Clinical Study Report Synopsis

Drug Substance	AZD3514
Study Code	D3760C00001
Edition Number	1
EudraCT Number	2010-020232-19

A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-Tumour Activity of Ascending Doses of AZD3514 in Patients with Metastatic Castration-Resistant Prostate Cancer

Study dates: First subject enrolled: 23 August 2010
Last subject last visit: 28 March 2013

Phase of development: Clinical pharmacology (I)

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

Publications

1. Loddick SA, et al. Mol Cancer Ther 2013;12(9):1715-27.

2. Bradbury RH, et al. Bioorg Med Chem Lett 2013;23(7):1945-8.

3. Omlin A, et al. J Clin Oncol 2013;31(15 Suppl May 20):Abstract 4511.

4. Loddick S, et al. Cancer Res 2012;72(8 Suppl 1):Abstract 3848.

5. Bradbury RH, et al. Bioorg Med Chem Lett 2011;21(18):5442-5.

Early termination of study

Early assessment of efficacy of AZD3514 in patients with metastatic castration-resistant prostate cancer (CRPC) did not show sufficient evidence of anti-tumour activity of the compound. As a result, on 7 December 2012, AstraZeneca made a decision to stop recruitment of new patients into Study D3760C00001 and discontinue development of AZD3514. Further, the ongoing review of unvalidated data from this study has not identified any new safety concerns or findings in comparison with the profile as highlighted in the Investigator's Brochure, Edition 4, dated 19 July 2012. The safety profile of AZD3514 therefore remains unchanged at the time of writing the Clinical Study Report (CSR) for this study. Hence, results of this study are presented as an abbreviated CSR.

Objectives and criteria for evaluation

Table S1 Study objectives and variables

Objective: priority (type)	Description of objective	Description of variable
Primary		
Safety	To investigate the safety and tolerability of AZD3514 when given orally to patients with CRPC.	DLTs, AEs, laboratory data, vital signs, physical examination, and ECG changes.
Secondary		
Safety	1. To define the MTD, if possible, a lower biologically effective dose(s), or maximum feasible dose (if decided by the SRC and AstraZeneca).	DLT.

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Objective: priority (type)	Description of objective	Description of variable
PK	2. To characterise the PK of AZD3514 after a single oral dose and at steady state after multiple oral doses.	Single-dose PK: C_{max}, t_{max}, λ_z, $t_{½\lambda z}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC, CL/F, V_{ss}/F, MRT, CL_R, fe. V_{ss}/F was determined from MRTxCL/F. Multiple-dose and/or combination cohort(s) PK: C_{ssmax}, t_{ssmax}, C_{ssmin}, $AUC_{ss(tau)}$, CL_{ss}/F, R_{AC}, CL_R, fe, and temporal change (TPC) of the PK. R_{AC} will not be reported for the combination cohorts.
Efficacy	3. To obtain a preliminary assessment of the anti-tumour activity of AZD3514 as monotherapy and/or in combination with abiraterone acetate by evaluation of tumour response using modified RECIST 1.1 for assessment of malignant soft tissue disease and a separate bone lesions assessment using the PCWG 2 criteria.	ORR[a], BOR, and PFS according to the modified RECIST 1.1 criteria; ORR[a], BOR, and PFS based on bone scan; ORR[a], BOR, and PFS based on modified RECIST 1.1 and bone scan combined; change in tumour size.
Pharmacodynamic	4. To obtain an assessment of the activity of AZD3514 as monotherapy and/or in combination with abiraterone acetate on the circulating levels of PSA.	%change from baseline, best %change from baseline, best %change on study, %change in PSA at Week 12, time to PSA progression, confirmed and single visit PSA response at 12 weeks, and confirmed and single visit response at any point during the study.
Pharmacodynamic	5. To obtain a preliminary assessment of the anti-tumour activity of AZD3514 as monotherapy and/or in combination with abiraterone acetate by evaluation of counts of CTCs.	This analysis was not done[b].
Safety and PK	6. To investigate safety, tolerability, MTD (and/or biologically effective dose[s] or maximum feasible dose), and PK of AZD3514 and abiraterone acetate when administered in combination in patients who have not received prior treatment with abiraterone acetate.	AEs, laboratory data, vital signs, physical examination, and ECG changes. The following PK parameters were assessed: C_{ssmax}, t_{ssmax}, C_{ssmin}, $AUC_{ss(tau)}$, CL/F, and TPC of the PK.
PK	7. To compare the PK of AZD3514 monotherapy in patients who were fed or fasted before the administration of study treatment.	This analysis was not done[c].

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Objective: priority (type)	Description of objective	Description of variable
Pharmacodynamic	8. To investigate the effect of AZD3514 on biomarkers of AR expression in paired pre- and post-dose tumour biopsies.	This analysis was not done[c].

[a] ORR was not estimated as few patients experienced a RECIST, bone scan, or RECIST and bone scan response and hence estimation of ORR was considered unnecessary. Conclusions on efficacy were therefore drawn from the BOR and PFS only.
[b] The CTC assays provided insufficient data to draw any conclusions and hence the analysis was not performed.
[c] The justification for not analysing the objective is provided in the study design section.
AE Adverse event; AR Androgen receptor; AUC Area under plasma concentration-time curve; $AUC_{ss\,(tau)}$ Area under the plasma concentration-time curve from zero to the end of the dosing interval; $AUC_{(0\text{-}t)}$ Area under the plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0\text{-}24)}$ Area under plasma concentration-time curve from zero to 24 hours; βCTx Beta C-terminal cross-linking telopeptide of Type I collagen; BOR Best objective response; CL/F Apparent oral clearance of drug from plasma; CL_R Renal clearance of drug from plasma; CL_{ss}/F Apparent oral clearance of drug from plasma at steady state; C_{max} Maximum observed plasma concentration; CRPC Castration-resistant prostate cancer; C_{ssmax} Maximum (peak) observed steady state drug concentration in plasma during dosing interval; C_{ssmin} Minimum observed plasma concentration at steady state; CSR Clinical Study Report; CTC Circulating tumour cells; DLT Dose limiting toxicity; ECG Electrocardiogram; fe Fraction of drug excreted unchanged in the urine; IHC Immunohistochemistry; λ_z Terminal elimination rate constant; MRT Mean residence time; MTD Maximum tolerated dose; ORR Overall response rate; PCWG Prostate Cancer Working Group; PFS Progression free survival; PINP N-terminal propeptide of Type I procollagen; PK Pharmacokinetics; PSA Prostate specific antigen; R_{AC} Accumulation ratio; RECIST Response Evaluation Criteria in Solid Tumours; SRC Safety Review Committee; $t_{1/2\lambda z}$ Terminal elimination half-life; t_{max} Time to maximum (peak) observed plasma concentration; TPC Temporal change; t_{ssmax} Time to maximum (peak) observed steady state drug concentration; V_{ss}/F Apparent volume of distribution at steady state.

Study design

This was a Phase I, first-time-in-human, open-label, multicentre study of AZD3514 administered orally in patients with metastatic CRPC. The study allowed an escalation of dose with intensive safety monitoring to ensure safety of the patients. Selected doses were to be expanded to further investigate the tolerability, pharmacokinetics (PK), and biological activity of AZD3514.

In this study, the starting dose of AZD3514 was 100 mg, and dose escalation was planned to continue until reaching either (1) the maximum tolerated dose (MTD) as defined by dose limiting toxicity (DLT), if possible; (2) a lower biologically effective dose(s); or (3) a maximum feasible dose. A rolling six design was employed for enrolment of patients in the dose cohorts. In each dose cohort, initially, at least 3 and up to 6 patients were required to receive active treatment. After each dose cohort, the Safety Review Committee evaluated the safety, tolerability, and PK of AZD3514 and decided the next dose (planned dose, increased or decreased dose, repeated dose, or dose stopped). After at least 12 weeks of therapy, patients at the AZD3514 100 mg and AZD3514 250 mg once daily (QD) dose levels could be dose escalated up to 500 mg QD. In parallel with the dose escalation, patient cohort(s) at selected dose(s) could be expanded to investigate further the tolerability, PK, and biological activity of AZD3514; a maximum of 20 evaluable patients could be enrolled in the dose expansion cohorts.

This study commenced with a capsule formulation. However, a tablet formulation was considered more convenient for patient administration because of the smaller number of tablets required to achieve an equivalent dose versus the capsule formulation. Therefore, a switch to the tablet formulation was performed when a suitable formulation was available.

Because of a strategy change within the project during the study, secondary objective 6 was not conducted. Patients receiving abiraterone acetate but showing biochemical evidence of disease progression was an area of unmet medical need. Additionally, treatment of patients showing evidence of resistance to abiraterone with AZD3514 offered an opportunity to distinguish the mechanism of drug response for this combination therapy, with evidence of response suggesting activity due to the administration of AZD3514 rather than the continued administration of abiraterone acetate. Further, secondary objective 7 was also not conducted as it was decided that the development with AZD3514 would continue only in combination with abiraterone acetate in the fasted state. Thus, it was felt that assessment of the PK of AZD3514 monotherapy in patients who were fed or fasted prior to the administration of study treatment was no longer appropriate. Furthermore, investigation of the effect of AZD3514 on biomarkers of androgen receptor expression in paired pre- and post-dose tumour biopsies (secondary objective 8) was not performed due to the limited availability of tumour tissue of sufficient quality for analysis. Exploratory objective 8, "To study the accumulation and biodistribution of fluoro-2-deoxy-D-glucose and fluorinated dihydrotestosterone in patients with progressive prostate cancer when treated with AZD3514 administered in combination with abiraterone acetate", was not conducted. This was because the scientific justification for these procedures was considered no longer sufficient to justify the resources required.

Target subject population and sample size

The target patient population included male patients aged 20 years and older with metastatic CRPC. Approximately 150 patients were planned to be enrolled in this study. At least 3 and up to 6 evaluable patients were required for each dose cohort in the dose escalation phase. The dose expansion cohorts allowed up to 20 evaluable patients in each expansion cohort. For the combination cohorts (AZD3514 administered in combination with abiraterone acetate), the first cohort consisted of 6 patients to assess safety, and the subsequent cohorts consisted of up to 20 patients.

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

Details of the investigational products (IPs) are as follows: AZD3514 oral hydroxypropyl methylcellulose (HPMC) capsule 50 mg (AstraZeneca), AZD3514 oral HPMC capsule 75 mg (AstraZeneca), AZD3514 oral tablet 100 mg (AstraZeneca), AZD3514 oral tablet 250 mg (AstraZeneca), and abiraterone acetate oral tablet 250 mg (Johnson & Johnson). For further information, refer to Appendix 12.1.6 (Listing of subjects receiving the various batches of investigational products).

Duration of treatment

In the dose escalation and dose expansion monotherapy cohorts, patients received a single dose on Day 1. After a 7±2-day washout period, multiple dosing, QD or twice daily (BID),

was initiated. The washout period could be changed if needed based on the emerging PK data. In the first cohort, there was a 7-day interval from the date of dosing the first patient in the cohort before the remaining patients could commence dosing.

For the cohorts of AZD3514 administered in combination with abiraterone acetate in patients who had not received prior treatment with abiraterone acetate, on Days 1 to 7, patients received AZD3514 monotherapy; from Day 8, abiraterone acetate was added. For the cohorts of AZD3514 administered in combination with abiraterone acetate in patients who were already receiving abiraterone acetate, patients received AZD3514 in addition to their existing abiraterone acetate from Day 1 onwards.

Statistical methods

The primary analysis took place a minimum of 12 weeks after the last recruited patient started the IP or approximately 30 days after the final patient discontinued the IP.

No formal analysis was performed on the demography, exposure, safety and tolerability, PK, and biomarker data of the patients in the study. The Kaplan-Meier method was used to derive time to prostate specific antigen (PSA) progression. Modified Response Evaluation Criteria in Soft Tissue (RECIST) 1.1 were used to assess malignant soft tissue disease while the Prostate Cancer Working Group 2 (PCWG 2) criteria were used for bone lesion assessment.

Log-transformed area under plasma concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) (single dosing) and area under plasma concentration-time curve during any dosing interval at steady state (AUC_{ss}) and maximum (peak) observed steady state drug concentration in plasma during dosing interval (C_{ssmax}) (multiple dosing) parameter estimates obtained from dose escalation cohorts were examined using the Power Model. Log transformed dose-normalised AUC and C_{max} (single dosing) and AUC_{ss} and C_{ssmax} (multiple dosing) of AZD3514 were analysed separately using a mixed effects model.

Subject population

The first patient was enrolled on 23 August 2010 and the last patient last visit was on 28 March 2013.

Fifty-seven patients were assigned to the treatment and 8 patients were not assigned to the treatment due to subject decision (2 patients) and eligibility criteria not fulfilled (6 patients). No patients (that received treatment) were excluded from the PK, efficacy, or DLT analysis sets. Of the 57 patients that received treatment, 49 (86.0%) patients received various doses of AZD3514 monotherapy (monotherapy cohorts) and 8 (14.0%) patients received 500 mg BID of AZD3514 along with abiraterone acetate (combination cohorts). Overall, 50 (87.7%) patients discontinued AZD3514, with the most common reason for discontinuation being condition under investigation worsened (22 [38.6%] patients). Overall, 36 (63.2%) patients had an important protocol deviation during the study. The most common protocol deviations were dosing time not recorded (12 [21.1%] patients) and PK sample not within the time window (10 [17.5%] patients). Overall, the mean age was 68.8 years (range 45 years to 86 years) and all patients were of White race.

Overall, 11 (19.3%) patients terminated the study, with the most common reason being adverse event (AE) in 5 (8.8%) patients. At data cut-off, dated 28 March 2013, 7 (12.3%) patients were still ongoing in the study.

Summary of pharmacokinetic results

AZD3514 was rapidly absorbed with median time to peak plasma concentration between 2 hours to 3 hours following oral administration at 100 mg to 2000 mg QD doses, after which plasma levels declined in a bi-phasic manner with the majority of AZD3514 removed by 24 hours post-dose. Increases in AZD3514 exposure were generally dose proportional over the 100 mg to 1000 mg QD dose range. There was no indication of dose-dependency in elimination half-life ($t_{½}$) (mean range 15.9 hours to19.2 hours), apparent oral clearance of drug from plasma (CL/F) (mean range 13.2 L/hour to 15.1 L/hour) or volume of distribution (apparent) at steady state after an oral dose (V_{ss}/F) (mean range 121 L to 138 L). Exposure increased greater than the increase in dose at 2000 mg QD suggesting possible saturation of clearance processes. Moderate inter-patient variability in PK was generally observed with AZD3514 monotherapy (Day 1 gmean C_{max} and AUC ranging from 19% to 31% CV and 1% to 28% CV, respectively). No accumulation upon multiple dosing was detected. Temporal change in the PK of AZD3514 on BID dosing at 1000 mg was observed with a 30% reduction in AUC_{ss} compared to single dose AUC. Renal elimination of unchanged AZD3514 was low (<7% of dose) and renal clearance was not dose dependent. Lower C_{ssmax} and AUC_{ss} of AZD3514 were detected in the patients already receiving abiraterone acetate after 29 days combination therapy with abiraterone acetate. This was likely due to temporal change in AZD3514 PK at the 500 mg BID dose rather than a result of combination with abiraterone acetate. The steady state exposure (mean C_{ssmax} 186 ng/mL; mean AUC_{ss} 951 ng.h/mL) and inter-patient variability (C_{ssmax} 49% CV; AUC_{ss} 40% CV) observed for abiraterone prior to start of the combination therapy were similar to the values reported in the literature. Due to the limited data and level of inter-patient variability for abiraterone, it was not possible to conclude whether the exposure of abiraterone was affected when administered in combination with AZD3514.

Summary of pharmacodynamic results

Mean best percentage change on study and best percentage change from baseline in PSA levels were similar (0.7 to 0.8 and 0.8 to 1.4, respectively) in AZD3514 monotherapy cohorts. The abiraterone acetate-naive patient combination cohort had lower mean best percentage change on study (0.3) and best percentage change from baseline (0.4) than those already receiving abiraterone acetate combination cohort (1.1 and 1.3, respectively). PSA responses (defined as PSA decline of ≥50% compared to baseline at Week 12) were only observed for AZD3514 doses of 500 mg QD to 2000 mg BID for monotherapy cohorts. Of the 38 patients in these cohorts, 7 (18.4%) patients had a PSA response. PSA responses were observed in the abiraterone acetate-naive combination cohort (2 out of 3 patients) but not in the cohort with prior abiraterone acetate therapy (5 patients).

Summary of efficacy results

At data cut-off, 21 (36.8%) patients had disease progression, of which 20 (35.1%) patients had RECIST/bone lesion progression and 1 (1.8%) patient died. There was little evidence of any anti-tumour activity as assessed by best objective RECIST (complete response 1 [1.8%] patient, partial response (PR) 2 [3.5%] patients), and RECIST and bone scan combination (PR 3 [5.3%] patients) from AZD3514 monotherapy or AZD3514 combination cohorts. RECIST responses and RECIST and bone scan combined responses were observed for the AZD3514 1000 mg QD cohort (2 patients) and the abiraterone acetate-naive combination cohort (1 patient) only. Overall, median progression-free survival (PFS) time (RECIST or bone scan) for all cohorts was 10.9 months and it ranged from 0.03 months to 27.63 months. The highest PFS time was observed in the 100 mg Cap QD cohort.

Summary of safety results

Overall, 57 (100%) patients received at least 1 dose of the IP and provided safety data. Overall, the median total treatment duration was 135 days (range 3 days to 894 days) and the median actual treatment duration was 134 days (range 3 days to 892 days). No MTD was established for the monotherapy and combination cohorts as the study was stopped. No DLTs were observed within the 29-day DLT evaluation period.

All patients (100%) experienced at least 1 AE. Most of the AEs were of mild to moderate intensity. The most common AEs were nausea (49 [86%] patients) and vomiting (34 [59.6%] patients). Overall, 55 (96.5%) patients had at least 1 AE considered to be causally related to AZD3514 by the investigator. Nausea (47 [82.5%] patients) and vomiting (31 [54.4%] patients) were the most common AEs considered to be causally related to AZD3514 by the investigator, most of which were of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. Overall, 7 (12.3%) patients had AEs with CTCAE Grade ≥3 that were considered to be causally related to AZD3514 by the investigator, and the most common AE was fatigue (3 [5.3%] patients). The AEs of special interest in this study were nausea and vomiting (51 [89.5%] patients), and thrombocytopenia or platelet counts decreased (6 [10.5%] patients).

One (1.8%) patient in the AZD3514 250 mg QD cohort died during the study. The primary cause of death was considered to be the disease under investigation by the investigator. In total, there were 15 (26.3%) patients who experienced 1 or more serious AEs with the most common events being nausea (3 [5.3%] patients) and vomiting (4 [7.0%] patients).

Overall, 11 (19.3%) patients had an AE leading to discontinuation of AZD3514. The most common AEs leading to discontinuation of AZD3514 were vomiting (2 [3.5%] patients) and dizziness (2 [3.5%] patients).

Higher doses of AZD3514 (≥1000 mg QD) had a greater reduction of platelet counts at discontinuation from baseline. No other clinically relevant treatment-related changes or trends in any other laboratory variables were observed in the patients.

No subjects had alanine aminotransferase ≥3x upper limit of normal (ULN) or aspartate aminotransferase ≥3xULN, and total bilirubin ≥2xULN. There were no clinically relevant treatment-related changes observed in the vital sign parameters, electrocardiogram, or physical examination parameters in the patients.