatin was done by measuring best objective response, duration and onset of objective response, and best percentage change from baseline in target lesion size. Of the 46 patients evaluable for response, 19 (41.3%) patients had partial response (PR) by RECIST criteria. No patient had complete response (CR). Confirmed PRs occurred in every cohort except Cohort 2 in which 4/12 unconfirmed responses were reported. All patients in Cohort 2

withdrew due to progressive disease (8 patients progressed within the first 4 cycles), and this cohort had a higher proportion of patients with PS score of 1 at baseline than the other cohorts. A higher proportion of patients in Cohorts 1 and 3 had response of PR compared with the other cohorts. Early responses were seen in all cohorts with median time to onset of response of 48 days (range 35 to 172). Anti-tumour activity was seen during combination and olaparib monotherapy phases, with 1 patient with duration of response for as long as 1092 days (ongoing at data cut-off).

Summary of pharmacokinetic results

Exposure was determined only for patients in the continuous dosing cohorts. The geometric mean for ratios of maximum plasma concentration (C_{max}) and corresponding area under plasma concentration-time curve from time 0 to the last measurable concentration (AUC_{0-t}) for olaparib when dosed in combination with cisplatin (Visit 3) or alone (Visit 2) ranged from 0.90 to 2.86 and 0.97 to 1.82, respectively. The geometric mean olaparib plasma concentration-time profiles were similar in all cohorts for drug dosed alone and in the presence of cisplatin with overlapping error bars at the majority of time points post dosing. Whilst the number of patients per dose group was small and relatively high variability was seen in the C_{max} and AUC_{0-t} ratio values within all the treatment cohorts, the parameter ratios for the majority of patients fell within the range 0.5 and 1.5, showing no clear indication that exposure to olaparib had been consistently increased or decreased when dosed in combination with cisplatin.

Summary of pharmacogenetic results

A blood sample (9 mL) was collected from each patient who gave consent to undergo blood sampling for genetic research. Samples were frozen and stored for later analysis. The results of the genetic study are not part of this CSR. The results of the genetic study may be pooled with genetic results from other studies and reported at a later date.

Summary of safety results

All patients received at least 1 cycle of olaparib in combination with cisplatin and 37/54 (69%) patients received at least 4 cycles of combination treatment. A higher proportion of patients in the intermittent dosing cohorts (Cohorts 4 to 6) received ≥4 cycles of combination therapy compared with the continuous dosing cohorts (Cohorts 1 to 3). In the intermittent dosing cohorts, 78% (25/32 patients) received ≥4 cycles and 41% (13/32) received ≥6 cycles. In the continuous dosing cohorts, 55% (12/22 patients) received ≥4 cycles and 36% (8/22 patients) received ≥6 cycles. Two patients in Cohort 2 and 2 patients in Cohort 6 completed at least 4 cycles at full dose and on schedule. Twenty-nine of 54 (53.7%) patients received at least 1 cycle of olaparib monotherapy following discontinuation of cisplatin. The majority of patients (62%) received fewer than 6 months of monotherapy olaparib treatment. Two patients each in Cohorts 5 and 6 had a total monotherapy treatment duration between 6 months and 12 months. Three patients had ≥12 to 24 months total monotherapy treatment duration (1 patient from Cohort 3 [26 months] and 2 patients from Cohort 4 [13 months and 21 months]). Two patients in Cohort 1 had a total treatment duration of 31 months and 36 months, respectively. No patient in Cohort 6 had completed over 1 year of olaparib treatment because

this was the last cohort to be enrolled and had the least opportunity to be on olaparib for a long period of time. A higher percentage of patients continued in the study in Cohorts 1 and 6 compared with the other cohorts. All patients in Cohorts 2 and 3 had discontinued from the study. The overall actual treatment exposure to olaparib (combination and monotherapy), was variable in this study with an overall median of 114 days (range 5 to 1144 days). Overall, 7/29 patients (24%) had received olaparib monotherapy for at least 12 months.

Overall, 37/54 (68.5%) patients had at least 1 dose modification of olaparib when given in combination with cisplatin. AEs (n=25) and haematological toxicity (n=12) were the most common reasons for dose modifications. The proportion of patients requiring dose modifications during the combination phase of the study increased with escalation of the dose of olaparib in the continuous dose cohorts, (1/3 [33.3%] patient, 6/13 [46.2%] patients, and 6/6 [100%] patients, for Cohorts 1, 2, and 3, respectively) and declined with decreasing of the dose of olaparib and cisplatin in the intermittent dosing cohorts (13/14 [92.9%] patients, 4/6 [66.7%] patients, and 7/12 [58.3%] patients, for Cohorts 4, 5, and 6, respectively). More patients in the continuous olaparib dose cohorts 1 to 3 required cisplatin dose modifications (dose delays and/or dose reductions) than patients in the intermittent dose cohorts 4 to 6 (19/22 patients [86.4%] versus 22/32 patients [68.8%], respectively. Eleven of the 29 (37.9%) patients who continued to receive olaparib monotherapy following discontinuation of cisplatin required dose modifications (dose interruptions and/or reductions) due to AEs (n=8) and haematological toxicity (n=3). Overall, 41/54 (76%) patients had at least 1 dose modification of cisplatin. All 6 patients in Cohort 3, 11/13 (85%) patients in Cohort 2, and 5/6 (83%) patients in Cohort 5 required the highest number of dose modifications. Cohort 6 had the least number of patients requiring cisplatin dose modification (7/12 patients [58%]) compared with the other cohorts, which was perhaps to be expected given that the starting dose of cisplatin was at 60 mg/m^2.

All patients reported at least 1 AE. All patients but 1 had at least 1 AE that was considered by the investigator to be causally related to olaparib and all patients had at least 1 AE that was considered causally related to cisplatin. The most commonly reported AEs reported during the study with incidence ≥30% by preferred term, arranged by SOC, are presented in Table S3. These AEs occurred across all cohorts without any specific pattern. Majority of the commonly reported AEs were of mild to moderate severity (CTCAE Grade 1 or 2). The most common AEs were nausea (78%), vomiting (54%), constipation (44%), fatigue (44%), tinnitus (43%), asthenia (41%), neutropenia (41%), and anaemia (37%). With the exception of constipation, these events were not unexpected given the known side effects of olaparib and cisplatin. The onset of the majority of these events occurred during the combination phase of the study. The profile and type of events observed in the 29 patients who continued to receive olaparib monotherapy following discontinuation of cisplatin was consistent with those seen in previous monotherapy studies.

There was no AE with a fatal outcome. There were 16 patients who reported serious adverse events (SAEs) and 3 patients had discontinuation of study treatment (both olaparib and cisplatin) due to AEs (2 patients in Cohort 3 and 1 patient in Cohort 2). There was no clinically significant pattern in the type and distribution of the reported AEs among the

cohorts. Only events of nausea, vomiting, dyspnoea, DVT, and pulmonary embolism were reported in more than 1 patient (2 patients for each event). The majority of SAEs were not considered by the investigator to be causally related to olaparib and/or cisplatin.

Table S3 Summary of number (%) of patients who had at least one AE by PT with incidence ≥30%, arranged by SOC (Safety analysis set)

	Number (%)of patients[a]						
System organ class/MedDRA preferred term	**Cohort 1 (N=3)**	**Cohort 2 (N=13)**	**Cohort 3 (N=6)**	**Cohort 4 (N=14)**	**Cohort 5 (N=6)**	**Cohort 6 (N=12)**	**Total (N=54)**
Patients with any AE	3 (100.0)	13 (100.0)	6 (100.0)	14 (100.0)	6 (100.0)	12 (100.0)	54 (100.0)
Blood and Lymphatic System Disorders	3 (100.0)	8 (61.5)	5 (83.3)	7 (50.0)	3 (50.0)	6 (50.0)	32 (59.3)
Anaemia	1 (33.3)	6 (46.2)	4 (66.7)	3 (21.4)	3 (50.0)	3 (25.0)	20 (37.0)
Neutropenia	3 (100.0)	5 (38.5)	4 (66.7)	6 (42.9)	1 (16.7)	3 (25.0)	22 (40.7)
Ear and Labyrinth Disorders	3 (100.0)	5 (38.5)	4 (66.7)	8 (57.1)	4 (66.7)	6 (50.0)	30 (55.6)
Tinnitus	1 (33.3)	4 (30.8)	4 (66.7)	7 (50.0)	3 (50.0)	4 (33.3)	23 (42.6)
Gastrointestinal disorders	3 (100.0)	13 (100.0)	6 (100.0)	14 (100.0)	4 (66.7)	12 (100.0)	52 (96.3)
Constipation	1 (33.3)	7 (53.8)	3 (50.0)	5 (35.7)	1 (16.7)	7 (58.3)	24 (44.4)
Diarrhoea	0 (0.0)	4 (30.8)	1 (16.7)	4 (28.6)	2 (33.3)	6 (50.0)	17 (31.5)
Nausea	2 (66.7)	9 (69.2)	4 (66.7)	13 (92.9)	4 (66.7)	10 (83.3)	42 (77.8)
Vomiting	2 (66.7)	8 (61.5)	2 (33.3)	8 (57.1)	4 (66.7)	5 (41.7)	29 (53.7)
General Disorders and Administration Site Conditions	3 (100.0)	12 (92.3)	6 (100.0)	12 (85.7)	5 (83.3)	9 (75.0)	47 (87.0)
Asthenia	1 (33.3)	6 (46.2)	3 (50.0)	6 (42.9)	4 (66.7)	2 (16.7)	22 (40.7)
Fatigue	2 (66.7)	6 (46.2)	3 (50.0)	5 (35.7)	1 (16.7)	7 (58.3)	24 (44.4)
Metabolism and Nutrition Disorders	2 (66.7)	10 (76.9)	3 (50.0)	3 (21.4)	3 (50.0)	6 (50.0)	27 (50.0)
Decreased appetite	0 (0.0)	7 (53.8)	2 (33.3)	2 (14.3)	2 (33.3)	3 (25.0)	16 (29.6)
Nervous System Disorders	3 (100.0)	9 (69.2)	6 (100.0)	11 (78.6)	6 (100.0)	9 (75.0)	44 (81.5)
Headache	1 (33.3)	1 (7.7)	3 (50.0)	4 (28.6)	3 (50.0)	4 (33.3)	16 (29.6)

[a] Number (%) of patients with AEs, sorted alphabetically by system organ class and preferred term.
A patient can have one or more preferred terms reported under a given system organ class.
Includes adverse events with an onset date between the date of first combination dose and 30 days following the date of last dose of study medication.
MedDRA version 14.1

AE Adverse event; MedDRA Medical dictionary for regulatory activities; PT Preferred term; SOC System organ class

Four patients had DLTs (Table S2) with 2 patients each developing Grade ≥3 neutropenia and lipase elevation in Cycle 1 of treatment. The proportion of patients who reported at least 1 AE of CTCAE Grade ≥3 was generally consistent across the different cohorts. Overall, 33 (61.1%) patients reported at least 1 AE of CTCAE Grade ≥3, and the proportion of patients who had at least 1 AE of CTCAE Grade ≥3 that was considered causality related to the study treatment by the investigator was higher in the continuous cohorts (Cohorts 1 to 3) compared with the intermittent cohorts (Cohorts 4 to 6). . The onset of majority of these AEs of Grade ≥3 was during the combination phase with only 4 patients reporting onset during monotherapy phase. The most commonly reported AEs of CTCAE Grade ≥3 were haematological events of neutropenia (9 [16.7%] patients), anaemia and leucopenia (both in 5 [9.3%] patients), lymphopenia (3 [5.6%] patients), and thrombocytopenia (2 [3.7%] patients). Fewer CTCAE Grade ≥3 haematological events occurred on the intermittent dosing cohorts than on the continuous dosing cohorts. The frequency of reporting AE of Grade ≥3 neutropenia was approximately 30% in Cohorts 1, 2, and 3 compared with 14.3% in Cohort 4 and none in Cohorts 5 and 6. No patients in Cohort 6 experienced Grade ≥3 AEs of reported neutropenia, anaemia, leucopenia, or thrombocytopenia.

The most commonly reported AEs of CTCAE Grade ≥3 were haematological events of neutropenia (9 [16.7%] patients), anaemia and leucopenia (both in 5 [9.3%] patients), lymphopenia (3 [5.6%] patients), and thrombocytopenia (2 [3.7%] patients). Fewer CTCAE Grade ≥3 haematological events occurred on the intermittent dosing cohorts than on the continuous dosing cohorts. Not all changes in laboratory parameter were reported as AEs. Overall, 12 22%) patients had at least 1 low neutrophil count value of CTCAE Grade ≥3, 7 (13%) patients had at least 1 low platelet level of CTCAE Grade ≥3, and 11 (20%) patients had at least 1 low haemoglobin value of CTCAE Grade ≥3; all of these patients had baseline values of Grade 0 or 1. Forty-four of 54 (82%) patients had normal MCV values at baseline of which 28 (64%) patients had developed an elevated MCV during the study to levels ranging from 110 to 115. MCV elevations were observed in all dose cohorts, were asymptomatic in nature, occurred at about the fourth cycle of treatment in majority of these patients, and did not appear to be dose related.