AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00011
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A Phase I/II Randomised, Double-Blind, Multi-Centre Study To Assess The Efficacy Of AZD2281 When Given In Combination With Paclitaxel In The 1st Or 2nd Line Treatment Of Patients With Metastatic Triple Negative Breast Cancer

Study dates: First patient enrolled: 15 September 2008
Data cut-off: 9 November 2009

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

A suitable dosing schedule to take into the Phase II part of the study could not be identified during Phase I. The Phase I part of the study only is presented in this synopsis.

Study centres

Patients were enrolled at 6 centres in 4 countries: Australia (3), Austria (1), Belgium (1) and Canada (1).

Publications

Dent RA, Lindeman GJ, Clemons M, Wildiers H, Chan A, McCarthy NJ, Singer CF, Lowe ES, Kemsley K, Carmichael J. Safety and efficacy of the oral PARP inhibitor olaparib (AZD2281) in combination with paclitaxel for the first- or second-line treatment of patients with metastatic triple-negative breast cancer: Results from the safety cohort of a phase I/II multicenter trial J Clin Oncol 2010;28(7S): 1018 (abstr).

Objectives

The primary objective of the Phase I part of this study was:

- To establish the appropriate doses of paclitaxel and olaparib in combination, based on safety and tolerability (for use in the randomised Phase II part of the study).

The secondary objective of the Phase I part of this study was:

- To identify any toxicities of olaparib in combination with paclitaxel.

Study design

The Phase I part of this open-label, intra-patient dose intensification study in the first- or second-line treatment of female patients with metastatic triple negative breast cancer (TNBC) was to establish the appropriate doses and schedule of paclitaxel and olaparib in combination to be used in the Phase II randomised part of the study. Patients with non-measurable disease at baseline (per Response Evaluation Criteria in Solid Tumours [RECIST]) were allowed in this phase of the study. Tumour markers (CA-153 and carcinoembryonic antigen) were assessed locally from blood samples taken at the beginning of each study treatment cycle.

A mandatory archived paraffin embedded tumour sample was collected from all patients. Optional blood samples for pharmacogenetic and circulating biomarkers were obtained from consenting patients and stored for long-term exploratory purposes. Patients did not have to consent to the optional samples in order to participate in the study. Biomarker work based on these samples will be performed separately and reported outside this CSR.

Occurrence of common toxicity criteria (CTC) Grade 2 neutropenia within the first 2 cycles of treatment in Cohort 1 led to paclitaxel dose modifications, which resulted in decreased dose intensity of paclitaxel. Prior to recruitment of a second cohort, a protocol amendment was made, allowing prophylactic administration of granulocyte colony-stimulating factor (G-CSF

[filgrastim] 300 µg subcutaneously on Days 3 to 5 after each weekly paclitaxel dose) to maintain the optimal dose intensity of paclitaxel. For Cohort 2, neutropenia was first to be managed by the use of a G-CSF followed by dose interruptions of olaparib as a second step, with dose reduction of paclitaxel as the final step.

Target patient population and sample size

For the Phase I part of the study, approximately 10 patients per cohort, with metastatic TNBC were planned to be enrolled from approximately 5 to10 centres world-wide. A minimum of 6 evaluable patients completing 2 cycles were required. In the event that a suitable dosing schedule was not identified to take into Phase II, the Clinical Study Protocol (CSP) allowed for additional cohorts to be recruited sequentially to assess alternative dose schedules or appropriate toxicity management.

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

Olaparib capsules were manufactured by Patheon Pharmaceuticals Inc, 2110 East Galbraith Road, Cincinnati, Ohio, 45237-1625, USA, and bottled, labelled and supplied by Fisher Clinical Services. The batch numbers were 3064515R and 3070199R.

Olaparib was administered at a dose of 200 mg twice daily (bd) throughout each 28-day cycle.

Paclitaxel, 90 mg/m^2 was administered as an intravenous infusion over 1 hour on Days 1, 8 and 15 of a 28-day cycle. The CSP allowed for doses of paclitaxel lower than 90 mg/m^2 to be explored dependent upon tolerability. Paclitaxel is commercially available and was supplied locally by the investigator's site pharmacy.

Duration of treatment

The treatment period was divided into cycles of 28 days. Patients were to be administered paclitaxel in line with normal clinical practice: it was expected that patients would receive between 6 and 10 cycles of paclitaxel, there was to be no maximum duration of treatment with olaparib. After paclitaxel was stopped, patients were to continue with olaparib treatment until objective disease progression or as long as in the Investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

The original protocol planned for an initial 21-day cycle in the first cohort. No tolerability issues were observed in the 21-day cycle in the first cohort and therefore, it was not necessary for the first cycle to be an abbreviated one (ie, 21 days).

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Efficacy analyses were not planned for the Phase I part of the study. However, because the study was terminated prematurely best objective response and median progression free survival have been evaluated.

Criteria for evaluation - safety (main variables)

Safety: Adverse events (AEs); physical examination; vital signs including blood pressure, pulse, electrocardiogram; and laboratory findings including clinical chemistry, haematology and urinalysis.

Statistical methods

The primary objective of the Phase I part of this study was to establish the appropriate doses and schedule of paclitaxel and olaparib in combination based on safety and tolerability, for use in the randomised Phase II part of the study. No formal statistical comparisons of Phase I data have been performed. Data are listed and summarised descriptively.

Subject population

The patient population participating in this study comprised 19 women with histologically or cytologically confirmed metastatic TNBC who had received ≤1 prior cytotoxic therapy. Nine patients were included in Cohort 1 and 10 patients in Cohort 2. All patients were White and female, with a mean age of 50 years (range 36 to 71 years). All patients had Eastern Cooperative Oncology Group performance status of 0 or 1.

There were 5 (26.3%) patients with protocol deviations; none of the patients were excluded from the analyses and these deviations are not expected to affect the interpretation of the study results. At the cut-off date for this report, 3 patients in Cohort 2 were ongoing in the study, 2 receiving olaparib and paclitaxel, and the other receiving olaparib only; one further patient in Cohort 1 was ongoing in the study at data cut-off, and had discontinued paclitaxel but was still receiving olaparib

Summary of efficacy results

Since a suitable dosing schedule could not be identified to take into Phase II, this study was terminated prematurely. Using the investigator's opinion of response (RECIST), the overall response rate (ORR) was 3/9 patients (33.3%; 90% confidence interval [CI]; 14.2 to 60.2%) in Cohort 1 and 4/10 patients (40%; 90% CI; 19.4 to 64.8%) in Cohort 2. Additionally, 1 and 2 patients in Cohorts 1 and 2, respectively, had an unconfirmed partial response. Median progression-free survival was 192.5 days (95% CI: 106.0, 272.0) in Cohort 1 and 159 days (95% CI: 106.0, NC) in Cohort 2. The estimated medians are based on very few events in each cohort and thus should be interpreted with caution.

Summary of pharmacokinetic, pharmacodynamic and pharmacogenetic results (Not applicable)

Summary of safety results

Overall median actual exposure to study treatment was 155 days (range 50 to 389 days), excluding dose interruptions. The median (range) actual treatment duration (excluding dose interruptions) was 168.0 days (50-389 days) in Cohort 1 and 151.0 days (57 to 243 days) in Cohort 2.

Median dose adherence for olaparib was 100% for both cohorts. Paclitaxel median dose intensity was 57.2% and 73.1% for Cohorts 1 and 2, respectively. Six patients in each cohort completed 6 cycles of olaparib treatment, and almost as many patients (5/9 and 6/10 in Cohorts 1 and 2, respectively) received 6 cycles of combination therapy. The majority of patients discontinued olaparib and paclitaxel due to disease progression (15/19 and 14/19, respectively).

With the exception of neutropenia, which led to dose modification of olaparib for 6 (31.6%) patients (4 [44.4%] patients in Cohort 1 and 2 [20%] patients in Cohort 2), all other events that led to dose modifications of olaparib were reported for single patients, and included anaemia, pyrexia, herpes zoster, infection, skin infection, blood bilirubin increased, blood lactate dehydrogenase abnormal, gamma-glutamyltransferase abnormal, aphasia and skin disorder.

More patients in Cohort 1 compared with Cohort 2 had paclitaxel dose modifications (dose delay and/or dose reduction): 8/9 (89%) vs 6/10 (60%), of which 6/9 (67%) patients versus 3/10 (30%) patients had both a delay and a dose reduction of paclitaxel.

The number of patients who had at least 1 AE in any category during the course of the study is presented in Table S1.

Table S1 Number (%) of patients who had at least 1 AE in any category (Safety analysis set)

Category of AE	Number (%) of patients[a]		
	Cohort 1 N=9	Cohort 2 N=10	Total N=19
Any AE	9 (100.0)	10 (100.0)	19 (100.0)
Any causally related AE[b]	7 (77.8)	9 (90.0)	16 (84.2)
Any AE of CTC Grade ≥3	8 (88.9)	5 (50.0)	13 (68.4)
Any causally related AE of CTC Grade ≥3[b]	4 (44.4)	4 (40.0)	8 (42.1)
Any AE with outcome of death	0	0	0
Any SAE (including events with outcome of death)	2 (22.2)	4 (40.0)	6 (31.6)
Any causally related SAE[b]	1 (11.1)	1 (10.0)	2 (10.5)
Any AE leading to discontinuation of olaparib	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] Causally related to olaparib as assessed by the investigator.
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study medication.
AE: Adverse event; CTCAE: Common terminology criteria for AEs; SAE: Serious adverse event.
Both Cohorts 1 and 2 received olaparib 200 mg bd continuously and paclitaxel 90 mg/m^2 on Days 1, 8 and 15 of each cycle. Cohort 2 only was permitted to receive G-CSF in the event of neutropenia (ANC <1.5x10^9/L) in the first cycle. Both Cohorts 1 and 2 were allowed to receive G-CSF in subsequent cycles.
Abbreviations: AE: adverse event; ANC: absolute neutrophil count; CTC: Common toxicity criteria; G-CSF: granulocyte colony stimulating factor; SAE: serious adverse event.

In Cohort 1, neutropenia was the most frequently reported AE (Table S2; 7 [77.8%] patients: CTCAE Grade 1 to 2 in 3 patients, Grade 3 in 3 patients, and Grade 4 in 1 patient). In Cohort 2, the most frequently reported AEs were diarrhoea and nausea (6 [60.0%] patients each).

Neutropenia, anaemia, abdominal pain (including upper abdominal pain), myalgia, dizziness, paraesthesia and cough appeared to have a higher incidence in Cohort 1 than in Cohort 2. There was a higher incidence of rash in Cohort 2 compared with Cohort 1.

Some of the commonly reported AEs seen in this study are not unexpected in patients with advanced breast cancer. The observed AE profile is not unexpected given the previous experience with olaparib and the known safety profile for paclitaxel. Many of the AEs are known side effects of paclitaxel, eg, neutropenia, anaemia, diarrhoea, nausea and vomiting, constipation, myalgia, peripheral neuropathy, bleeding, alopecia and upper respiratory tract infection.

Table S2 Summary of AEs occurring in >25% of patients in either cohort by SOC and PT (Safety analysis set)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of patients[a]		
	Cohort 1 N=9	Cohort 2 N=10	Total N=19
Any AE	9 (100.0)	10 (100.0)	19 (100.0)
Blood and lymphatic system disorders			
Neutropenia[b]	7 (77.8)	4 (40.0)	11 (57.9)
Anaemia[b]	5 (55.6)	1 (10.0)	6 (31.6)
Gastrointestinal disorders			
Diarrhoea	6 (66.7)	6 (60.0)	12 (63.2)
Nausea	5 (55.6)	6 (60.0)	11 (57.9)
Vomiting	3 (33.3)	3 (30.0)	6 (31.6)
Constipation	4 (44.4)	2 (20.0)	6 (31.6)
Abdominal pain upper	4 (44.4)	1 (10.0)	5 (26.3)
Abdominal pain	3 (33.3)	1 (10.0)	4 (21.1)
General disorders and administration site conditions			
Fatigue	6 (66.7)	4 (40.0)	10 (52.6)
Infections and infestations			
Upper respiratory tract infection	2 (22.2)	3 (30.0)	5 (26.3)
Musculoskeletal and connective tissue disorders			
Back pain	2 (22.2)	3 (30.0)	5 (26.3)
Myalgia	4 (44.4)	1 (10.0)	5 (26.3)
Nervous system disorders			
Neuropathy peripheral	3 (33.3)	3 (30.0)	6 (31.6)
Dysgeusia	2 (22.2)	3 (30.0)	5 (26.3)
Lethargy	2 (22.2)	3 (30.0)	5 (26.3)

Table S2 Summary of AEs occurring in >25% of patients in either cohort by SOC and PT (Safety analysis set)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of patients[a]		
	Cohort 1 N=9	Cohort 2 N=10	Total N=19
Headache	3 (33.3)	1 (10.0)	4 (21.1)
Dizziness	3 (33.3)	0	3 (15.8)
Paraesthesia	3 (33.3)	0	3 (15.8)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	3 (33.3)	2 (20.0)	5 (26.3)
Epistaxis	2 (22.2)	3 (30.0)	5 (26.3)
Cough	3 (33.3)	0	3 (15.8)
Skin and subcutaneous tissue disorders			
Alopecia	6 (66.7)	4 (40.0)	10 (52.6)
Rash	1 (11.1)	5 (50.0)	6 (31.6)

[a] Number (%) of patients with AEs, sorted in decreasing frequency order of total number across cohorts. A patient could have one or more preferred terms reported under a given system organ class.
[b] Based on AEs reported by the investigator; additionally, 4 patients in Cohort 1 and 8 patients in Cohort 2 had laboratory abnormalities of haemoglobin, and a further patient in Cohort 1 (worst CTC Grade 1) and 2 patients (for both, worst CTC Grade 2) in Cohort 2 had laboratory abnormalities of neutrophils, which were not reported as AEs by the investigator.
Note: Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study medication.
Both Cohorts 1 and 2 received olaparib 200 mg bd continuously and paclitaxel 90 mg/m^2 on Days 1, 8 and 15 of each cycle. Cohort 2 only was permitted to receive G-CSF in the event of neutropenia (ANC <1.5x10^9/L) in the first cycle. Both Cohorts 1 and 2 were allowed to receive G-CSF in subsequent cycles.

A high proportion of patients (13 [68.4%]) had at least 1 AE of CTC Grade ≥3. With the exception of anaemia, which was reported for 2 (22%) patients in Cohort 1, and neutropenia, which was reported for 4 (44.4%) patients in Cohort 1 and 2 (20%) patients in Cohort 2, all other AEs of CTC Grade ≥3 were reported for single patients.

There was 1 patient death in Cohort 1. The investigator recorded the primary cause of death as disease progression and secondary cause as multi-organ failure.

Overall, 6 (31.6%) patients had 8 SAEs reported during treatment or within 30 days of the end of their treatment; these included febrile neutropenia, pyrexia, cellulitis, device related infection, infection, aphasia, deep vein thrombosis and haemodynamic instability. None of the SAEs were reported for more than 1 patient in either treatment group. There were no patients with an AE leading to discontinuation of olaparib.

The clinical laboratory findings were consistent with the known safety profile of olaparib and paclitaxel, 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.