AstraZeneca

Clinical Study Report Synopsis

Drug Substance	olaparib(AZD2281, KU-0059436)
Study Code	D0810C00005 (KU36-29)
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A Phase I, Open-Label, Study of the Safety and Tolerability of KU-0059436 in combination with Gemcitabine in the Treatment of Patients with Advanced Solid Tumours.

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

Study centre(s)

Publications

None at the time of writing this report.

Objectives

Table S1 Objectives and outcome variables

Objective	Outcome Variable	Type (Priority)
The primary objective was to investigate the safety and tolerability and establish either the dose of olaparib which is: the Maximum Tolerated Dose (MTD) of olaparib administered orally in combination with gemcitabine to patients with advanced malignant solid tumours. Or if an MTD cannot be determined: a tolerable and effective dose of olaparib in combination with an active dose of gemcitabine (in the opinion of the investigators and sponsor).	Adverse Events (AEs), laboratory tests, Physical examination and vital signs. Incident of dose limiting toxicities (DLT) in Cycle 1	Safety (Primary)
To identify the DLT of the combination of olaparib and gemcitabine	AEs, laboratory tests, Physical examination and vital signs. Incident of DLTs in cycle 1	Safety (Secondary)
To enable a preliminary assessment of the anti-tumour activity of olaparib when given in combination with gemcitabine compared to gemcitabine alone in terms of progression free survival (PFS) and maximum tumour reduction	Overall response (RECIST), duration of response, PFS, overall survival and tumour reduction	Efficacy (Secondary)
To determine the plasma pharmacokinetic profile of olaparib alone and in combination with gemcitabine	Pharmacokinetic variables	Pharmacokinetic (Secondary)
To determine the plasma pharmacokinetic profile of gemcitabine alone and in combination with olaparib	Pharmacokinetic variables	Pharmacokinetic (Secondary)
To determine the safety and tolerability profile of olaparib Melt-Extrusion [tablet] formulation in combination with gemcitabine	AEs, laboratory tests, Physical examination and vital signs.	Safety (Secondary)
To investigate exploratory biomarkers in whole blood, serum, urine and tumour biopsies (on treatment and historical) 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.	(This will not form part of the CSR.)	Pharmacodynamic (Exploratory)

Study design

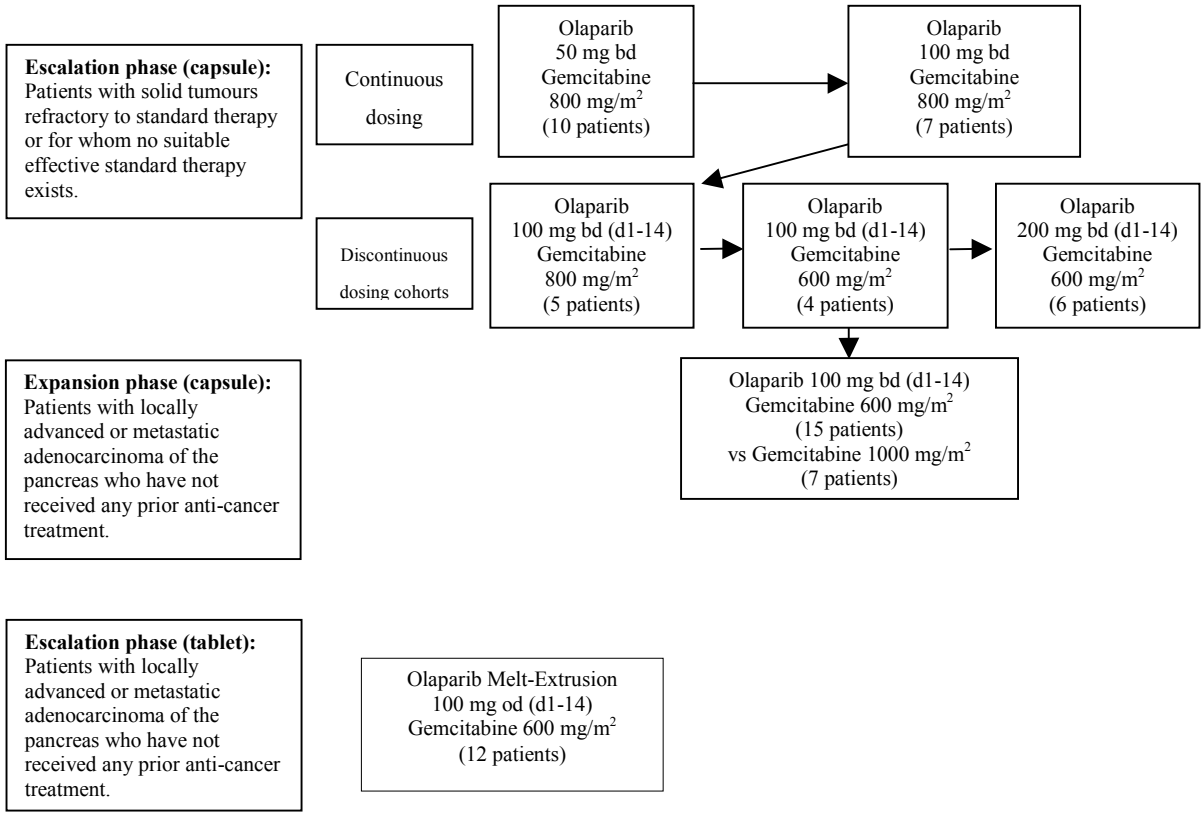
This was an open-label, multi-centre, phase I study of olaparib administered orally in combination with gemcitabine. The study consisted of two distinct phases:

(i) A dose escalation phase to test both continuous and discontinuous olaparib dosing (capsule formulation) to establish either the MTD, or a dose of olaparib (capsule formulation) in combination with an active dose of gemcitabine that could be administered safely.

A separate dose escalation phase to determine a tolerable dose of olaparib Melt-Extrusion [tablet] formulation in combination with gemcitabine.

(ii) A dose expansion phase of the selected combination dose (olaparib capsule formulation plus gemcitabine) compared to gemcitabine alone to further establish the safety and preliminary response data of the two treatment groups.

Figure S1 Flow chart of implemented study steps (ITT population)



Target subject population and sample size

The target population in the escalation phase was patients with histologically confirmed advanced solid tumours, refractory to standard therapy or for which no suitable therapy exists or for which gemcitabine would be considered a suitable therapy. A maximum of 47 evaluable patients were to be enrolled.

The target population in the expansion phase was patients with histologically confirmed adenocarcinoma of the pancreas with locally advanced or metastatic unresectable disease. A maximum of 23 evaluable patients were to be enrolled. The randomisation ratio for this study was 2:1 in favour of the combination arm.

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

The olaparib capsule formulation was supplied by Quay Pharmaceutical as hydroxypropyl methycellulose (HPMC) white (50 mg) and red (10 mg) capsules to be taken orally. The olaparib Melt-Extrusion [tablet] formulation was supplied by AstraZeneca as green, film-coated tablets containing either 25 mg or 100 mg olaparib to be taken orally.

Fifteen batches of olaparib were used in this study. Individual batch numbers and further information are included in the CSR.

Gemcitabine was supplied by the study sites' pharmacy.

Duration of treatment

In the dose escalation phase olaparib was to be administered orally twice-daily, on days 1 through 28 (or days 1-14 if in a discontinuous dosing cohort) at an escalating dose for each new cohort. Gemcitabine was to be administered on days 1, 8, 15 and 22 in cycle 1 and on days 1, 8 and 15 of subsequent cycles.

Patients in the tablet escalation phase were to be administered olaparib once daily on days 1 to 14, with a rest period from day 15 to 28 for all cycles. Gemcitabine was to be administered on days 1, 8, 15, and 22 in cycle 1 and on days 1, 8 and 15 of subsequent cycles.

Patients in the combination arm of the dose expansion phase were to be administered olaparib (capsule formulation) twice daily on days 1 through 14 for all cycles. In both arms of the dose expansion phase gemcitabine was to be administered on days 1, 8, 15, and 22 in cycle 1 and on days 1, 8 and 15 of subsequent cycles.

In all phases cycles were to be repeated every 28 days. Patients could be dosed for up to 6 cycles. At the discretion of the investigator, patients could receive more than 6 cycles if they were tolerating the treatment and had at least stable disease.

Statistical methods

No formal statistical analyses were performed on safety (primary objective), and the data were only summarised descriptively. For efficacy, in the dose escalation cohorts no formal

statistical analyses were performed and the data were summarised descriptively. For the dose expansion phase, statistical analysis was performed using time-to-event methods comparing the combination arm with the gemcitabine alone arm. Where appropriate, confidence intervals were presented. For efficacy, categorisation of response rate was based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

Subject population

Dose Escalation Phase

Forty six patients with advanced solid tumours were enrolled into the dose escalation phase and of these, 44 received study medication. The population comprised 25 (56.8%) male and 19 (43.2%) female patients, aged between 29 years and 79 years; the median ages for the various cohorts ranged from 59.0 to 71.5 years. Thirty-nine (88.6%) patients were Caucasian, 3 (6.8%) were black or African American and 2 (4.5%) were Asian. The majority of patients had an ECOG performance status of 0 or 1 at baseline; only 1 (2.3%) patient had a baseline status of 2.

Dose Expansion Phase

Twenty three patients with advanced pancreatic cancer were enrolled into the randomised dose expansion phase, patients were randomised 2:1 (stratification for randomisation was based on severity of disease, ie, locally advanced or metastatic unresectable disease). Fifteen patients received olaparib plus gemcitabine and 7 patients received gemcitabine alone. One patient randomised to the gemcitabine alone arm did not receive study medication.

Demographics and other baseline characteristics were well balanced between the randomised groups. The median age was 65.0 years in the combination arm and 66.0 years in the gemcitabine alone arm. All patients were Caucasian. There were very slight imbalances between arms with regard to ECOG performance status and extent of disease; a higher proportion of patients had ECOG PS 0 at baseline in the gemcitabine alone arm compared with the combination arm, and a greater proportion of patients had locally advanced pancreatic cancer in the gemcitabine alone arm compared to the combination arm.

Summary of efficacy results

A preliminary assessment of the anti-tumour activity of olaparib when given in combination with gemcitabine was done by measuring overall response rate, progression free survival, overall survival.

The overall response rate (CR + PR) in the dose escalation phase was 9.8% (4 of 41 patients). In the randomised dose expansion phase, the overall response rate for the combination arm was 26.7% (4 of 15 patients) compared with 14.3% (1 of 7 patients) in the gemcitabine alone arm, although this is not a statistically significant result.

Within the randomised dose expansion population, no improvement in either PFS or overall survival was observed for patients receiving olaparib capsule 100 mg bd (14 days) / 600 mg/m^2 gemcitabine compared with those receiving gemcitabine 1000 mg/m^2 alone; HR 1.18 (95% CI 0.45 to 3.09) and HR 1.12 (95% CI 0.43 to 2.94), respectively.

Summary of pharmacokinetic results

Olaparib (AZD2281)

Fourteen patients from two continuous and one discontinuous dosing regimens were included in the PK analysis.

The olaparib geometric mean plasma concentration-time profiles are similar in all treatment groups for drug alone and in the presence of gemcitabine with error bars overlapping. Whilst some variability is seen in the $AUC_{0\text{-}7}$ and $C_{max,ss}$ ratio values within all the treatment groups and numbers of patients are small, there is no evident trend for olaparib exposure to be increased or decreased when dosed in combination with gemcitabine.

Gemcitabine (dFdC) and gemcitabine metabolite (dFdU)

Six patients from two continuous and one discontinuous dosing regimens were included in the dFdC and dFdU PK Analysis Sets.

The dFdC geometric mean and individual plasma concentration-time profiles are similar in all treatment groups for drug alone and in the presence of olaaprib with error bars overlapping. Whilst some variability is seen in the $AUC_{0\text{-common t}}$ and C_{inf} ratio values within all the treatment groups and numbers of patients are small, there is no evident trend for dFdC exposure to be increased or decreased when dosed in combination with olaparib.

The dFdU geometric mean and individual plasma concentration-time profiles are similar in all treatment groups for drug alone and in the presence of olaparib with error bars overlapping. Whilst some variability is seen in the $AUC_{0\text{-common t}}$ and C_{max} ratio values within all the treatment groups and numbers of patients are small, there is no evident trend for dFdU exposure to be increased or decreased when dosed in combination with olaparib.

Summary of safety results

Four patients (6.1%) in the dose escalation phase experienced DLTs during cycle 1. Three occurred in continuous olaparib dosing cohorts and one in a discontinuous olaparib cohort.

Continuous dosing of olaparib capsules together with gemcitabine dose levels of >600 mg/m^2 was not considered to have an acceptable tolerability profile for further study. The dose level of olaparib capsule 100 mg bd (14 days) / 600 mg/m^2 gemcitabine selected for the expansion phase was considered to have an acceptable tolerability profile for further study.

All patients (dose escalation and dose expansion) received a median of 4.5 cycles of therapy (range 1 to 18 cycles). The median duration of exposure to olaparib ranged from 65 days to 192.5 days. The median duration of exposure to gemcitabine ranged from 46 days to 186 days.

In the randomised dose expansion phase, the number of gemcitabine cycles initiated was similar in both arms; median 6, range 1-18 on the olaparib combination arm compared to median 6, range 1-14 on the gemcitabine alone arm.

All patients reported at least 1 adverse event (Table S1 and Table S2). The predominant AEs encountered in the olaparib capsule cohorts (≥ 30% of patients) were fatigue (31 patients; 66.0%); nausea (30 patients, 63.8%); thrombocytopenia (26 patients, 55.3%); anaemia (25 patients, 53.2%); neutropenia (21 patients; 44.7%); constipation (17 patients; 36.2%); diarrhoea, and oedema peripheral (each in 16 patients; 34.0%); and anorexia (15 patients; 31.9%).

Table S1 Summary of number (%) of patients who had at least one AE in any category: Safety population

	N (%) of patients						
	Initial dose level (olaparib mg bd (days) / gemcitabine mg/m²)					Olaparib tablet mg od (days) / gemcitabine (mg/m²)	gemcitabine alone (mg/m²)
Drug administration	**50(28) / 800**	**100(14) / 600**	**100(14) / 800**	**100(28) / 800**	**200(14) / 600**	**100(14) / 600**	**1000**
Number of patients	**10**	**19**	**5**	**7**	**6**	**12**	**7**
Number of events of any AEs	129	311	86	147	136	152	102
Patients with any AEs[b]	10 (100)	19 (100)	5 (100)	7 (100)	6 (100)	12 (100)	7 (100)
Drug-related AEs[b,c]	7 (70.0)	16 (84.2)	5 (100)	7 (100)	6 (100)	11 (91.7)	0
Olaparib-related AEs[b]	8 (80.0)	16 (84.2)	5 (100)	7 (100)	6 (100)	11 (91.7)	0
Gemcitabine-related AEs[b]	7 (70.0)	19 (100)	5 (100)	7 (100)	6 (100)	12 (100)	7 (100)
AEs of CTCAE grade ≥3[b,d]	9 (90.0)	14 (73.7)	3 (60.0)	6 (85.7)	6 (100)	9 (75.0)	6 (85.7)
Olaparib-related AEs of CTCAE grade ≥3[b,d]	5 (50.0)	8 (42.1)	3 (60.0)	6 (85.7)	2 (33.3)	5 (41.7)	0
Gemcitabine-related AEs of CTCAE grade ≥3[b,d]	6 (60.0)	12 (63.2)	3 (60.0)	6 (85.7)	5 (83.3)	6 (50.0)	4 (57.1)
AEs with outcome=death[b]	1 (10.0)	1 (5.3)	0	0	0	0	0
SAEs (including events with outcome=death)[b]	6 (60.0)	8 (42.1)	1 (20.0)	5 (71.4)	2 (33.3)	4 (33.3)	3 (42.9)
AEs leading to discontinuation of treatment[b]	1 (10.0)	1 (5.3)	0	1 (14.3)	0	2 (16.7)	0

[a] Patients with multiple events in a category were counted only once in that category. Patients with events in more than one category were counted once in each category. Includes TEAEs and AEs occurring post-treatment during the 30 day f/u. Treatment-Emergent AEs (TEAEs) are defined as all AEs that occurred after the first dose of study medication or within 30 day post-treatment period.
[b] Percentages were calculated using number of patients as the denominator.
[c] Relationship to olaparib = Yes and relationship to gemcitabine = Yes for a given preferred term
[d] CTCAE Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening or disabling, 5=Death related to AE.

The most commonly occurring AEs during the study by preferred term, arranged by SOC are presented in Table S2.

Table S2 Summary of AEs occurring in at least 10% of patients overall by SOC and PT: Safety population

	N (%) of patients						
	Initial dose level (olaparib mg bd (days) / gemcitabine mg/m²)					Olaparib tablet mg od (days) / gemcitabine (mg/m²)	gemcitabine alone (mg/m²)
System Organ Class[a] Preferred Term[a,b,c]	**50(28) / 800**	**100(14) / 600**	**100(14) / 800**	**100(28) / 800**	**200(14) / 600**	**100(14) / 600**	**1000**
Number of patients	**10**	**19**	**5**	**7**	**6**	**12**	**7**
Patients with any TEAEs[b]	10 (100)	19 (100)	5 (100)	7 (100)	6 (100)	12 (100)	7 (100)
Blood and lymphatic system disorders							
Anaemia	7 (70.0)	7 (36.8)	1 (20.0)	6 (85.7)	4 (66.7)	1 (8.3)	2 (28.6)
Neutropenia	3 (30.0)	6 (31.6)	3 (60.0)	6 (85.7)	3 (50.0)	4 (33.3)	3 (42.9)
Thrombocytopenia	2 (20.0)	11 (57.9)	3 (60.0)	4 (57.1)	6 (100)	4 (33.3)	3 (42.9)
Gastrointestinal disorders							
Abdominal pain	3 (30.0)	3 (15.8)	0	1 (14.3)	3 (50.0)	5 (41.7)	1 (14.3)
Abdominal pain upper	1 (10.0)	2 (10.5)	1 (20.0)	0	1 (16.7)	1 (8.3)	1 (14.3)
Constipation	3 (30.0)	11 (57.9)	1 (20.0)	0	2 (33.3)	3 (25.0)	1 (14.3)
Diarrhoea	3 (30.0)	7 (36.8)	2 (40.0)	1 (14.3)	3 (50.0)	3 (25.0)	1 (14.3)
Nausea	9 (90.0)	11 (57.9)	4 (80.0)	3 (42.9)	3 (50.0)	11 (91.7)	6 (85.7)
Vomiting	4 (40.0)	2 (10.5)	2 (40.0)	3 (42.9)	1 (16.7)	5 (41.7)	1 (14.3)
General disorders and administration site conditions							
Chills	0	2 (10.5)	0	1 (14.3)	0	1 (8.3)	3 (42.9)
Fatigue	8 (80.0)	13 (68.4)	3 (60.0)	3 (42.9)	4 (66.7)	9 (75.0)	3 (42.9)
Oedema peripheral	1 (10.0)	11 (57.9)	0	2 (28.6)	2 (33.3)	1 (8.3)	2 (28.6)
Pyrexia	1 (10.0)	7 (36.8)	0	4 (57.1)	0	1 (8.3)	2 (28.6)
Investigations							
Alanine aminotransferase increased	2 (20.0)	0	1 (20.0)	4 (57.1)	1 (16.7)	1 (8.3)	2 (28.6)
Aspartate aminotransferase increased	1 (10.0)	0	0	3 (42.9)	0	1 (8.3)	2 (28.6)
Weight decreased	2 (20.0)	4 (21.1)	1 (20.0)	2 (28.6)	1 (16.7)	0	0
Metabolism and nutrition disorders							
Anorexia	4 (40.0)	4 (21.1)	1 (20.0)	3 (42.9)	3 (50.0)	5 (41.7)	1 (14.3)

Table S2 Summary of AEs occurring in at least 10% of patients overall by SOC and PT: Safety population

	N (%) of patients						
	Initial dose level (olaparib mg bd (days) / gemcitabine mg/m²)					Olaparib tablet mg od (days) / gemcitabine (mg/m²)	gemcitabine alone (mg/m²)
System Organ Class[a] Preferred Term[a,b,c]	**50(28) / 800**	**100(14) / 600**	**100(14) / 800**	**100(28) / 800**	**200(14) / 600**	**100(14) / 600**	**1000**
Number of patients	**10**	**19**	**5**	**7**	**6**	**12**	**7**
Musculoskeletal and connective tissue disorders							
Arthralgia	1 (10.0)	2 (10.5)	0	1 (14.3)	0	1 (8.3)	2 (28.6)
Back pain	0	4 (21.1)	1 (20.0)	1 (14.3)	2 (33.3)	3 (25.0)	0
Nervous system disorders							
Dizziness	1 (10.0)	2 (10.5)	0	3 (42.9)	1 (16.7)	0	0
Headache	1 (10.0)	2 (10.5)	1 (20.0)	0	1 (16.7)	2 (16.7)	1 (14.3)
Psychiatric disorders							
Insomnia	1 (10.0)	3 (15.8)	1 (20.0)	2 (28.6)	0	0	2 (28.6)
Respiratory, thoracic and mediastinal disorders							
Cough	1 (10.0)	4 (21.1)	0	2 (28.6)	1 (16.7)	0	1 (14.3)
Dyspnoea	1 (10.0)	6 (31.6)	1 (20.0)	3 (42.9)	2 (33.3)	3 (25.0)	0
Epistaxis	0	2 (10.5)	2 (40.0)	0	2 (33.3)	1 (8.3)	0
Skin and subcutaneous tissue disorders							
Rash	3 (30.0)	2 (10.5)	1 (20.0)	4 (57.1)	1 (16.7)	4 (33.3)	1 (14.3)
Vascular disorders							
Deep vein thrombosis	4 (40.0)	3 (15.8)	0	2 (28.6)	1 (16.7)	0	2 (28.6)

[a] MedDRA™ version 10.0
[b] Percentages were calculated using number of patients as the denominator.
[c] Patients with multiple events in a category were counted only once in that category. Patients with events in more than one category were counted once in each category. Includes AEs occurring post-treatment during the 30 day f/u..

Twenty-nine patients (44%) experienced SAEs during the study. The most common SAEs were: dyspnoea, abdominal pain, vomiting and DVT and were generally considered unrelated to the study medication.

Two patients died as a result of AEs. One patient died due to drug-related neutropenic sepsis and the other patient died due to renal failure, streptococcal bacteraemia and bacterial peritonitis, these events were also considered drug-related with the exception of the streptococcal bacteraemia.

There were no clinically important changes from baseline in any of the haematology or chemistry parameters following treatment with olaparib plus gemcitabine or gemcitabine alone.

There were no signals of potential drug induced liver injury; no patients had liver parameters which met “Hy’s Law” criteria.

Conclusion(s)