AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3514
Study Code	D3760C00003
Edition Number	1
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A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumour Activity of Ascending Doses of AZD3514 in Japanese Patients with Metastatic Castration-Resistant Prostate Cancer

Study dates: First patient enrolled: 24 August 2011
Last patient last visit: 31 March 2013

Phase of development: Clinical pharmacology (I)

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

Study centres

This study was conducted at 2 centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and outcome variables are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD3514 when given orally to Japanese patients with metastatic CRPC.	Safety and tolerability was assessed in terms of AEs, laboratory data, vital signs, ECG changes, and AEs of special interest
Secondary	Safety	To define the maximum tolerated dose if possible, a lower biologically-effective dose or maximum feasible dose (if decided by the SRC and AstraZeneca) in Japanese patients with CRPC.	Number of patients with a DLT.
Secondary	Efficacy	To obtain a preliminary assessment of the anti-tumour activity of AZD3514 by evaluation of tumour response using RECIST 1.1 for assessment of malignant soft tissue disease and a separate bone lesions assessment using the Prostate Cancer Trials Working Group 2 criteria in Japanese patients with CRPC.	Tumour response in terms of Response rate, Best objective response, and Changes in tumour size.

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
	PK	To characterise the PK of AZD3514 after a single oral dose and at steady state after multiple dosing when given orally to Japanese patients with CRPC.	AZD3514 PK For single dosing : C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC, CL/F, V_{ss}/F, V_z/F, MRT, CL_R, $A_{e,\ and}$ $F_{e.}$ For multiple dosing : $C_{ss,max,}$ $t_{ss,max}$, $C_{ss,min}$, AUC_{ss}, CL_{ss}/F, R_{ac}, TPC of the PK, CL_{Rss}, and $A_{e,ss}$.
	Pharmacodynamics	To obtain an assessment of the activity of AZD3514 on the circulating levels of PSA in Japanese patients with CRPC	Percentage change from baseline in PSA levels and PSA response. Percentage change from baseline at 12 weeks. Best percentage change from baseline.
Exploratory	Efficacy	To investigate the effect of AZD3514 on CTC	CTC counts , M65, βCTX, and Cyfra 21-1
Additional	Efficacy	To obtain a preliminary assessment of the anti-tumour activity of AZD3514 by evaluation of PFS based on RECIST and bone disease data combined	PFS

AE Adverse Event; A_e Amount of drug excreted unchanged; $A_{e,ss}$ Amount of drug excreted unchanged at steady state; AUC Area under the plasma concentration-time curve from zero to infinity; AUC_{ss} Area under the plasma concentration-time curve during any dosing interval at steady state; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0-24)}$ Area under the plasma concentration-time curve from zero to 24 hours; CL/F Apparent plasma clearance; CL_{ss}/F Apparent plasma clearance at steady state; CL_R Renal clearance; CL_{Rss} Renal clearance at steady state; C_{max} Maximum plasma concentration; $C_{ss,max}$ Maximum plasma concentration at steady state;, $C_{ss,min}$ Minimum plasma concentration at steady state, CRPC Castration-Resistant Prostate Cancer; CTC Circulating tumour cells; CSP Clinical Study Protocol; ECG Electrocardiogram; DLT Dose-Limiting Toxicity; Fe Fraction of drug excreted unchanged in the urine; MRT Mean residence time; t_{max} time to C_{max}; PK Pharmacokinetics; PFS Progression-free survival; PSA Prostate-specific antigen; R_{ac} Extent of accumulation on multiple dosing, time dependency of the PK; RECIST Response Evaluation Criteria in Solid Tumours; SRC Safety Review Committee; $t_{1/2\lambda z}$ Terminal elimination half life; $t_{ss,max}$ Time to $C_{ss,max}$; TPC Temporal change; V_{ss}/F Volume of distribution (apparent) at steady state after an oral dose, V_z/F Apparent volume of distribution; λ_z Terminal elimination rate constant.

Study design

This was a Phase I, open-label, multicentre study of AZD3514 administered orally in patients with metastatic castration-resistant prostate cancer (CRPC). The study design allowed an

escalation of dose with intensive safety monitoring to ensure safety of the patients. Selected doses were planned to be expanded to further investigate the tolerability, pharmacokinetic (PK) and biological activity of AZD3514. The study consisted of 2 phases: the dose escalation phase and the dose expansion phase. In the dose escalation phase of the study, there was evidence of reduction in the Prostate-specific antigen (PSA) level and partial tumour response in some patients. The efficacy seen had not approached the threshold level required to support further business investment to develop this drug. Therefore, the dose expansion phase of the study was not conducted.

This Clinical Study Report has results for the dose escalation phase of the study.

Target subject population and sample size

The target population included Japanese male patients with metastatic CRPC, aged ≥20 years with presence of progressive disease.

Approximately, 16 evaluable patients were enrolled in this study. Patients with CRPC were enrolled in the dose escalation phase of this study. The total number of patients depended upon the number of dose escalations necessary to define the maximum tolerated dose (MTD), a lower biologically-effective dose or maximum feasible dose. At least 3, and up to 6 evaluable patients were required for each dose cohort.

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

AZD3514 Hydroxypropyl Methylcellulose (HPMC) capsule 50 mg was administered orally, manufactured by AstraZeneca; batch number: 11-000300AZ.

AZD3514 tablet 250 mg was administered orally, manufactured by AstraZeneca; batch number: 11-000503AZ, 11-002036AZ, and 11-002076AZ.

In this study, the tablet formulation of AZD3514 250 mg was used mainly, and in case of dose reduction to 100 mg or an intermediary dose, the AZD3514 HPMC 50 mg capsule formulation was used.

Duration of treatment

The duration of treatment was 29 days, after which patients continued to receive AZD3514 as long as they continued to show clinical benefit without apparent clinical progression.

Statistical methods

Safety and tolerability were the primary objectives of this study. All patients who received at least 1 dose of AZD3514 were included in the assessment of the safety profile (safety analysis set). Appropriate summaries of all safety data were produced.

Plasma concentrations were summarised by initial dose level and nominal sample time and derived PK parameters were summarised by initial dose level. Parameters following single and multiple dosing were summarised separately. The time dependency of the PK on multiple

dosing was assessed by the calculation of the ratio of area under plasma concentration-time curve (AUC) during any dosing interval at steady state on Day 29/AUC on Day 1.

The evaluable for efficacy analysis set comprising patients with non-missing observation at baseline was used for the analysis of tumour response data. Response rate was calculated as the number and percentage of patients with a tumour response (complete response [CR] or partial response [PR]) along with 80% exact confidence interval (Clopper-Pearson method).

PSA data was evaluated in terms of percentage change from baseline which was derived for each post-dose visit where PSA data was available, best percentage change from baseline, best percentage change on study, and percentage change in PSA at Week 12.

The parameters M65, CTC, βCTX, and Cyfra 21-1 were listed and summarised.

Subject population

The disposition of the patients in this study is summarised in Table S2.

A total of 16 patients were enrolled in this study from 2 centres in Japan. Of these, 13 patients were assigned to the study treatment.

All 13 patients received AZD3514 (4 patients in the AZD3514 250 mg once-daily [QD] cohort, 4 patients in the AZD3514 500 mg QD cohort, and 5 patients in the AZD3514 500 mg twice-daily [BID] cohort). At the time of data cut-off (31 March 2013), 12 (92.3%) patients had discontinued treatment and 1 patient in the AZD3514 250 mg QD cohort continued to receive study treatment. The most common reason for treatment discontinuation across the 3 cohorts was worsening of the condition under investigation (9 [69.2%] patients).

At the time of data cut-off, 1 patient in the AZD3514 250 mg QD cohort was ongoing in the study and all 12 patients who had discontinued study treatment were terminated from the study.

Table S2 Summary of patient disposition (All patients)

	Number (%) of patients			
	AZD3514 250mg QD	**AZD3514 500 mg QD**	**AZD3514 500 mg BID**	**Total**
Patients enrolled[a]				16
Patients assigned to treatment	4 (100.0)	4 (100.0)	5 (100.0)	13 (100.0)
Patients who were not assigned to treatment				3
Patients who received AZD3514	4 (100.0)	4 (100.0)	5 (100.0)	13 (100.0)

Table S2 Summary of patient disposition (All patients)

	Number (%) of patients			
	AZD3514 250mg QD	**AZD3514 500 mg QD**	**AZD3514 500 mg BID**	**Total**
Patients ongoing on AZD3514 at data cut-off[b]	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)
Patients who discontinued treatment[b]	3 (75.0)	4 (100.0)	5 (100.0)	12 (92.3)
Treatment stopped due to adverse event	0 (0.0)	1 (25.0)	1 (20.0)	2 (15.4)
Treatment stopped due to condition under investigation worsened	3 (75.0)	2 (50.0)	4 (80.0)	9 (69.2)
Treatment stopped due to other	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)
Patient ongoing study at data cut-off	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)
Patients who terminated study	3 (75.0)	4 (100.0)	5 (100.0)	12 (92.3)
Withdrawn from study due to adverse event	0 (0.0)	1 (25.0)	1 (20.0)	2 (15.4)
Withdrawn from study due to condition under investigation worsened	3 (75.0)	1 (25.0)	4 (80.0)	8 (61.5)
Withdrawn from study due to death	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)
Withdrawn from study due to subject decision	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.7)

[a] Informed consent received.
[b] Percentages are calculated from number of patients who received treatment.
BID Twice-daily; QD Once-daily.

Summary of efficacy results

Six patients (46.2%) had Response Evaluation Criteria in Solid Tumours (RECIST) progression, 3 (23.1%) patient had bone lesion progression, and 8 (61.5%) patient had RECIST or bone lesion progression.

There was no evidence of any anti-tumour activity as assessed by best objective response (no complete response [CR] or partial response [PR] occurrences) by RECIST, bone scan, or RECIST and bone scan combination.

Stable disease ≥12 weeks by RECIST was reported for 2 (50%) patients of the AZD3514 250 mg QD cohort, 4 (80%) patients of the AZD3514 500 mg BID cohort. Stable disease by bone scan was reported for 4 (100%) patients of the AZD3514 250 mg QD cohort, 2 (50%) patients of the AZD3514 500 mg QD cohort, and 3 (60%) patient of the AZD3514 500 mg BID cohort. Stable disease ≥12 weeks by RECIST and bone scan was reported for 2 (50%) patients of the AZD3514 250 mg QD cohort, 2 (50%) patients of the AZD3514 500 mg QD cohort, and 4 (80%) patients of the AZD3514 500 mg BID cohort.

The median progression-free survival (PFS) time (RECIST or bone scan) were 13.7 months, 7.6 months, and 5.8 months for the AZD3514 250 mg QD cohort, the AZD3514 500 mg QD cohort, and the AZD3514 500 mg BID cohort, respectively. The PFS time varied from 1.74 months to 16.56 months (Table 11.2.1.1.7).

Summary of pharmacokinetic results

The following PK parameters were changed from the planned calculation or derivation variables in the protocol. Apparent volume of distribution (V_z/F) for single dose part was not reported. Fraction of drug excreted unchanged in the urine (f_e) for single and multiple doses part was reported.

All 13 patients were included in the PK analysis set. AZD3514 plasma concentration-versus-time profiles were determined on Day 1 at 250 mg, 500 mg, and 1000 mg single dose and on Day 29 (after 21 days of daily doses) at 250 mg QD, 500 mg QD, and 500 mg BID dose in fasted male Japanese patients. AZD3514 was rapidly absorbed with the median time to maximum plasma concentration (t_{max}) of about 2 hours after the 250 mg and 500 mg single dosing and about 3 hours after the 1000 mg single dosing. The plasma levels declined in a bi-phasic manner with the terminal half-life ($t_{1/2}$) ranging from 8.2 hours to 12.0 hours. The amount of AZD3514 excreted in urine was generally low. Increase in AZD3514 exposure, in terms of maximum plasma concentration (C_{max}) and AUC, was approximately proportional with the range of 250 mg to 1000 mg of single dose. Minimal accumulation on multiple once-daily (QD) dosing of 250 mg and 500 mg was observed. The minimal time-dependent change in AUC with temporal parameter change after multiple QD dosing of 250 mg and 500 mg was observed.

Summary of pharmacodynamic results

The mean best percentage change on study and the mean best percentage change from baseline in PSA levels were similar across all cohorts (0.6 to 0.8 and 0.8 to 1.4, respectively). Mean percentage change from baseline at 12 weeks in PSA level were also similar across the cohorts ranging from 1.4 to 1.9

PSA responses (defined as PSA decline of ≥50% compared to baseline at Week 12) were not observed in any patient. In addition, PSA decline of ≥30% compared to baseline at Week 12 also was not observed.

During the study, PSA response was observed in 1 (25%) patient in the AZD3514 250 mg QD cohort and 1 (20%) patient in the AZD3514 500 mg BID cohort

Summary of safety results

A total of 13 patients received at least 1 dose of AZD3514 and provided safety data.

The median total treatment duration was 246 days in the AZD3514 250 mg QD cohort, 198 days in the AZD3514 500 mg QD cohort, and 164 days in the AZD3514 500 mg BID cohort. The median total time on study was 292.5 days in the AZD3514 250 mg QD cohort, 262.0 days in the AZD3514 500 mg QD cohort, and 212.0 days in the AZD3514 500 mg BID cohort. During the first 29 days of receiving the study treatment, 1 (25%) patient in the AZD3514 500 mg QD cohort had a dose reduction, whereas, no dose modification was reported in the AZD3514 250 mg QD cohort and the AZD3514 500 mg BID cohort.

All 13 patients experienced at least 1 adverse event (AE). Most patients experienced Gastrointestinal disorders and Metabolism and nutrition disorders. Overall, the most common AEs reported were: Nausea (10 [76.9%] patients), decreased appetite (6 [46.2%] patients), and vomiting (5 [38.5%] patients).

In this study, the AEs of special interest were nausea (2 [15.4%] patients) and platelet count decreased (2 [15.4%] patients), which lead to dose modification. These 2 patients experienced thrombocytopenia of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or more.

One patient in the AZD3514 500 mg QD cohort died during the study. The primary cause of death was considered to be the disease under investigation by the investigator.

There were 4 patients who experienced a serious adverse event (SAE). Of these, 2 patients experienced a SAE which was considered by the investigator to be causally-related to AZD3514. The SAEs considered to be causally-related were decreased appetite and cholecystitis.

There were 2 patients who experienced AEs which led to discontinuation of AZD3514 and were considered by the investigator to be causally-related to AZD3514. The AEs were vomiting and decreased appetite.

An MTD for AZD3514 was not established. There was no dose-limiting toxicity (DLT) reported within the 29-day DLT evaluation period.

There were no clinically relevant treatment-related changes or trends in any laboratory variables, except decrease in platelet count, measured in patients exposed to AZD3514 during the study. There were no clinically significant changes in vital signs, ECG, and physical findings observed during the study.