AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00006
Edition Number	1
EudraCT Number	2011-005194-23

A Phase IIa, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Pharmacokinetics of AZD8931 in Combination with Paclitaxel Versus Paclitaxel Alone in Patients with Metastatic, Gastric or Gastro-Oesophageal Junction Cancer Who Progress Following First-Line Therapy and Are Ineligible for Treatment with Trastuzumab by HER2 Status (SAGE)

Study dates: First patient enrolled: 19 April 2012
Last patient last visit: 20 March 2013

Phase of development: Therapeutic exploratory (IIa)

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.

Closure of AZD8931 studies

The report of this study is in a synopsis format because AstraZeneca development of AZD8931 has been permanently stopped.

Objectives and criteria for evaluation

Objectives and outcome variables are described in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the relative efficacy of AZD8931 plus paclitaxel compared with paclitaxel alone by comparison of the change in tumour size at 8 weeks	Change in tumour size at 8 weeks
Secondary[a]	Efficacy	To assess the relative efficacy of AZD8931 plus paclitaxel compared with paclitaxel alone by assessment of PFS	PFS: Time from the date of randomisation until the date of objective disease progression (as per RECIST 1.1) or the date of death (by any cause in the absence of progression)
Secondary	Efficacy	To investigate the efficacy of AZD8931 plus paclitaxel compared with paclitaxel alone by assessment of ORR	ORR: The number (%) of patients who had at least 1 visit response of CR or PR (as defined by RECIST 1.1)
Secondary[a]	Efficacy	To assess the efficacy of AZD8931 plus paclitaxel compared with paclitaxel alone by assessment of the percentage of patients without progressive disease (ie, patients with CR, PR, or SD) at 8 weeks	The proportion of patients without progressive disease at 8 weeks as the percentage of patients with an 8-week visit response of CR, PR, or SD (as defined by RECIST 1.1) with no evidence of previous progression
Secondary[a]	Efficacy	To assess the efficacy of AZD8931 plus paclitaxel compared with paclitaxel alone by assessment of OS	OS: The time from randomisation to date of death by any cause
Secondary	Safety	To compare and assess the safety and tolerability of AZD8931 plus paclitaxel compared with paclitaxel alone	AEs, physical examination, cardiac monitoring (including 12-lead ECGs and echocardiography/MUGA), laboratory assessments (clinical chemistry and haematology), and clinically significant abnormalities detected in ophthalmic assessment

Table S1 Objectives and outcome variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Secondary	PK	To investigate the PK of AZD8931 and AZD8931 O-desmethyl metabolite in a metastatic, gastric or gastro-oesophageal junction cancer patient population	Plasma concentrations of AZD8931 (AUC_{ss}, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, CL_{ss}/F, and t_{last}) and AZD8931 O-desmethyl metabolite (AUC_{0-t}, C_{max}, t_{max}, and AUC_{0-t} metobolite:parent ratio)
Secondary[a]	Efficacy	To explore the relationship between patient response to AZD8931 and the baseline (pre-treatment) tumour status of HER hetero/homodimer pairs	Patient response to AZD8931
Secondary[a]	Efficacy	To explore the relationship between patient response to AZD8931 and the baseline (pre-treatment) tumour status of the HER2 and HER3 receptor	Patient response to AZD8931

[a] Due to early termination of the study, insufficient data was available and hence this analysis was not performed. Exploratory objectives are not a part of this CSR.

AEs Adverse events; AUC_{0-t} Area under the concentration-time curve up to the last quantifiable sample; AUC_{ss} Area under the concentration-time curve across the dosing interval; CL_{ss}/F Apparent clearance following multiple dosing; C_{max} Maximum plasma concentration; CR Complete response; CSR Clinical Study Report; $C_{ss,max}$ Maximum plasma concentration at steady state; $C_{ss,min}$ Minimum plasma concentration at steady state; ECG Electrocardiogram; HER Human epidermal growth factor receptor type; HER2 Human epidermal growth factor receptor type 2; HER3 Human epidermal growth factor receptor type 3; MUGA Multiple uptake gated acquisition; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics; PR Partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD Stable disease; t_{last} Time to the last quantifiable plasma concentration; t_{max} Time to maximum plasma concentration; $t_{ss,max}$ Time to maximum concentration at steady state.

Study design

This was a randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy, safety, and pharmacokinetics (PK) of AZD8931 in combination with paclitaxel versus paclitaxel alone in patients with metastatic, gastric or gastro-oesophageal junction cancer.

Eligible patients were stratified according to human epidermal growth factor receptor type 2 (HER2) status (per local standard testing) as HER2 immunohistochemistry (IHC) 0 or HER2 IHC 1+/2+. These patients were randomised in a 1:1 ratio to receive:

- AZD8931 40 mg twice daily (bd) orally in combination with paclitaxel or
- AZD8931 matching placebo bd orally in combination with paclitaxel.

Patients were to have received weekly paclitaxel (3 weeks on, 1 week off therapy) in addition to oral AZD8931/placebo bd until disease progression was determined according to Response

Evaluation Criteria in Solid Tumours (RECIST 1.1) or until any study withdrawal criterion was met.

Tumour assessment was performed at 8 weeks and patients were to have been followed for the assessment of progression-free survival (PFS) and overall survival (OS).

Target subject population and sample size

Male or female patients aged ≥18 years (≥20 years in Japan) with metastatic, gastric adenocarcinoma (including adenocarcinoma of the gastro-oesophageal junction), that had progressed (confirmed radiologically) following first-line fluoropyrimidine and platinum-based chemotherapeutic regimen, and who were ineligible for treatment with trastuzumab, were enrolled in the study.

Sixty patients were planned to be enrolled in the study. At a 1-sided significance level of 10%, this study was expected to have 90% power to detect a -20% difference in the estimated average percentage change in tumour size at 8 weeks for AZD8931 in combination with paclitaxel compared with paclitaxel alone. This was based on a standard deviation of 30% for tumour data (on an absolute scale) that was estimated from AstraZeneca's historical data. A difference of -10% or more between the randomised treatment groups was to be considered as statistically significant at the 1-sided 10% level. PFS was planned to be analysed when approximately 42 PFS events had occurred. This was expected to provide >80% power to detect a hazard ratio of 0.5 with the 1-sided 10% significance level. However, because of an early termination, 25 patients were randomised at the time of the statistical analysis and therefore the study had approximately 65% power to assess the primary objective. Also, PFS data were planned to be analysed after if at least 10 PFS events had occurred in each treatment group. The PFS data were not sufficient to perform a PFS analysis. The secondary objective of OS was not assessed due to insufficient data.

Investigational product and comparator: Dosage, mode of administration, and batch numbers

AstraZeneca supplied AZD8931 and matching placebo as plain, beige film coated, biconvex round tablets to the investigational sites.

Two batches of AZD8931 20 mg and 2 batches of ADZ8931 40 mg, along with 4 batches of the matching placebo, were used in the study. Individual batch numbers and further information are provided in the clinical study report appendix.

AZD8931 40 mg or the matched placebo tablet was administered orally bd (approximately 12 hours apart) on every day of each 28-day cycle.

Paclitaxel was sourced locally as the background medication and administered as a 1 hour intravenous infusion of 80 mg/m^2 weekly on Days 1, 8, and 15 of a 28-day cycle.

Duration of treatment

Patients received paclitaxel treatment in addition to AZD8931/placebo until objective disease progression as determined by RECIST 1.1. The patients were planned to continue to receive AZD8931/placebo if, in the investigator's/delegate's opinion, they were benefiting from treatment or until any study withdrawal criterion was met. However, all patients were withdrawn from treatment on early termination of the study.

Statistical methods

The primary outcome variable was the effect of AZD8931 on change in tumour size at 8 weeks. This was estimated from the analysis of covariance (ANCOVA) model with the following covariates: Baseline tumour size, time from the baseline scan to randomisation, and HER2 status. The secondary variable, PFS, was planned to be analysed using the Cox proportional hazards model including covariates for baseline tumour size for the time from the baseline scan to randomisation and with a term for HER2 status, but this analysis was not performed since the PFS events were <10 for each treatment group. For objective response rate (ORR), summaries of best overall response and best response at 8 weeks were presented as number and percentage of patients in each treatment group for each category.

The full analysis set was the primary set used for the efficacy analyses. The full analysis set included all randomised patients, regardless of whether they took study medication or not. The safety analysis set included all patients who received at least 1 dose of AZD8931/placebo. The PK analysis set included all randomised patients with reportable plasma concentrations and PK parameters for AZD8931 and who had no important adverse events (AEs) or protocol deviations that could impact PK.

The plasma concentrations of AZD8931 and AZD8931 O-desmethyl metabolite were listed for all patients in the safety analysis set who had provided samples. The plasma concentration and PK parameter data were summarised overall and by gastric surgery type using the PK analysis set. The Surgery Type 2 group included patients with oesophagoenterostomy, the Surgery Type 1 group included patients with gastrectomy, and the Surgery Type 0 group included patients without gastrectomy and oesophagoenterostomy. Safety data were listed and summarised using the safety analysis set according to the treatment received.

Because of the early termination of the study, the primary and secondary analyses were performed when all data had been cleaned, rather than at the time points defined in the Clinical Study Protocol (CSP). The data cut-off date (4 December 2012) for the analysis of this study was the date of approval of CSP amendment 3. All patients who were not continuing on AZD8931 and had completed the 30-day safety follow-up were also included in the analysis.

Subject population

Overall, 39 patients were enrolled in the study from 5 centres in Japan (patients were randomised to treatment from only 4 centres), 5 centres in Korea, and 2 centres in Taiwan. Of these, 25 patients were randomised to treatment and received treatment (13 patients received AZD8931+paclitaxel and 12 patients received placebo+paclitaxel); while 14 patients were not randomised.

Overall, 22 (88.0%) patients discontinued AZD8931/placebo; 10 (76.9%) patients in the AZD8931+paclitaxel group and 12 (100.0%) patients in the placebo+paclitaxel group at the time of data cut-off (4 December 2012 [date of approval of CSP amendment 3]). Overall, the most common reason for discontinuation of AZD8931/placebo was other (10 [40.0%] patients); 5 (38.5%) patients (progressive disease) in the AZD8931+paclitaxel group and 5 (41.7%) patients in the placebo+paclitaxel group. Overall, 20 (80.0%) patients discontinued paclitaxel; 10 (76.9%) patients in the AZD8931+paclitaxel group and 10 (83.3%) patients in the placebo+paclitaxel group. Overall, the most common reason for discontinuation of paclitaxel was condition under investigation worsened (9 [36.0%] patients); 3 (23.1%) patients in the AZD8931+paclitaxel group and 6 (50.0%) patients in the placebo+paclitaxel group.

Both the groups were balanced for the demographic and baseline characteristics. Overall, the mean age was 60.2 years; 57.9 years in the AZD8931+paclitaxel group and 62.7 years in the placebo+paclitaxel group. Majority of the patients were males (18 [72.0%] patients); 9 (69.2%) patients in the AZD8931+paclitaxel group and 9 (75.0%) patients in the placebo+paclitaxel group. All patients (100.0%) were of the Asian race. Overall, the mean BMI was 21.2 kg/m^2; 20.8 kg/m^2 in the AZD8931+paclitaxel group and 21.7 kg/m^2 in the placebo+paclitaxel group. Both the groups were balanced for tumour characteristics, HER2 status, and baseline disease characteristics.

Summary of efficacy results

Percentage change in tumour size at 8 weeks

No clinically significant difference was observed between the AZD8931+paclitaxel group and the placebo+paclitaxel group with respect to percentage change in tumour size at 8 weeks. The Least-Square (LS) mean percentage change in tumour size was -7.7% for the AZD8931+paclitaxel group and -2.7% for the placebo+paclitaxel group. The LS mean difference between AZD8931+paclitaxel and placebo+paclitaxel groups was -5.0% (80% CI -21.3 to 11.3) which was not statistically significant (1-sided p-value 0.344).

Progression-free survival

There were insufficient progression events at the time of data cut-off to perform the secondary analysis of PFS. There were 8 (61.5%) progression events (7 RECIST progressions and

1 death) in the AZD8931+paclitaxel group with a median PFS of 3.7 months and 8 (66.7%) progression events (8 RECIST progressions) in the placebo+paclitaxel group with a median PFS of 3.5 months.

Objective response rate

The ORR of the AZD8931+paclitaxel group was 23.1% (3 patients [partial response]) and the ORR of the placebo+paclitaxel group was 0% (no patients).

Summary of pharmacokinetic results

Overall, 11 gastric cancer patients provided PK concentration and parameter data eligible for inclusion in the PK analysis set. Of these, 8 patients were in the group that had no surgical interventions (Surgery Type 0) while 3 patients were in the group that had surgical interventions (all Surgery Type 1). There were no patients with reportable PK parameters from the Surgery Type 2 group.

The AZD8931 PK data show that the Surgery Type 1 group had higher geometric mean (gmean) peak plasma concentrations at steady state ($C_{ss,max}$), trough concentrations at steady state ($C_{ss,min}$) and area under the curve at steady state (AUC_{ss}) than the Surgery Type 0 group (2-fold higher $C_{ss,max}$, 1.4-fold higher $C_{ss,min,}$ and 1.4-fold higher AUC_{ss}). The higher exposure may be a function of slower clearance at steady state (apparent clearance [CL_{ss}/F] is 27% lower) or more likely of a difference in the fraction of dose absorbed (F). The median time to peak concentration at steady state ($t_{ss,max}$) is also achieved more quickly for the Surgery Type 1 group than the Surgery Type 0 group (0.5 hours compared with 4 hours) indicating a faster rate of absorption for those patients with surgical intervention. However, since the number of patients is small and inter-patient variability high, this difference may not be real or clinically relevant.

The AZD8931 O-desmethyl metabolite data show that the gmean exposure (peak plasma concentration [C_{max}] and area under the concentration-time curve up to the last quantifiable sample [AUC_{0-t}]) are lower for the Surgery Type 1 group than for the Surgery Type 0 group (19% and 13%, respectively) as is the parent: metabolite ratio (39% lower) but again this analysis is based on a very small number of patients with very high inter-patient variability.

Both the with and without surgical intervention patients in this study have a different PK profile to the patients in the AZD8931 Phase I Study D0102C00002 in that they have higher exposure ($C_{ss,max}$ and AUC_{ss}) and a slower apparent clearance (CL_{ss}/F) following administration of the same dose (40 mg bd). The patients that had no surgical intervention also had a slower absorption rate than the Study D0102C00002 patients indicated by a longer $t_{ss,max}$ whereas those that had surgical intervention had a similar $t_{ss,max}$ to the Study D0102C00002 patients (approximately 1 hour). The metabolite: parent ratios are within a similar range across the 2 studies.

Summary of safety results

Both the total and actual median study drug exposure was 60 days in the AZD8931+paclitaxel group and was 59.5 days and 58.5 days, respectively, in the placebo+paclitaxel group.

Overall, all patients experienced at least 1 AE. Higher incidence of AEs causally related to AZD8931/placebo was observed in the AZD8931+paclitaxel group (11 [84.6%] patients) compared with the placebo+paclitaxel group (7 [58.3%] patients). Also, a slightly higher incidence of AEs causally related to paclitaxel, as assessed by the investigator was observed in the AZD8931+paclitaxel group (13 [100.0%] patients) as compared with the placebo+paclitaxel group (11 [91.7%] patients). A marginally lower incidence of AEs with CTCAE Grade ≥3 was observed in the AZD8931+paclitaxel group (7 [53.8%] patients) compared with the placebo +paclitaxel group (8 [66.7%] patients). Also, a higher incidence of serious adverse events (SAEs) was observed in the AZD8931+paclitaxel group (6 [46.2%] patients) compared with the placebo+paclitaxel group (3 [25.0%] patients). Of these patients who experienced SAEs, only 1 (7.7%) patient from the AZD8931+paclitaxel group had an SAE (diarrhoea) that was considered by the investigator to be causally related to AZD8931. Two (15.4%) patients in the AZD8931+paclitaxel group and 1 (8.3%) patient in the placebo+paclitaxel group had SAEs that were considered to be causally related to paclitaxel by the investigator.

AEs that occurred more commonly in the AZD8931+paclitaxel group compared with the placebo+paclitaxel group included those belonging to the following system organ classes (SOC): Gastrointestinal Disorders (13 [100%] versus 8 [66.7%] patients); Skin and Subcutaneous Tissue Disorders (10 [76.9%] versus 4 [33.3%] patients); Metabolism and Nutritional Disorders (9 [69.2%] versus 4 [33.3%] patients); and Eye Disorders (5 [38.5%] versus 0 patients), respectively. AEs that occurred more commonly in the AZD8931+paclitaxel group compared with the placebo+paclitaxel group included diarrhoea (8 [61.5%] versus 5 [41.7%] patients), neutropenia (6 [46.2%] versus 3 [25.0%] patients), stomatitis (6 [46.2%] versus 1 [8.3%] patients), decreased appetite (6 [46.2%] versus 3 [25.0%] patients), hypoalbuminaemia (5 [38.5%] versus 3 [25.0%] patients), acneiform rash (dermatitis acneiform [5 {38.5%} versus 2 {16.7%} patients], rash [5 {38.5%} versus 0 patients], rash maculopapular [2 {15.4%} versus 1 {8.3%} patients]), and vision blurred (3 [23.1%] versus 0 patients).

Overall, 6 (24.0%) patients died during the study; 4 (30.8%) patients in the AZD8931+paclitaxel group and 2 (16.7%) patients in the placebo+paclitaxel group. In the AZD8931+paclitaxel group, the primary cause of death in 3 (23.1%) patients was considered to be the disease under investigation and in 1 (7.7%) patient the cause of death was unknown as assessed by the investigator. In the placebo+paclitaxel group, the primary cause of death in both the patients who died was considered to be the disease under investigation by the

investigator. One (7.7%) patient from the AZD8931+paclitaxel group experienced an AE (asthenia) which led to discontinuation of AZD8931.

There were no findings of clinical concern for vital signs, electrocardiograms, ophthalmological assessments, haematology, and biochemical parameters.