AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2281 (OLAPARIB)
Study Code	D0810L00001
Edition Number	Final Version 1
Date	06 September 2012
EudraCT Number	2008-007680-17

A Phase I, Open Label, Multicenter Study to Assess the Safety, Tolerability and Pharmacology of AZD2281 in Combination with Liposomal Doxorubicin (Caelyx®) in Patients with Advanced Solid Tumors

Study dates: First subject enrolled: 5 January 2009
Last subject last visit: 30 November 2011
Date of study early termination: Not applicable

Phase of development: I

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

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To determine the recommended dose (RD) of continuous twice daily oral doses of AZD2281 when administered in combination with liposomal doxorubicin (LD)	Incidence of dose limiting toxicities (DLTs) at cycle 1
Secondary	Pharmacokinetics	To investigate the pharmacokinetics (PK) of AZD2281	▪ maximum concentration in plasma (C_{max}) ▪ time to reach maximum concentration (t_{max}) ▪ area under the plasma concentration-time curve from 0 to 10 h after dosing (AUC_{0-10h}) ▪ minimum concentration in plasma (C_{min})
Secondary	Pharmacokinetics	To test two different schedules of administration of AZD2281: a) AZD2281 twice daily (bid) for 7 days out of a 28-day cycle b) AZD2281 bid continuously for 28 days	
Secondary	Pharmacokinetics	To investigate the PK interaction of AZD2281 with LD: exposure to AZD2281 when given alone or in combination with LD to be compared by assessment of appropriate derived PK parameters at cycle 1 in patients treated according to the 7-day schedule to identify any marked change when dosed alone or together with LD	The following PK variables derived from a single dose of AZD2281 given on day 1 of cycle 1 were to be compared with those calculated on day 2, when the single dose was administered with LD: ▪ C_{max} ▪ t_{max} ▪ AUC_{0-10h} ▪ minimum concentration in plasma (C_{min}) For LD only an inter-patient comparison was to be done to clarify any dose-dependent or schedule-dependent PK interference for the following parameters: ▪ C_{max} ▪ t_{max} ▪ area under the plasma concentration-time curve from 0 to infinity after dosing ($AUC_{0-infinity}$) ▪ volume in steady state (V_{ss}) ▪ total body clearance (Cl_{TB})

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Pharmacodynamics	To investigate the effects of the combination on DNA repair mechanisms by the determination, in isolated PBMCs, of histone H2AX phosphorylation	Histone H2AX phosphorylation levels in PBMCs, before and after treatment with AZD2281 and LD, on days 1, 8, 15, 28 of Cycle1

Study design

This was a Phase I, open label, multicenter, dose finding study to evaluate the safety, tolerability and pharmacokinetics of twice daily oral dosing with AZD2281 when administered in combination with LD at a fixed dose of 40 mg/m^2 every 28 days to patients with advanced solid tumours.

Dose Escalation Phase

A maximum of 7 dose cohorts of AZD2281 were foreseen: a Pilot Dose of 50 mg bid for 1 week in combination with LD 40 mg/m^2, followed by 6 dose levels of 100, 200 and 400 mg bid, each dose administered according to two dosing schedules:

a) 1 week dosing out of a 28-day cycle

b) 28 days continuous dosing

in combination with LD at a fixed dose of 40 mg/m^2.

A design of concerted escalation of dose and dosing duration was to be applied, according to which the shorter schedule (7 day-dosing) was to be tested first; if proven tolerable, the tolerability of the same dose given continuously for 28 days was to be assessed, while the tolerability of a higher dose given for 7 days was to be assessed concomitantly.

Toxicity was to be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. DLT was defined as the following effects considered related to the combination of AZD2281 and LD during cycle 1:

- Grade 4 thrombocytopenia
- Grade 4 neutropenia lasting >5 days
- Grade 3/4 febrile neutropenia
- Grade 3 or greater nausea and/or vomiting despite maximal anti emetic therapy
- Other CTCAE grade 3 or higher non haematological toxicities

A minimum of 3 patients was to be enrolled in each dose cohort. If 1 out of 3 patients experienced DLT the cohort was to be expanded up to 6 patients. If ≤ 1 DLT occurred in the same dose cohort out of 1 - 6 patients dose escalation could continue, while the Maximal Tolerated Dose (MTD) was considered to have been exceeded if ≥ 2 DLT in 6 or less patients had occurred, and the two lower cohorts were then to be expanded to confirm the RD.

Expansion Phase

The 2 cohorts below the MTD were to be expanded to a maximum of 12 patients, to confirm the RD.

Pharmacokinetics

In the 7-day cohorts only (including the Pilot Dose Cohort), the following dosing schedule was to be applied at cycle 1 for PK purposes: one AZD2281 dose on day 1 followed by AZD2281 twice daily from day 2 to day 8 and LD on day 2. PK sampling was to be performed to collect single dose data of AZD2281 alone and of both drugs when given in combination. A further one or two (for the 7-day and 28-day schedule, respectively) plasma samples were to be collected to provide a measure of multiple dose exposure to AZD2281 in combination with LD. In the 28-day cohorts (Cohorts 2, 4, 6) LD was to be administered on day 1 and AZD2281 bid was to be started on the same day. From cycle 2 onwards, LD was to be given on day 1 in all cohorts.

A full PK profile for AZD2281 and doxorubicin was to be taken for patients entering the expansion phase of the trial.

Target subject population and sample size

The main patient selection criteria were:

Age 18 years or older

Histologically or cytologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent

Eastern Cooperative Oncology Group (ECOG) Performance status (PS) 0 – 2

Adequate bone marrow, hepatic and renal function

No more than 3 prior lines of chemotherapy for advanced disease

Lack of resistance to anthracyclines, i.e., no disease progression within 6 months after last anthracycline dose

In each Dose Cohort, the DLT occurrence was to be assessed in a minimum of 3 and a maximum of 6 evaluable patients. A maximum of 12 patients were to be treated in the expanded cohorts for an adequate evaluation of the RD.

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

The investigational treatment tested in the study consisted of a combination of AZD2281 (olaparib) and liposomal doxorubicin (Caelyx®).

AZD2281 was supplied as an oral capsule in one dosage strength of 50 mg.

Commercial Caelyx® was provided in vials of 10 mL, containing 20 mg of doxorubicin hydrochloride in a pegylated liposomal formulation for intravenous infusion.

XX and YY batches of AZD2281 and Caelyx® (LD) were used in the study. All relevant batch numbers are listed in Appendix 12.1.6 of the Clinical Study Report.

Duration of treatment

The duration of AZD2281 and LD combination treatment was planned to be of 56 days (until the end of the second cycle), assuming patients did not meet any withdrawal criterion before that time. However, patients who showed an objective response or stable disease were allowed to continue combinational study treatment in the originally assigned cohort until they met a withdrawal criterion or until a maximum number of 6 cycles in total was reached. Thereafter, patients who, in the investigator's opinion, received some benefit from the therapy could continue with AZD2281 as monotherapy in the originally assigned cohort.

Statistical methods

Because of the study nature and design (non-comparative Phase I study, with RD determination as primary objective), no formal statistical analyses were planned, but descriptive statistics only were to be provided. Summary statistics were to be generated by Dose Cohort and, where appropriate, overall. All patients who received at least one dose of study drug were to be included in the summary statistics.

Subject population

Overall, 44 patients were enrolled from 3 centres in 2 Countries and were assigned to 7 Dose Cohorts as follows:

	Any Dose Cohort (N=44)	AZD50 x 7d (N=3)	AZD100 x 7d (N=3)	AZD100 x 28d (N=4)	AZD200 x 7d (N=3)	AZD200 x 28d (N=7)	AZD400 x 7d (N=12)	AZD400 x 28d (N=12)
	N	N	N	N	N	N	N	N
Enrolled	44	3	3	4	3	7	12	12
Treated	44	3	3	4	3	7	12	12
Evaluable for Safety	44	3	3	4	3	7	12	12
Evaluable for First Cycle DLT	42	3	3	3	3	6	12	12
Evaluable for Efficacy	42	3	3	3	3	6	12	12

Forty-one patients had discontinued the study treatment at the time of the cut-off date for the final analysis, i.e., 30 November 2011, while 3 patients enrolled in Dose Cohort 6 (AZD2281 400 mg bid x 28d) were still on treatment at that time, when all of them had already received 6 cycles of the combination, followed by 11, 7 and 5 cycles of AZD2281 single agent, respectively.

Summary of efficacy results

Tumour lesions evaluation was foreseen at baseline and every other cycle as part of the study plan to obtain a preliminary evaluation of the anti-tumour activity of AZD2281 in combination with LD. All efficacy variables are therefore described as secondary endpoints.

Objective responses (i.e., complete and partial responses) assessed according to RECIST criteria Version 1.0 were observed in all dose cohorts but Dose Cohort 2. Overall 14 objective responses were observed out of 42 patients evaluable for efficacy: 3 patients showed a complete response (CR) and 11 a partial response (PR), resulting in an overall response rate (ORR) of 33.3% (CI 95%: 19.6-49.6).

Ovarian cancer was the most frequent tumour type, affecting 28 study patients in total, of whom 26 were evaluable for efficacy and for 19 of them the BRCA1/2 mutation status was available. These patients were further classified based on their response to prior platinum-containing chemotherapy into Platinum-sensitive and Platinum-resistant (sensitivity was defined as a progression-free interval > 6 months since the end of the last platinum-containing regimen).

The overall analysis showed an ORR in ovarian cancer patients of 50%, with 3 out of 26 (11.5%) achieving a CR, while the analysis by subgroups showed an ORR in Platinum-sensitive and Platinum-resistant patients of 71.4% (CI 95%: 41.9-91.6) and 25% (CI 95%: 5.5-57.2), respectively. In addition, the ORR observed in the BRCA-positive group regardless of platinum-sensitivity was 61.1%, as compared to patients with negative or unknown BRCA mutation status, who showed a 25% ORR. Finally, the group of 12 patients characterized by Platinum-sensitivity and positive BRCA mutation status showed an ORR of 66.7%.

Nine out of the 13 responding ovarian cancer patients were treated in the last 2 dose cohorts (Dose Cohort 5 and 6) foreseeing an AZD2281 dose of 400 mg bid to be administered for 7 and 28 days, respectively. The highest ORR was observed at Dose Level 6 (AZD2281 400 mg bid x 28d) with 6/12 responding patients (50%), while the ORR in the 12 patients treated at Dose Level 5 (AZD2281 400 mg bid x 7d) was 25%.

Summary of pharmacokinetic results

PK of AZD2281 was evaluated in 20 patients treated with the 1-week schedule. In this group the comparison of PK parameters of single dose given alone (on day 1) or concomitantly with LD 40 mg/m^2 (on day 2) in the same patient was performed. PK of AZD2281 given twice daily was also analyzed in 23 patients treated with the continuous 28-day schedule.

The comparison of the main PK parameters of AZD2281 assessed following a single dose on day 1 (AZD2281 alone) with those achieved on day 2 (AZD2281 with LD 40 mg/m^2) at increasing doses, showed a trend to increment of $AUC_{0\text{-}10h}$, $AUC_{0\text{-}inf}$ and C_{max} and differences were statistically significant by a two-tailed paired Student t-test analysis at the dose of 400 mg (p=0.0097, p=0.0364 and p= 0.0023, respectively), while T_{max} and $T_{1/2(0\text{-}10h)}$ did not change between day 1 and day 2. The results of this PK analysis suggest that the observed increase in C_{max} and AUC on day 2 was most likely due to an effect of accumulation between the two successive doses rather than to an acute effect of LD on the pharmacokinetics of AZD2281 in the first 10 hours after administration.

In patients treated according to the continuous 28-day schedule and who took the experimental drug concomitantly with LD starting from day 1, the Steady-state level was reached on day 8 with the doses of 200 and 400 mg bid. The mean minimum concentrations (C_{min}) were similar: 3.14 µg/mL with 200 mg bid and 3.56 µg/mL with 400 mg bid, and were maintained until day 28 (3.20 and 3.92 µg/mL respectively). With the 100 mg bid dose, the mean C_{min} obtained on day 28 was 2.68 µg/mL. These observations suggest the presence of a mechanism of saturation of drug absorption.

In general, C_{max} and $AUC_{0\text{–}10h}$ in the presence of LD increased with increasing doses, therefore a lack of acute interference on the absorption and distribution of AZD2281 in the first 10 hours after administration can be assumed.

LD PK was evaluated in 37 patients. After the 1-hour infusion of 40 mg/m^2 LD, the means of the main PK parameters were C_{max} 34.2 µM, $t_{1/2}$ 78 hours, Vss 1.7 L/m^2 and CL TB 17.4 mL/h/m^2, all consistent with published data. In the 1-week schedule cohorts, the $AUC_{0\text{-}inf}$ showed a high inter-patient variability that was not present in the 28-day schedule cohorts. The differences in LD disposition observed with different doses and same AZD2281 schedule did not result statistically significant by one-way ANOVA analysis, while the comparison between the two AZD2281 schedules performed for each AZD2281 dose by two-tailed Student t-test showed a statistically significant difference at the AZD2281 dose of 400 mg bid, consisting of an increase in $AUC_{0\text{-}inf}$ and a reduction in CL_{TB} with the 28-day continuous schedule with respect to the 1-week schedule.

Summary of pharmacodynamic results

Flow cytometry data were obtained for 41 out of 44 patients and a decrease in H2AX phosphorylation in PBMCs was generally observed on day 8 and day 15, with both AZD2281 schedules and independently of AZD2281 dose. A transient, statistically significant (paired Student's t-test), downregulation of H2AX levels over baseline was observed after 8 and/or 15 days in Resistant ovarian cancer patients, both when receiving AZD2281 continuously for 28 days (day 15, p=0.036) and when receiving the drug for 1 week (day 8, p=0.037; day 15, p=0.046), while in the Sensitive group no variation in H2AX phosphorylation levels was detected, neither considering the entire 28-day cycle nor considering the first week of treatment only. In the overall population, CR, PR and SD appeared to be generally associated with decreased levels of H2AX phosphorylation during the first week of treatment, followed by a rebound to pre-treatment or higher values by day 28 of cycle 1, while in patients with PD as best overall response the decrease in phosphorylated H2AX appeared to be maintained without rebound. The same pattern of H2AX phosphorylation reduction on day 8 and 15 in patients achieving an objective response or disease stabilization, was particularly observed in the Resistant ovarian cancer subgroup, while in the Sensitive subgroup the level of H2AX phosphorylation was not substantially affected.

Summary of safety results

The median exposure to the combination of AZD2281 and LD was 4 cycles overall and ranged from 1 to 8 cycles. In addition, 14 patients received in total 73 cycles of AZD2281 single agent following LD discontinuation after a minimum of 4 cycles of the combination. The mean relative dose intensity was 85.9% overall and it was > 75% in all of the dose cohorts, with no significant differences between initial and subsequent cycles. The absolute dose intensity mean values increased almost proportionally within each dosing schedule along with dose levels escalation from 50 to 400 mg bid, suggesting that in general the number of missed doses was not greater at the higher dose levels as compared to the lower ones.

Stomatitis was overall the most prevalent treatment-related adverse event (32 patients, 72.7%), followed by nausea (28 patients, 63.6%) and asthenia (21 patients, 47.7%). Severe treatment-related AEs (CTCAE Grade ≥ 3) were reported in 23 patients in total (52.3%) and consisted of neutropenia (20.5%), stomatitis (15.9%), nausea (11.4%), anaemia and pneumonitis (6.8% each), fatigue, thrombocytopenia, leucopoenia, anorexia and dyspnoea (4.5% each), vomiting, asthenia, dizziness and tachypnoea (2.3% each). AEs were observed across all dose cohorts, with no apparent relationship with AZD2281 dose or schedule.

Four patients died on study and 8 further patients experienced non-fatal SAEs. In total 15 SAEs were reported in 12 patients, of which 7 were considered related to the study treatment and 6 led to study treatment withdrawal. No SAE report was completed for one of the patients who died because malignant disease progression was the cause of death and was therefore not to be reported according to the study protocol. Of the 5 patients experiencing treatment-related SAEs, 3 suffered from pneumonitis, resulting in death in 2 cases. The 2 remaining patients with treatment-related SAEs experienced grade 3 thrombocytopenia and grade 3 oesophagitis, both completely resolved.

Although the entire range of escalating doses/schedules planned by protocol was tested, the criteria for MTD were never met, as no more than 1 DLT per cohort was observed. For this reason the last 2 cohorts were expanded to include 12 patients each to compare the respective toxic and biological effects.

Two patients in total experienced first cycle drug-related DLTs:

- 1 out of 6 evaluable patients belonging to Dose Cohort 4 – AZD2281 400 mg bid x 28d developed fatal pneumonia and pneumonitis with worsening dyspnoea: the infectious pneumonia was considered related to both study drugs, while pneumonitis was attributed to AZD2281 only. The patient also suffered from grade 3 tachypnoea and stomatitis, both related to the study combination, which were still ongoing when patient died;
- 1 out of 12 evaluable patients in Dose Cohort 5 – AZD2281 400 mg bid x 7d experienced grade 4 thrombocytopenia, which was deemed to be due to both study drugs.

The RD was finally defined as AZD2281 400 mg bid x 28d / LD 40 mg/m^2, which tolerability was fully confirmed in the Expansion Phase of the study.