AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Zibotentan (ZD4054)
Study Code	D4320C00036
Edition Number	1
Date	20 December 2011

A Phase II, Double-blind, Placebo-controlled, Multi-centre, Randomised Study of ZD4054 plus Carboplatin and Paclitaxel or Placebo plus Carboplatin and Paclitaxel in Patients with Advanced Ovarian Cancer Sensitive to Platinum-based Chemotherapy

Study dates:

First subject enrolled: 26 June 2009
Last subject last visit (PRIMA): 01 June 2011
Data cut off: 29 May 2011

Phase of development:

Therapeutic exploratory (II)

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

Study centres

Patients were recruited from 39 centres in Germany (21) and Italy (18).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare PFS in patients treated with ZD4054 in combination with carboplatin+paclitaxel versus placebo in combination with carboplatin+paclitaxel	Time from randomisation until objective disease progression according to the response evaluation in solid tumours (RECIST) version 1.0 (RE1CIST2 and RE2CIST) Death (from any cause) in the absence of objective progression	Efficacy
Secondary	**Secondary**	
To compare OS in patients treated with ZD4054 in combination with carboplatin+paclitaxel versus placebo in combination with carboplatin+paclitaxel.a	The length of time from randomisation to death from any cause	Efficacy
To compare the objective tumour response rate in patients treated with ZD4054 in combination with carboplatin+paclitaxel versus placebo in combination with carboplatin+paclitaxel	Objective tumour response ((CR) and (PR)) as determined by RECIST criteria in patients with measurable disease at study entry	Efficacy
To investigate the safety and tolerability of ZD4054 given in combination with carboplatin+paclitaxel in patients with advanced ovarian cancer	AEs, vital signs, laboratory data, ECGs and physical examination assessments were to be collected and summarised, as described in Section 4.2.7 of the SAP. No formal statistical analyses were performed on these data.	Safety
To investigate the PK of ZD4054 as given in combination with carboplatin+paclitaxela	To obtain estimates of PK variables and quantify variability. A covariate analysis could be performed. Drug concentrations were determined using high-performance liquid chromatography with tandem mass-spectrometry (HPLC-MS-MS)	PK

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To explore the effect of adding ZD4054 to a chemotherapy regimen of carboplatin+paclitaxel on patients' health related quality of life (HRQoL)	As measured by the EORTC QLQ-CLC30 + OV28 questionnaire	HRQoL

[a] Not analysed as this study was terminated early.
Details of explorative objectives can be found in the CSR. Results from exploratory objectives investigating pharmacogenetics will be reported separately from this CSR
PFS Progression free survival; eCRF Electronic case record form; RECIST Response evaluation criteria in solid tumours; OS Overall survival; CR Complete response; PR Partial response; AEs Adverse events; ECG Electrocardiogram; SAP Satistical analysis plan; PK Pharmacokinetics; EORTC European organisation for research and treatment of cancer; QLQ Quality of life questionnaire; ULN ; Upper limit of normal

Study design

This was a randomised, double-blind, parallel-group, multi-centre, 2-arm, placebo-controlled Phase II study to assess the efficacy and safety of ZD4054 (10 mg) in combination with carboplatin/paclitaxel, compared with placebo in combination with carboplatin/paclitaxel in patients with advanced ovarian cancer sensitive to platinum based chemotherapy.

Patients were randomised in a 1:1 ratio to ZD4054 10 mg or matched placebo, stratified by country and platinum-free interval (6 to 12 months or > 12 months).

Target subject population and sample size

Patients with advanced disease not amenable to curative surgery or radiotherapy at the time of study entry with evidence of disease recurrence or progression at least 6 months following treatment cessation of first-line platinum-containing therapy and having stopped any maintenance therapy at least 30 days prior to first dose of treatment with study, were enrolled in the study.

The primary analysis was to be performed when 70 progression events had occurred to determine a true hazard ratio of 0.60 for ZD4054 versus placebo with 80% power. The nominal type I error rate used for the study was 20%; all statistical tests were performed at the 2-sided 20% significance level.

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

Blinded doses of oral ZD4054 10 mg (batch numbers 61729K08 and 71353H09) and matching placebo (51255J07 and 61024F08) were supplied by AstraZeneca and administered once daily orally.

Paclitaxel 175mg/m^2 administered as an intravenous (iv) infusion over approximately 3 hours on day 1 every 3 weeks. Carboplatin administered as an iv infusion (after paclitaxel) over approximately 30 to 60 minutes on day 1 every 3 weeks, consistent with a target AUC of 5.0 (derived using the Calvert Formula).

Duration of treatment

Patients were to receive up to 6 cycles of combination chemotherapy (paclitaxel and carboplatin in addition to ZD4054 10 mg or matching placebo); however, at the discretion of the investigator, patients could receive up to 8 cycles. Following completion of the chemotherapy regimen, patients were to continue receiving randomised trial therapy (ZD405410 mg or matching placebo) until study discontinuation and/or other withdrawal criteria were met.

Statistical methods

The statistical analysis was planned to be performed after 70 progression events had occurred on the full analysis set.

Progression Free Survival (PFS) was analysed using Cox proportional hazards models while objective response rate was analysed using logistic regression. These analyses included terms for treatment and the covariates country and platinum free interval (6-12 months; > 12 months).

Subject population

Patient disposition is summarised in Table S2 below. In total 132 patients were enrolled of whom 120 patients were randomised (59 and 61 patients in the ZD4054 10 mg and placebo groups, respectively). The mean age was 57 years and 99.2% patients were Caucasian. The study population was representative of the intended target population and both treatment groups were well balanced in terms of demographic and patient characteristics.

Table S2 Summary of patient disposition

Disposition	Number (%) of patients		
	ZD4054 10 mg	Placebo	Total
Patients enrolled [a]			132
Patients who failed screening			9
Patients who passed screening but were not randomised			3
Patients randomised	59 (100.0)	61 (100.0)	120 (100.0)
Full analysis set	59 (100.0)	61 (100.0)	120 (100.0)
Patients who received treatment	58 (98.3)	58 (95.1)	116 (96.7)
Patients who did not receive treatment	1 (1.7)	3 (4.9)	4 (3.3)

Table S2 Summary of patient disposition

Disposition	Number (%) of patients		
	ZD4054 10 mg	Placebo	Total
Patients currently ongoing [b]	11 (18.6)	19 (31.1)	30 (25.0)
Patients who discontinued ZD4054/Placebo	48 (81.4)	40 (65.6)	88 (73.3)
Adverse Event	8 (13.6)	5 (8.2)	13 (10.8)
Development of Study Specific Discontinuation Criteria	32 (54.2)	30 (49.2)	62 (51.7)
Voluntary Discontinuation by Subject	3 (5.1)	1 (1.6)	4 (3.3)
Other [c]	5 (8.5)	4 (6.6)	9 (7.5)
Patients who discontinued Carboplatin	59 (100.0)	57 (93.4)	116 (96.7)
Adverse Event	18 (30.5)	15 (24.6)	33 (27.5)
Development of Study Specific Discontinuation Criteria	7 (11.9)	5 (8.2)	12 (10.0)
Voluntary Discontinuation by Subject	3 (5.1)	1 (1.6)	4 (3.3)
Maximum Cycle of Chemotherapy Reached	8 (13.6)	15 (24.6)	23 (19.2)
Other [c]	23 (39.0)	21 (34.4)	44 (36.7)
Patients who discontinued Paclitaxel	59 (100.0)	57 (93.4)	116 (96.7)
Adverse Event	7 (11.9)	8 (13.1)	15 (12.5)
Development of Study Specific Discontinuation Criteria	9 (15.3)	6 (9.8)	15 (12.5)
Voluntary Discontinuation by Subject	2 (3.4)	1 (1.6)	3 (2.5)
Maximum Cycle of Chemotherapy Reached	14 (23.7)	19 (31.1)	33 (27.5)
Other [c]	27 (45.8)	23 (37.7)	50 (41.7)
Patients who terminated Study	19 (32.2)	8 (13.1)	27 (22.5)
Patients continuing on study off treatment [d] at data cut-off	30 (50.8)	34 (55.7)	64 (53.3)

a Informed consent received.
b Receiving treatment at the data cut-off.
c Any other reason not otherwise captured.
d May include patients that never received treatment.
Data cut off 29 May 2011;

Summary of efficacy results

No significant improvement in progression free survival was seen for patients receiving ZD4054 10 mg compared to placebo (HR = 1.46, 80% CI 1.10 to 1.94, p=0.0870; Table S3).

The analysis of PFS was generally consistent across the prognostic and geographic factors of age, country and platinum-free treatment interval.

Table S3 Analysis of progression-free survival (Full analysis set)

Group	N	Number (%) Events	Hazard Ratio	80%CI	2 sided p-value
ZD4054 10mg	59	45 (76.3)	1.46	1.10. 1.94	0.0870
Placebo	61	38 (62.3)			

The analysis was performed using a Cox proportional hazards model with factors for treatment, country and platinum-free interval.
A hazard ratio <1 indicates ZD4054 is associated with a longer time to progression than placebo.
Data cut-off 29 May 2011.

There was no significant improvement in the objective response rate in the ZD4054 10 mg group compared to placebo group (OR 0.43, 80% CI 0.26 to 0.71, p=0.0288).

There was no significant improvement in change in tumour size at week 9, health related quality of life (HRQoL). CA-125 progression or RECIST/CA-125 progression for patients receiving ZD4054 10 mg compared with those receiving placebo.

Summary of safety results

Median actual exposure, accounting for dose interruptions, was lower (6.59 months) in the ZD4054 10 mg group, compared to the placebo group (8.39 months). Total dose of chemotherapy received was also lower for patients on ZD4054 10 mg than those on placebo. There was no specific reason for the discrepancy in duration.

A summary of AEs in each category reported during the study is presented in Table S4 below. The number of patients experiencing at least 1 AE was comparable in both treatment groups. Overall safety and tolerability data appear consistent with the known profiles of ZD4054 and carboplatin/paclitaxel. Most of the commonly reported AEs in the ZD4054 10 mg group were pharmacologically mediated, principally anaemia, headache and peripheral oedema. Other AEs that were reported at a higher percentage in the ZD4054 10 mg group were neutropenia, leukopenia, mucosal inflammation and hypokalaemia, although these could be attributed to paclitaxel or carboplatin treatment as these are expected events with these treatments, as documented in the prescribing information. Dyspnoea and drug hypersensitivity were also commonly reported in the ZD4054 10 mg group, although none of the cases events were considered to be related to ZD4054 as assessed by the investigator. There were no AEs of cardiac failure in this study. Most commonly reported AEs of CTCAE grade 3 or higher (neutropenia, anaemia and leukopenia) are known to be commonly associated with paclitaxel treatment.

In total, there were 21 (18.1%) deaths, of which the majority (20 [17.2%]) were due to ovarian cancer. One patient in the ZD4054 10 mg group died due to pulmonary embolism 16 weeks after the study treatment had stopped. Number of patients experiencing SAE was slightly

higher (19 [32.8%]) in the ZD4054 10 mg group compared to the placebo group (13 [22.4%]). The most commonly reported SAE (abdominal pain and subileus) were likely to be due to underlying disease. Discontinuation due to AEs were similar in both groups, with headache as the most common reason.

Decreases in mean Hb levels were slightly higher in the ZD4054 10 mg group. These reductions in Hb were early in onset, non-progressive and returned to baseline by week 39. Consistent with these findings, anaemia was reported as an AE at a higher frequency in the patients on ZD4054 compared with placebo (28 [48.3%] vs 23 [39.7%]. This reduction in Hb levels is likely to be due to haemodilution as a consequence of the vasodilatory effect of ZD4054. Neutropenia (25 [43.1%] and 22 [37.9%]); and leukopenia (20 [34.5%] and 15 [25.9%]); were commonly reported AEs for patients on ZD4054 10 mg and placebo, respectively. None of these events were considered to be serious or resulted in discontinuation of the study treatment.

Small asymptomatic decreases from baseline in mean systolic and diastolic blood pressures were observed in the ZD4054 10 mg group, with no accompanying increases in pulse rate. As these were evident at Week 3, after the start of dosing and sustained during treatment, this suggests that they are a consequence of the vasodilatory effect of ZD4054 10 mg.

The safety and tolerability of ZD4054 was consistent with that seen previously for CRPC patients and as detailed in the Investigator's Brochure.

Table S4 Summary of number (%) of patients who had at least one AE in any category

	Number (%) of patients [a]		
	ZD4054 10 mg (N=58)	**Placebo (N=58)**	**Total (N=116)**
AE category			
Any AE	57 (98.3)	58 (100.0)	115 (99.1)
Any AE causally related to ZD4054/placebo [b]	38 (65.5)	25 (43.1)	63 (54.3)
Any AE of CTCAE grade 3 or higher	46 (79.3)	29 (50.0)	75 (64.7)
Any AE of CTCAE grade 3 or higher, causally related to ZD4054/placebo [b]	8 (13.8)	2 (3.4)	10 (8.6)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)
Any AE with outcome = death, causally related to ZD4054/placebo [b]	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	19 (32.8)	13 (22.4)	32 (27.6)
Any SAE (including events with outcome = death), causally related to ZD4054/placebo [b]	1 (1.7)	1 (1.7)	2 (1.7)
Any SAE with outcome other than death [c]	19 (32.8)	13 (22.4)	32 (27.6)

Table S4 Summary of number (%) of patients who had at least one AE in any category

	Number (%) of patients [a]		
	ZD4054 10 mg (N=58)	**Placebo (N=58)**	**Total (N=116)**
AE category			
Any SAE causing discontinuation of IP	3 (5.2)	3 (5.2)	6 (5.2)
Any SAE causing discontinuation of IP, causally related to ZD4054/placebo [b]	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to discontinuation of IP	8 (13.8)	6 (10.3)	14 (12.1)
Any AE leading to discontinuation of IP, causally related to ZD4054/placebo [b]	4 (6.9)	2 (3.4)	6 (5.2)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the investigator.
C All patients who had an SAE with a non-fatal outcome (regardless if they later had a fatal SAE)
Includes adverse events with an onset date between the date of first dose and 28 days following the date of last dose of study medication.
Data cut off 29 May 2011