Clinical Study Report Synopsis

Drug Substance	ZD6474 (ZACTIMA)
Study Code	D4200L00003
Edition Number	Version 1
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Dose escalation study of the combination of ZD6474 and gemcitabine in locally advanced unresectable or metastatic pancreatic adenocarcinoma

Study dates: First subject enrolled: 14 July 2006
Last subject last visit: 02 June 2009

Phase of development: I

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

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary study objective was to define the maximum tolerated dose (MTD) and recommended dose (RD) of ZD6474 in combination with a fixed standard dose of gemcitabine, in patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma (PAC)	Primary endpoint was the occurrence of one or more dose limiting toxicities (DLTs). - DLT was defined as the occurrence of drug-related haematological toxicities (neutropenia Grade ≥ 3, lasting for more than 5 days, or Grade 4 neutropenia associated with fever, or Grade 4 thrombocytopenia, symptomatic thrombocytopenia, or bleeding) and/or Grade ≥ 3 non-haematological toxicities, with the exception of diarrhoea (DLT defined as Grade ≥ 2 diarrhoea) - The MTD of ZD6474 was defined as the dose at which ≥2 of 3 or ≥2 of 6 patients experienced a DLT at the first cycle - The RD was defined as the dose level immediately below the MTD	Safety
Secondary	**Secondary**	
Secondary study objectives were to determine the antitumour activity and to evaluate the safety profile of escalating doses of ZD6474 in combination with a fixed standard dose of gemcitabine	- Efficacy (objective tumour response) was to be evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST). Efficacy variables were defined as follows: *Overall response rate*, defined as the proportion of patients with complete response (CR) or partial response (PR); *Rate of controlled response*, defined as the proportion of patients with PR, CR or stable disease (SD); *Progression-free survival (PFS),* defined as the interval between the date of the first dose of study medication and the date of death or the date of progressive disease (PD); *Duration of response*, defined as the interval between the date of the first documented response and the date of death or the date of PD.	Efficacy
	- Safety was to be evaluated by assessing nature, incidence, severity and drug-relation of adverse events and serious adverse events (SAEs), incidence of and reasons withdrawal of study medication, drug exposure, physical examination findings, vital signs, ECG and laboratory tests.	Safety

Study design

The study was designed as a two-centre, open label, uncontrolled, Phase I trial, aimed at determining the MTD and RD of oral ZD6474 given at ascending doses (100 mg/day and 300 mg/day) in combination with gemcitabine in patients with unresectable locally advanced or metastatic PAC. Sequential cohorts of 3-6 patients each were to be enrolled at each dose level, until the MTD was achieved. Because of inadequate patient accrual, the study was prematurely terminated when a total of 15 patients had been enrolled.

Target subject population and sample size

Main inclusion criteria were: female and male patients, aged ≥18 years (negative pregnancy test for women of childbearing potential); histologically or cytologically confirmed diagnosis of PAC; measurable disease, according to RECIST; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2; adequate bone marrow reserve defined as white blood cells (WBC) $\geq 3.5 \times 10^9$/L, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and haemoglobin >10 g/dL; provision of informed consent. Main exclusion criteria were: serum bilirubin >1.5 x the upper normal limit (UNL); creatinine >1.5 x UNL or creatinine clearance $\leq$ 50 mL/min; potassium <4.0 mmol/L; calcium or magnesium out of normal range; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × UNL or alkaline phosphatase (ALP) >2.5 x UNL; history of clinically significant cardiac events or of arrhythmia or of QTc prolongation; congenital long QT syndrome; presence of left bundle branch block; corrected QTc ≥480 msec on screening electrocardiogram (ECG); any concomitant medication that may cause QTc prolongation; uncontrolled hypertension; active diarrhoea; current or previous malignancies within the last 5 years; any unresolved toxicity greater than CTCAE Grade 1 from previous anti-cancer therapy.

As this was a Phase I study, and patients were to be enrolled until occurrence of drug-related DLTs at the first cycle, the precise number of patients to enrol could not be anticipated. Depending on whether one or both planned dose levels of ZD6474 were investigated, it was assumed that a minimum of 6 up to a maximum of 18 patients would be enrolled in the trial.

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

The investigational treatment consisted of ZD6474, to be given by oral route at ascending doses (100 mg/day and 300 mg/day) in combination with gemcitabine. ZD6474 was to be given continuously, whereas gemcitabine (1000 mg/m^2 by iv infusion) was to be given on D1, D8, and D15 in a 28-day cycle. ZD6474 was provided by AstraZeneca AG as white film-coated tablets of 100 mg and 300 mg; Gemcitabine was supplied by AstraZeneca AG as the commercially available product (Gemzar®, Eli Lilly), provided as lyophilized powder in vials of 200 mg and 1000 mg, to be reconstituted with sterile 0.9% sodium chloride for injection without preservatives. Appendix 12.1.6 of the clinical study report details batches received by individual patients.

Duration of treatment

Treatment was to continue for sequential cycles, unless unacceptable toxicity, disease progression (PD) or patient consent withdrawal occurred.

Statistical methods

Because of the study nature and design, no formal statistical analyses were planned, but descriptive statistics only were to be provided by dose level and, where appropriate, overall. For the purpose of the analysis, three populations were considered. The "Safety" population was defined as all patients who received at least one dose of study medication (either ZD6474 or gemcitabine, or both). The "Efficacy evaluable" population was defined as all treated patients with no major deviations from the eligibility criteria, who completed at least two treatment cycles, and who had at least one post-treatment tumour assessment. The "DLT evaluable" population was defined as those patients fulfilling the Safety population criteria and having received at least one day of the combination therapy.

As compared with the study protocol, the statistical analysis plan (SAP) introduced a few additional efficacy endpoints and deleted other ones: as SAP was finalized before database closure, these changes were not interpreted as changes in the planned analysis. Duration of response (CR/PR) and duration of stable disease (CR/PR/SD) were to be analyzed as time-to-event variables, using the Kaplan-Meier method. Time to progression (TTP) was defined as the time interval between the date of the first administration of study medication and the date of documented disease progression. Overall survival (OS) was defined as the time interval between the date of the first administration of study medication and the date of death. Also TTP and OS were to be analysed as time-to-event variables, using the Kaplan-Meier method.

Treatment emergent adverse events were to be coded using the medical dictionary for regulatory activities (MedDRA) and graded using the National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) scale, and summarized by system organ class (SOC) and Primary Preferred Term (PPT). Treatment-related adverse events were those considered definitely, probably or possibly related to study drug. Patients reporting SAE were to be described, as well as patients reporting adverse events leading to study discontinuation, dose change, or treatment delay. First cycle drug-related DLTs were to be summarized by dose level. All laboratory data obtained from local laboratories were to be converted into standard units, graded according to CTCAE scale, classified with respect to baseline grade and worst grade during the study, and the worst grade per cycle considered for summary purposes. Results were to be summarized per cycle (cycle 1 and cycles >1) and overall. For neutrophils and platelets, also time to nadir, time to recovery (to 1.5 x 10^9/L for neutrophils, and to 150.0 x 10^9/L for platelets), and duration of absolute neutrophil count (ANC) < 0.5 x 10^9/L were to be calculated and summarised.

Subject population

The study was conducted as per protocol, the major change occurring in the study conduct being the premature study termination. Overall, 15 patients were enrolled in the 2 centres over a period of 14 months. The first 3 patients were assigned at the 100 mg/day dose level: since

no DLTs occurred, the next dose level (300 mg/day) was explored, which included a total of 12 patients, as 1 DLT out of the first 6 patients treated occurred. All patients enrolled received at least one cycle of study medication. At any dose level, ≥ 50% of patients received 2 or 3 cycles; minimum number of cycles received was 1 and maximum was 6. At the time of database closure, all patients were off study. Primary reason for treatment withdrawal were adverse events (9 cases, 6 of which considered drug-related), or disease progression (3 cases); other reasons were death in 1 case, and patient's request in 2 cases. The demographic and the other baseline characteristics of the patients enrolled in the study were as expected for a patient population with metastatic/advanced PAC. Concomitant medications used throughout the study were consistent with the primary disease and the other baseline disorders. In general, baseline characteristics did not show major variations in-between dose level cohorts; because of the large difference in the sample size of the two cohorts (3 *versus* 12 subjects), however, no meaningful comparison can be performed. All 15 patients enrolled were valuable for safety; all were valuable for 1st cycle DLT; 14 of them were valuable for efficacy (one patient in the 300 mg/day dose group was not valuable for efficacy because of absence of any post-treatment tumour assessment).

Summary of efficacy results

No patient in the study had an objective tumour response. Best overall response was SD in 11 patients (73.3%), and PD in 2 patients (13.3%). Response rate did not appear to differ in the two dose level groups, SD being reported in 66.7% and 75.0% of patients in the 100 and 300 mg/day cohorts respectively. Overall median TPP and its 95 % Confidence Interval (CI) was 4.4 months (CI 4.2, 5.7); overall median duration of SD was 4.9 months (CI 4.2, 7.6). The Kaplan-Meier estimates of OS rates were 73.3% at 6 months, 60.0% at 9 months, and 36% at 12 months. Median duration of OS was 9.5 months (CI 6.6, 14.5).

Summary of safety results

No patients experienced first cycle drug-related DLTs at the 100 mg/day dose level and 3/12 patients experienced DLTs at the 300 mg/day dose level, which consisted in 1 case of haematological toxicity (Grade 3 neutropenia lasting > 5 days), and in 2 cases of non-haematological toxicities, (Grade 3 increased ALP, AST and ALT in one case and Grade 3 aphasia in the other one).

All patients at all dose levels reported at least one adverse event. Severe adverse events (Grade ≥3) were reported in 10 patients, 8 at the 300 mg/day dose level. A total of 7 patients reported SAEs, 6 at the 300 mg/day dose level. One patient (100 mg/day) died on study during the 6th treatment cycle: death was not considered drug-related, but was attributed to progression of disease. All SAEs reported in the other 6 patients resolved. Most adverse events were considered related to study medication (13 patients, 10 at 300 mg/day); 9 patients had severe drug-related events, 7 at 300 mg/day; 4 patients at 300 mg/day had drug-related SAEs. A total of 11 patients (2 at 100 mg/day and 9 at 300 mg/day) had study medication discontinued because of adverse events.

Most frequently reported adverse events at all dose levels were gastrointestinal disorders (93.3%), followed by general disorders (73.3%), skin disorders and abnormalities in

investigations (60%), respiratory disorders (53.3%), metabolic disorders (46.7%), infections, nervous system and psychiatric disorders (26.7%). Most frequently reported abnormal investigations were increased ALT (33.33%), AST (26.67%), and ALP (20%). QTc prolongation and hypertension were infrequently reported, exclusively at the 300 mg/day dose level: there was one single occurrence (6.7%) of an asymptomatic QTc prolongation (Grade 3), and 2 occurrences of hypertension, both Grade 2.

Most frequently reported Grade ≥3 events were abnormal investigations (8 patients), followed by gastrointestinal events and general disorders (3 patients each); Grade ≥3 metabolism, nervous system, psychiatric and respiratory disorders were reported by 1 patient each. The large majority of these events had severity Grade 3: one single case of Grade 4 event occurred (vomiting in a patient at 300 mg/day). The overall frequency of severe events was no different between the two dose level groups, with the exception of Grade ≥3 abnormal value investigations which were higher at the 300 mg/day dose level.

Haematological toxicities were frequent but short-lasting and easily manageable by treatment interruption or dose delay. Haematological parameters mostly affected by study medication were WBC count and ANC. Grade ≥3 toxicities occurred in 8 patients for ANC (7 at 300 mg/day), 4 patients for WBC count (3 at 300 mg/day), and 1 patient for platelets (both at 300 mg/day). Blood chemistry parameters mostly affected by treatment were liver enzymes: one or more Grade 3 abnormalities were developed by a total of 8 patients (all at 300 mg/day), in most cases consisting in increased ALT and/or AST and/or ALP.