Clinical Study Report Synopsis

Drug Substance	Saracatinib
Study Code	D8180C00015
Edition Number	Draft 1
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A Phase II, Double-blind, Placebo-controlled, Multi-centre, Randomised Study of Saracatinib (AZD0530) in Patients with Advanced Ovarian Cancer Sensitive to Platinum-based Chemotherapy (OVERT-1)

Study dates:

First subject enrolled: 18 April 2008
Last subject last visit: 17 March 2009
Analysis data cut off: 31 January 2010

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 enrolled from 58 sites in 12 countries (Bulgaria, Canada, Denmark, France, Netherlands, Norway, Peru, Portugal, Romania, Russia, Spain and UK).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary, secondary and exploratory objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the objective tumour response rate, as evaluated according to RECIST guidelines, in patients treated with saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	Objective response rate as evaluated by RECIST.	Efficacy
Secondary	**Secondary**	
To investigate the safety and tolerability of saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	Incidence, maximum CTCAE grade and type of AEs, HRCT scans, clinically significant laboratory abnormalities and changes in vital signs and ECG changes.	Safety
To compare PFS in patients treated with saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	PFS as evaluated by RECIST (including death by any cause in the absence of RECIST progression).	Efficacy
To estimate OS in patients treated with saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	OS	Efficacy
To investigate the steady-state PK of saracatinib and the N-desmethyl metabolite (M594347) in combination with carboplatin plus paclitaxel.	Saracatinib: Css_{min}, Css_{max}, AUCss and CLss/F. N-desmethyl metabolite: Css_{min}, Css_{max}, AUCss and metabolite:saracatinib ratio.	PK
To measure plasma concentrations of total platinum 24 hours after administration of carboplatin to enable the estimation of carboplatin AUC.	Estimated AUC of carboplatin.	PK
Exploratory[a]	**Exploratory**	
To compare the percentage change in tumour size in RECIST-measurable patients treated with saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	Longest diameter (cm) as measured by RECIST.	Efficacy

Objectives	Outcome variables	Type
To compare time to CA-125 progression in patients treated with saracatinib in combination with carboplatin plus paclitaxel versus carboplatin plus paclitaxel alone.	CA-125 level (kU/L) as measured by central laboratory.	Efficacy

a Other exploratory variables were defined in the clinical study protocol, but are not reported in this clinical study report.

AE = adverse event, AUC = area under the plasma concentration-time curve from zero to infinity, AUCss = area under the plasma concentration-time curve at steady state, CA-125 = cancer antigen 125, CLss/F = plasma clearance at steady state, Css_{max} = maximum plasma concentration at steady-state, Css_{min} = minimum plasma concentration at steady-state, CTCAE = Common Terminology Criteria for Adverse Events version 3.0, ECG = electrocardiogram, HRCT = high resolution computed tomography, OS = overall survival, PFS = progression-free survival, PK = pharmacokinetics, RECIST = response evaluation criteria in solid tumours.

Study design

This was a Phase II, double-blind, placebo-controlled, multi centre, randomised study comparing the objective tumour response rate obtained with saracatinib in combination with carboplatin plus paclitaxel therapy to that obtained by carboplatin in combination with paclitaxel. Patients were randomised (1:1) to receive:

1. Saracatinib 175 mg once daily (od)[1] administered orally in combination with carboplatin and paclitaxel, or

2. Saracatinib matching placebo od administered orally in combination with carboplatin and paclitaxel.

Target subject population and sample size

Female patients 18 years and older with histologically proven diagnosis of advanced, evaluable ovarian cancer, not amenable to curative surgery or radiotherapy at the time of study entry. Radiological evidence of disease recurrence or progression at least 6 months following treatment cessation of first- or second-line platinum containing therapy (including platinum-based maintenance therapy).

This study was sized based on the primary outcome variable of objective response rate (ORR). Assuming a 45% response rate in the placebo arm, and a 65% response rate in the saracatinib arm, 55 patients were needed in each arm to demonstrate a difference between treatment arms with 80% power and a 1-sided type I error of 10%. It was expected that approximately 60% of patients would have measurable disease; therefore, approximately 200 patients were to be randomised in order to attain at least 110 randomised patients with measurable disease.

[1] An initial cohort of patients randomised to the study received saracatinib 125 mg, prior to saracatinib 175 mg being deemed tolerable in combination with carboplatin plus paclitaxel in a phase I dose escalation study (D8180C00023).

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

Saracatinib (AZD0530) and matching placebo tablets for oral administration were manufactured and supplied by AstraZeneca. Batch numbers were as follows: saracatinib 50 mg tablets: 41127F06, 43536D06, ST76108-001-FA01; saracatinib 125 mg tablets: 41129K06, 43538I06, 43537A06, ST76109-001-FA01; placebo 50 mg tablets: FC33314B05; placebo 125 mg tablets: 33315J05, ST76111-001-FA01, ST76110-001-FA01.

Paclitaxel 175 mg/m^2, from commercially available supplies, was administered intravenously on day 1 every 3 weeks. Carboplatin, from commercially available supplies, was administered intravenously over 30 to 60 minutes on day 1 (after paclitaxel) every 3 weeks, consistent with a target area under the plasma concentration-time curve (AUC) of 6.0 mg/mL/min.

Duration of treatment

Up to 8 cycles of chemotherapy, in combination with either saracatinib or matching placebo, were allowed. Following completion of chemotherapy, patients continued to receive monotherapy with saracatinib or matching placebo until objective radiological disease progression, unacceptable toxicity or other specific discontinuation criteria were met. A 3-week schedule defined a cycle of chemotherapy treatment and multiple cycles were administered.

Statistical methods

ORR was analysed using logistic regression, including terms for randomised treatment and stratification variables (prior lines of platinum-containing treatment [1 or 2 lines] and platinum treatment-free interval [6-12 months or >12 months]). PFS was analysed using a Cox proportional hazard model including terms for randomised treatment and the same stratification variables.

Analysis of efficacy was conducted when a minimum of 78 PFS events had occurred (78-event analysis); the cut-off for this analysis was 31 August 2009. An updated estimate of efficacy with a cut-off of 31 January 2010 was done.

Subject population

A total of 211 patients (saracatinib 175 mg: 96 patients; matching placebo 175 mg: 93 patients; saracatinib 125 mg: 9 patients; matching placebo 125 mg: 13 patients) were enrolled and randomised from 58 centres in 12 countries. As of the data cut-off of 31 January 2010, 181 patients had discontinued investigational product and 50 patients had discontinued from the study. All 211 patients were included in the safety analysis set. At both data cut-off dates, there were 175 patients with measurable disease in the 175 mg arms (saracatinib 175 mg arm: 88; matching placebo: 87).

Demographic characteristics were generally balanced across the 2 treatment groups. However, there was a slight excess of patients with poor prognostic indicators on the

saracatinib 175 mg arm, compared with the matching placebo arm, respectively, with respect to WHO Performance Status 2 category (4% versus 0%), more than 2 prior chemotherapies (8% versus 4%) and clear cell and mucinous histologies (7% versus 2%). Overall, approximately 40% of patients had a platinum treatment-free interval of 6-12 months prior to study entry, and approximately 60% had a platinum treatment-free interval of >12 months prior to study entry, with general balance between treatment arms.

Summary of efficacy results

- At the 78-event analysis, there was no statistically significant difference between saracatinib 175 mg and matching placebo for ORR in the overall population (odds ratio 0.914; 95% CI: 0.500, 1.672; p=0.7708). Objective tumour responses were achieved for 53% of patients in the saracatinib 175 mg arm and 52% of patients in the matching placebo arm. An updated estimate of ORR (data cut-off 31 January 2010) was consistent with the 78-event analysis.

- At the 78-event analysis, there was no statistically significant difference between saracatinib 175 mg and matching placebo for PFS in the overall population (hazard ratio 0.9946; 95% CI: 0.65, 1.51; p=0.9797); median PFS was 8.3 months for the saracatinib 175 mg arm and 7.8 months for matching placebo. An updated estimate of PFS (data cut-off 31 January 2010) when 136 PFS events had been reported was consistent with the 78-event analysis.

- At the 78-event analysis, there were few deaths and an analysis of overall survival was not done. At data cut-off of 31 January 2010, data were still immature (26 deaths in 175 mg arms: 12 in the saracatinib arm and 14 in the matching placebo arm; 14% maturity). Median overall survival was not reached for this population, but there was no apparent detriment between saracatinib and placebo.

Summary of pharmacokinetic results

A sparse sampling regime was employed in the study for determination of saracatinib plasma concentrations and these were utilised to derive steady state PK parameters using population PK methods. The primary PK parameters for saracatinib and the N-desmethyl metabolite in the presence of carboplatin and paclitaxel at steady state are summarised in Table S1.

Table S1 Summary of PK parameters for saracatinib and N-desmethyl metabolite at steady state

Parameter	Summary statistic	Saracatinib 125 mg + C+P	Saracatinib 175 mg + C+P
n		7	71
AUC_{ss} (ng.h/mL)	Gmean (range)	4492 (3720 to 5580)	5261 (1720 to 15500)
$C_{ss,max}$ (ng/mL)	Gmean (range)	215 (168 to 258)	249 (97.0 to 697)
Metabolite:parent AUC_{ss} ratio	Gmean (range)	0.208 (0.135 to 0.236)	0.221 (0.119 to 0.422)

C=carboplatin; P=paclitaxel; n = number of patients with reportable PK parameters; Gmean = geometric mean.

In order to confirm that the target carboplatin AUC of 6.0 mg/mL/min (AUC6) was achieved, a single blood sample was taken 24 hours after carboplatin administration for determination of total platinum concentration from which an estimate of carboplatin AUC could be made. The estimated carboplatin AUC data are summarised in Table S2. For all treatments the geometric mean AUC was 8 to 15% higher than the targeted AUC at chemotherapy Cycle 1 and 60 to 71% higher at chemotherapy Cycle 3. Variability was high with estimated AUCs ranging from 1.34 to 23.9 mg/mL/min at Cycle 1 and from 0.661 to 98.3 mg/mL/min at Cycle 3.

Table S2 Summary of carboplatin AUC (mg/mL/min) by visit

Visit	Summary statistic	Saracatinib 125 mg + C+P	Saracatinib 175 mg + C+P	Placebo 125 mg + C+P	Placebo 175 mg + C+P
Visit 2	n	7	60	8	65
(cycle 1)	Gmean	6.93	6.53	6.68	6.50
	Range	(2.90 to 13.3)	(1.34 to 16.8)	(5.42 to 9.07)	(1.62 to 23.9)
Visit 4	n	4	45	8	52
(cycle 3)	Gmean	10.3	9.64	10.03	9.58
	Range	(5.46 to 15.7)	(4.50 to 98.3)	(1.97 to 85.4)	(0.661 to 89.7)

C=carboplatin; P=paclitaxel; n = number of patients with reportable PK parameters; Gmean = geometric mean.

Summary of safety results

- The majority of patients in each arm reported at least 1 AE during the study (97% in the saracatinib 175 mg arm and 99% in the matching placebo arm). The majority of events were CTCAE grade 1 or 2.

- The administration of saracatinib in combination with carboplatin and paclitaxel resulted in additional AEs compared to placebo in combination with carboplatin and paclitaxel. The additional AEs were reported during the combination period, and were mainly gastrointestinal and haematological AEs.

- Reporting of AEs was balanced between saracatinib and placebo arms during the monotherapy maintenance period, after completion of carboplatin or paclitaxel chemotherapy.

- The most frequently reported AEs (≥30% of patients) in the saracatinib 175 mg arm and matching placebo arm, respectively, were nausea (66% versus 57%), alopecia (53% versus 62%), diarrhoea (44% versus 34%), vomiting (42% versus 37%), neutropenia (41% versus 34%), fatigue (39% versus 42%), anaemia (36% versus 32%), decreased appetite (33% versus 22%), asthenia (32% versus 26%) and constipation (29% versus 30%).

- AEs reported more frequently (≥8% difference) in the saracatinib 175 mg arm than the matching placebo arm, respectively, were nausea (66% versus 57%), diarrhoea (44% versus 34%), decreased appetite (33% versus 22%), pyrexia (25% versus 9%), febrile neutropenia (including one patient in each of the 175 mg arms with a reported term of febrile bone marrow aplasia) (23% versus 3%) and hypokalaemia (10% versus 1%).

- AEs reported more frequently (≥8% difference) in the matching placebo arm than the saracatinib 175 mg arm, respectively, were alopecia (62% versus 53%), drug hypersensitivity (27% versus 18%), myalgia (26% versus 17%), dyspnoea (17% versus 9%), back pain (13% versus 5%), anxiety (12% versus 1%) and bone pain (9% versus 0%).

- There were no differences in the incidence of deaths between the saracatinib 175 mg and matching placebo arms (12 patients versus 14 patients, respectively); the majority of deaths were due to disease progression or worsening. There were 4 SAEs with an outcome of death, all in the saracatinib 175 mg arm (intestinal obstruction [2 cases], paraneoplastic syndrome and acute respiratory distress syndrome). One of these fatal SAEs was considered by the investigator to be related to investigational product (acute respiratory distress syndrome).

- SAEs were reported more frequently in the saracatinib 175 mg arm than the matching placebo arm (45% versus 26%, respectively); the greatest imbalance was seen for febrile neutropenia (16% versus 3%, respectively). Other SAEs reported more frequently in the saracatinib 175 mg arm than the matching placebo arm, respectively, were pyrexia (4% versus 1%), thrombocytopenia (3% versus 0%), ileus (3% versus 0%), vomiting (3% versus 0%), anaemia (2% versus 0%), asthenia (2% versus 0%) and intestinal obstruction (2% versus 0%).

- Discontinuation of investigational product due to AEs was balanced between saracatinib 175 mg and matching placebo arms (19% versus 17%, respectively). A larger proportion of patients in the saracatinib 175 mg arm than the matching placebo arm had a dose reduction due to AEs (20% versus 6%, respectively). The majority of AEs were manageable without discontinuation or dose modification.

- AEs of CTCAE grade ≥3 were reported for 80% of patients in the saracatinib 175 mg arm and 73% of patients in the placebo arm. The most common AEs of CTCAE grade ≥3 in the saracatinib 175 mg arm versus the matching placebo arm, respectively, were neutropenia (31% versus 24%), febrile neutropenia (20% versus 3%), thrombocytopenia (13% versus 9%) and anaemia (10% versus 8%).

- All events consistent with febrile neutropenia (23% versus 3% in saracatinib 175 mg and matching placebo arms, respectively) occurred during the combination period. Events of febrile neutropenia were predominantly reported at CTCAE grade ≥3 (20% versus 3%, respectively) and the majority were considered to be SAEs

(16% versus 3%, respectively). The events of febrile neutropenia occurred during the first cycle of chemotherapy in the majority of patients and resolved in all patients. One episode of febrile neutropenia resulted in discontinuation of saracatinib 175 mg. Two patients had concurrent infections (nasopharyngitis and recurrence of a urinary tract infection), but most events of febrile neutropenia were not associated with events of infection. There were no complications of renal failure, multisystem failure or fatalities.

- More patients in the saracatinib 175 mg arm than the matching placebo arm had reductions in haematological parameters (45% versus 26% for neutrophils of CTCAE grade ≥3; 34% versus 22% for lymphocytes of CTCAE grade ≥2; 16% versus 8% for platelets of CTCAE grade ≥3; 44% versus 37% for haemoglobin of CTCAE grade ≥2, respectively). These changes generally occurred during the first or second month of treatment. No differences in discontinuations for haematological parameters were observed between the study arms and there were no fatal haematological AEs.

- In the saracatinib 175 mg arm compared with the matching placebo arm, there were more CTCAE grade 3 events of hypokalaemia (7% versus 2%, respectively), more reductions in serum sodium levels below the lower limit of normal (mostly CTCAE grade 1) (35% versus 10%, respectively), mild increases in creatinine and mild increases in liver transaminases. Episodes of hypokalaemia and mild reductions in serum sodium levels occurred predominantly during the combination period.

- No clinically significant changes in vital signs or ECGs were observed.

- Radiological changes suggestive of interstitial lung disease (ILD) were reported for 2 patients in the saracatinib 175 mg arm and 1 patient in the matching placebo arm. For all 3 of these patients, there was evidence of some reversibility following cessation (2 patients) or interruption (1 patient) of investigational product and treatments directed at multiple aetiologies, with investigators reporting no changes suggestive of ILD on subsequent HRCT scans.