Clinical Study Report Synopsis

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00003 (KU36-73)
Edition Number	1
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A Phase I, Open-Label, Study of the Safety and Tolerability of KU-0059436 and Dacarbazine in the Treatment of Patients with Advanced Solid Tumours.

Study dates: First patient started: 10th January 2007
Last patient off-study: 2nd January 2009

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 study was a multi-centre study conducted in the UK (3 study centres), and the USA (1 study centre). All patients in this study were enrolled in the UK.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective was:

- To determine the safety, tolerability and dose-limiting toxicity (DLT) of a combination of oral olaparib and intravenous (iv) dacarbazine (DTIC) in patients with advanced solid tumours.

The secondary objectives were:

- To determine the pharmacokinetic (PK) profile of olaparib in combination with DTIC.
- To determine the PK profile of DTIC in combination with olaparib.
- To investigate the PK - pharmacodynamic (PD) profile of olaparib and DTIC in surrogate and tumour tissues when given in combination.
- To enable a preliminary assessment of the anti-tumour activity of olaparib when given in combination with DTIC compared to DTIC alone in terms of progression free survival (PFS) and maximum tumour reduction (as per amendment 4).

The primary and secondary objectives of the study are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Title and description**
Primary	Safety	To determine the safety, tolerability and DLT of a combination of oral olaparib and iv DTIC in patients with advanced solid tumours.	AEs, laboratory tests, physical examination and vital signs. Incidence of DLTs during Cycle 1 of treatment with olaparib
Secondary	PK	To determine the PK profile of olaparib in combination with DTIC.	Blood sampling for pharmacokinetic analysis
Secondary	Efficacy	To determine the PK profile of DTIC in combination with olaparib.	Blood sampling for pharmacokinetic analysis
Secondary	PK / PD	To investigate the PK-PD profile of olaparib and DTIC in surrogate and tumour tissues when given in combination.	Blood sampling for pharmacokinetic analysis Blood and tumour sampling for PD analysis.
Secondary	Efficacy	To enable a preliminary assessment of the anti-tumour activity of olaparib when given in combination with DTIC compared to DTIC alone in terms of PFS and maximum tumour reduction.	Overall response, duration of stable disease, duration of response, time to disease progression

AE Adverse event; DLT Dose-limiting toxicity; DTIC Dacarbazine; iv Intravenous; PD Pharmacokinetic; PFS Progression free survival; PK Pharmacokinetic.

Study design

This was an open-label, dose-escalating, non-randomised, multi-centre Phase I study of the safety, tolerability and DLT of oral olaparib given in combination with iv DTIC to patients with advanced solid tumours. The study design comprised a 2-part dose escalation phase followed by an expansion phase. The starting dose of the combination treatment in the dose escalation phase was 10 mg twice daily (bd) olaparib for 7 days and 600 mg/m^2 DTIC (subtherapeutic doses) in advanced solid tumour patients. Part II was initially designed to investigate higher doses of DTIC in combination with olaparib in chemotherapy naive melanoma but based on emerging safety and efficacy data was later amended to include 600 mg/m^2 DTIC. The dose expansion phase was designed in 2 parts, namely a 10 patient dose confirmation part and a subsequent randomised expansion part, to be conducted only if 20% overall response rate threshold was reached in the dose confirmation part. However, as a 20%

overall response rate threshold was not determined in the dose confirmation part, the randomised expansion part was not carried out.

Target patient population and sample size

The target populations were patients presenting with solid tumours refractory to standard therapy or for which no suitable effective standard therapy (Part I of the study) and chemotherapy-naïve advanced melanoma patients (Part II, confirmation phase and expansion phase of the study). Patients had to fulfil all inclusion criteria to be included in the study. Patients had to have adequate bone marrow, hepatic and renal function and have a performance status at entry of Eastern Cooperative Oncology Group (ECOG) 0 to 2. The maximum overall total of patients that could be enrolled was increased to 95 following protocol amendment 4, with the introduction of the expansion phase of the study (45 patients). However, the study closed to recruitment after enrolling 40 patients, because the requirement for an objective response rate of ≥20% in the confirmation phase after 4 cycles of treatment was not met.

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

Olaparib was manufactured to good manufacturing practice (GMP) standards and was supplied as hydroxypropyl methycellulose (HPMC) white (50 mg) and red (10 mg) capsules to be taken orally. For the 50 mg capsules, the following formulation numbers were used: BMR/05/261, BMR/05/376, BMR/06/377, BMR/07/429, BMR/07/513, BMR/07/538 and BMR/07/559. For the 10 mg capsules, the following formulation number was used: BMR/06/260. Individual batch numbers are included in the clinical study report (CSR).

DTIC was supplied by the study sites' pharmacy. The costs were reimbursed by KuDOS Pharmaceuticals. DTIC was to be reconstituted with Water for Injections British Pharmacopoeia (BP) so that the resulting solution contained the equivalent of 10 mg/ml of DTIC. The reconstituted solution was to be further diluted with 125-250 ml of Dextrose Injection BP 5% or Sodium Chloride Injection BP 0.9% for iv infusion.

Duration of treatment

Each cycle was 21 days' duration. Olaparib was to be administered bd for 7 consecutive days of each cycle (Days 1 to 7 or Days 2 to 8 for Cycle 2 only) with DTIC administered by iv infusion on Day 1 of each cycle. The starting dose was 600 mg/m^2 DTIC with 10 mg bd olaparib. The study allowed each patient to receive up to 6 cycles, or more at the discretion of the investigator if they had at least stable disease (SD).

Statistical methods

No formal statistical analyses were carried out; descriptive statistical analyses were performed by Theradex®, Princeton, NJ, USA using SAS™ version 8.01, and were performed in accordance with the statistical analysis plan (SAP) which was finalised before database soft

lock. The safety and tolerability profile of olaparib in combination with DTIC was assessed by adverse events (AEs), laboratory tests, physical examination and vital signs. AEs were summarised by system organ class and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary.

Subject population

In total, 40 patients (28 male and 12 female) were enrolled and treated in this study. All patients were White, with a mean age of 53.3 years for the whole group. Most patients on the study had a performance status of ECOG 0 or 1. Only 2 (5.0%) patients had ECOG 2 at baseline.

All patients had prior surgery. Thirty-three patients (82.5%) had a diagnosis of melanoma, of which 30 (75.0%) patients were included in the malignant melanoma, not otherwise specified category, 3 patients (7.5%) were coded to other malignant melanoma categories, and 7 patients (17.5%) had tumours of other histological types. Of the patients diagnosed with melanoma, the primary sites of disease were 30 patients (75.0%) skin, 1 patient (2.5%) eyeball, 1 patient (2.5%) unknown and 1 patient (2.5%) oesophagus. The median duration of disease from the date of initial diagnosis until the date of registration on the study was 25.91 months with a range of 2.8 months to 225.0 months.

Twenty patients (50%) had refractory advanced solid tumours, including 13 patients (32.5%) with melanoma, and 20 patients (50%) were first line melanoma patients.

All patients are off-study. Patients were discontinued from the study for the following reasons:

- 34 (85.0%) patients were discontinued because their disease worsened/progressed.
- 3 (7.5%) patients were discontinued for “other” reasons, including investigator decision and sponsor decision.
- 2 (5.0%) patients were discontinued due to AEs.
- One (2.5%) patient discontinued voluntarily.

Summary of efficacy results

No complete responses (CR) were seen in this study. Two of 40 patients (5.0%), both with refractory melanoma, had a confirmed partial response (PR) as their overall best response, per Response Evaluation Criteria in Solid Tumours (RECIST). Eight patients (20.0%) had stable disease (SD) and 25 patients (62.5%) had progressive disease (PD). Five patients (12.5%) could not be evaluated for objective response, because, though stable at earlier assessments 4 patients did not reach the minimum period of 84 days cut-off for assignment of SD as per the statistical analysis plan (SAP). One additional patient did not have an evaluable assessment until they had PD at 149 days, this exceeded the required 112-day interval between assessments as defined by the SAP. The median time to disease progression for the overall

population was 43 days (95% confidence interval [CI]: 38, 108 days). Six patients (15.0%) were censored in the analysis. The median time to disease progression was 82 days (95% CI: 38, 108 days) for the refractory solid tumour patients and 42 days (95% CI: 36, 84 days) for the chemotherapy-naïve melanoma patients.

Summary of pharmacokinetic results

There was no evident trend for olaparib exposure to increase or decrease either with increasing dose of olaparib or of DTIC, or vice versa, although it should be noted the analysis was based on a dataset with relatively small numbers of patients in each dose cohort with reportable PK parameters.

Summary of pharmacodynamic results

Blood samples for peripheral blood mononuclear cell (PBMC) analysis were taken during the study but had not been analysed at the time of this report. The data from the poly ADP-ribose polymerase (PARP)-1PD assay in PBMC samples will be reported separately at a later date. The results for the exploratory assessment of N-methylpurine-DNA-glycosylase (MPG) and N7-methylguanine (7meG) levels in deoxyribonucleic acid (DNA) are reported in the appendices of the CSR. Tumour samples will be analysed at a later date and the results will be reported with the PBMC data. No hair follicle samples were collected during this study.

Summary of pharmacogenetic results

The results of the genetic study may be pooled with genetic results from other studies and reported at a later date.

Summary of pharmacokinetic/pharmacodynamic relationships

The PK/PD relationships from this study will be reported separately at a later date

Summary of safety results

The overall median duration of exposure to olaparib was 46.0 days. Patient compliance with olaparib treatment was notably good in the study with a mean of 100.51% of the prescribed dose and overall mean adherence to the prescribed dose of 99.96%. Compliance with olaparib treatment was more than 100% for 4 patients because the number of days dosed in that cycle exceeded by 1 day only the assigned 7 days per protocol. No patient took an overdose (more than the prescribed dose) on any one day. Six patients (15.0%) each missed 1 dose of olaparib. These dose interruptions were all associated with patient non-compliance; none was due to an AE.

The overall median duration of exposure to DTIC was 39.5 days. The overall mean DTIC compliance was 100% of prescribed dose and the overall mean adherence to the prescribed dose was 99.69%. Four patients (10.0%) each had 1 interruption of their DTIC treatment during infusion; all interruptions were due to pain in the arm during infusion. Five patients (12.5%) had at least 1 dose reduction, due primarily to haematological toxicities.

Seven patients had a delay (usually 1 week) to their treatment between Cycles 1 and 2 due to AEs, particularly neutropenia occurring on Day 22. Six patients had treatment delays between later cycles, despite DTIC dose reductions in some cases. For 5 of these patients, the delays were due to a low absolute neutrophil count (ANC) on the scheduled day of treatment. Neutropenia also appeared to be dose dependent, with 4 of 6 patients (66.7%) at the 40 mg bd olaparib and 800 mg/m^2 DTIC dose level, and 3 of 6 patients (50.0%) at the 200 mg bd olaparib and 600 mg/m^2 DTIC dose level having significant nadirs in the first cycle of treatment.

As expected in patients with advanced cancer, all of the patients (100%) experienced at least 1 treatment-emergent adverse event (TEAE) (Table S2). Overall, 26 patients (65.0%) had at least 1 drug-related TEAE (ie, an adverse event considered by the investigator to be related to both olaparib and DTIC). Overall, 29 (72.5%) patients had TEAEs of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or higher. The percentage of patients with treatment-related AEs of CTCAE ≥grade 3 was 27.5% (11 patients).

The combination was generally tolerable at all dose levels tested with the most common TEAEs (occurring in ≥20% of patients) overall being fatigue (24 patients, 60.0%); nausea (22 patients, 55.0%); constipation (20 patients, 50.0%); neutropenia (13 patients, 32.5%); diarrhoea and cough (each in 11 patients, 27.5%); vomiting and insomnia (each in 10 patients, 25.0%) and anaemia and dyspnoea (each in 9 patients, 22.5%). Nausea, vomiting and fatigue are AEs considered to be associated with administration of olaparib and DTIC. Cases of nausea and vomiting were mainly of mild to moderate intensity (CTCAE grade 1 or 2), intermittent and manageable with standard anti-emetic therapies on continued treatment. Cases of fatigue were generally intermittent and of mild to moderate intensity (CTCAE grade 1 or 2).

Within the haematological parameters, myelotoxicity, especially neutropenia, emerged as the principal toxicity. There potentially is a dose/toxicity relationship. At the highest doses of DTIC or olaparib, neutropenic nadirs of <1.0 x10^9/L during Cycle 1 or <1.5 x10^9/L on Day 22 of Cycle 1 leading to dose delays in Cycle 2 occurred in 66.7% of patients in the 40 mg bd olaparib and 800 mg/m^2 DTIC cohort and 50.0% of patients in the 200 mg bd olaparib and 600 mg/m^2 DTIC cohort.

The dose limiting toxicities were CTCAE grade 3 hypophosphataemia and grade 4 leukopenia experienced by Patient 003-01-0016 at the 40 mg bd olaparib and 800 mg/m^2 DTIC dose level; and CTCAE grade 4 neutropenia experienced by Patients 002-01-0021 and 002-01-0025, both in the 200 mg bd olaparib and 600 mg/m^2 DTIC dose level. The highest combination doses that were chosen by the sponsor and investigators to have clinical utility were 100 mg bd olaparib and 600 mg/m^2 DTIC and 20 mg bd olaparib and 800 mg/m^2 DTIC. The 100 mg bd olaparib and 600 mg/m^2 DTIC dose combination was chosen for the dose confirmation component of the study.

In total 13 patients (35.0%) experienced serious adverse events (SAEs) during the study. The majority of SAEs were considered unrelated to the study medication, and no SAEs were

attributed to olaparib. Three patients (001-01-006, 002-01-0017 and 002-01-0025) had SAEs that were considered by the investigator to have a causal relationship to DTIC; these were 2 cases of respiratory infections and 1 febrile neutropenia.

Overall, 5 patients (12.5%) experienced TEAEs leading to dose reduction of DTIC. The most commonly reported TEAE leading to treatment delay in any cycle was neutropenia (8 patients, 20.0%). Five patients (12.5%) experienced neutropenic nadirs of $<1.5 \times 10^9$/L on Day 22 of Cycle 1 leading to a DTIC dose delay between Cycle 1 and Cycle 2.

Three patients (7.5%) experienced AEs leading to discontinuation of the study medication. One patient was withdrawn due to grade 3 hypophosphataemia and thrombocytopenia considered related to the study drugs. One patient had CTCAE grade 3 myocardial ischaemia unrelated to the study drugs and died 47 days after the last study drug administration from myocardial ischaemia. One patient, whose primary site of disease was the lumbar spine, experienced serious back pain and was discontinued due to symptomatic progression of disease.

In total, 26 deaths (65.0%) were recorded, 24 of which were considered disease-related and the majority occurred more than 30 days following the last study drug administration. Two deaths were linked to TEAEs; these were both considered by the investigator to be unrelated to either study drug.

Table S2 Summary of number (%) of patients who had at least one TEAE in any category: Safety population

	Initial Dose Level (Olaparib mg bd / DTIC mg/m^2)							
Treatment-emergent AEs[a,b]	**10/600**	**20/600**	**20/800**	**40/600**	**40/800**	**100/600**	**200/600**	**Overall**
Number of patients	**3**	**4**	**4**	**4**	**6**	**13**	**6**	**40**
Any TEAE	3 (100%)	4 (100%)	4 (100%)	4 (100%)	6 (100%)	13 (100%)	6 (100%)	40 (100%)
TEAE of CTCAE graded 3, 4 or 5	2 (66.7%)	4 (100%)	1 (25.0%)	2 (50.0%)	5 (83.3%)	9 (69.2%)	6 (100%)	29 (72.5%)
TEAE with fatal outcome	0	0	0	0	0	2 (15.4%)	0	2 (5.0%)
TEAE leading to discontinuation of treatment	0	0	0	0	1 (16.7%)	2 (15.4%)	0	3 (7.5%)
SAE (including events with fatal outcome)	1 (33.3%)	3 (75.0%)	0	0	1 (16.7%)	6 (46.2%)	2 (33.3%)	13 (32.5%)

[a] Patients with multiple events in a category are counted only once in that category. Patients with events in more than 1 category are counted once in each category. Includes TEAEs and AEs occurring post-treatment during the 30-day f/u. TEAEs are AEs that occurred after the first dose of study medication or within 30-day post-treatment period.

[b] Percentages of TEAEs were calculated using number of patients as the denominator.

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DTIC

dacarbazine; SAE Serious adverse event; TEAE Treatment-emergent adverse event.