PHASE I STUDIES

AZD3514, an oral selective androgen receptor down-regulator in patients with castration-resistant prostate cancer – results of two parallel first-in-human phase I studies

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Summary *Background* AZD3514 is a first-in-class, orally bio-available, androgen-dependent and -independent androgen receptor inhibitor and selective androgen-receptor down-regulator (SARD). *Methods* In study 1 and 2, castration-resistant prostate cancer (CRPC) patients (pts) were initially recruited into a once daily (QD) oral schedule (A). In study 1, pharmacokinetic assessments led to twice daily (BID) dosing (schedule B) to increase exposure. Study 2 explored a once daily schedule. *Results* In study 1, 49 pts were treated with escalating doses of AZD3514 (A 35 pts, B 14 pts). Starting doses were 100 mg (A) and 1000 mg (B). The AZD3514 formulation was switched from capsules to tablets at 1000 mg QD. 2000 mg BID was considered non-tolerable due to grade (G) 2 toxicities (nausea [N], vomiting [V]). No adverse events (AEs) met the dose-limiting toxicity (DLT) definition. Thirteen pts received

AZD3514 in study 2, with starting doses of 250 mg QD. The most frequent drug-related AEs were N: G1/2 in 55/70 pts (79 %); G3 in 1 pt (1.4 %); & V: G1/2 in 34/70 pts (49 %) & G3 in 1 pt (1.4 %). PSA declines (≥50 %) were documented in 9/70 patients (13 %). Objective soft tissue responses per RECIST1.1 were observed in 4/24 (17 %) pts in study 1. *Conclusion* AZD3514 has moderate anti-tumour activity in pts with advanced CRPC but with significant levels of nausea and vomiting. However, anti-tumour activity as judged by significant PSA declines, objective responses and durable disease stabilisations, provides the rationale for future development of SARD compounds.

Keywords (5) Castration-resistant prostate cancer · Phase I · First-in-human · AZD3514 · Selective androgen receptor down-regulator

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Introduction

Prostate cancer is the second leading cause of cancer mortality in men in Western society [1]. The key role of the androgen receptor (AR) signalling pathway in the advanced disease setting has been demonstrated by the impressive survival benefit of abiraterone acetate, a potent CYP17 inhibitor that blocks androgen and oestrogen synthesis, and enzalutamide, a novel potent anti-androgen that also blocks AR-shuttling into the nucleus and binding of the AR to DNA [2–5]. However, the activity of these novel compounds, measured as decline of PSA ≥50 % from baseline, is limited to 40–60 % of patients, with generally higher response rates in the pre-docetaxel setting [5, 6, 4, 3]. Furthermore, evidence of cross-resistance between abiraterone and enzalutamide is emerging [7–10]. Resistance to abiraterone and enzalutamide has been associated with ligand-independent mechanisms, such as expression of AR splice variants, Src-related AR phosphorylation or mutations of the ligand-binding domain of the AR [11–14].

Effective and novel strategies targeting the AR in advanced prostate cancer are therefore an important unmet need in this patient population. AZD3514 (AstraZeneca, Macclesfield, UK) is a first-in-class, orally bio-available drug that inhibits androgen-dependent and AR-independent signalling through two distinct mechanisms; inhibition of ligand-driven nuclear AR translocation and down-regulation of AR levels (selective androgen receptor down-regulator, SARD) [15, 16]. AZD3514 binds to the AR ligand-binding domain (LBD) with an IC_{50} of 23 μM but has no measurable binding property (>100 μM) to other nuclear hormone receptors. AZD3514 caused a dose-dependent inhibition of cell survival in a sub clone of LNCaP cells serially maintained in the presence of bicalutamide and an androgen-independent sub clone (of LNCaP) that was serially maintained in steroid-depleted medium. AZD3514 also reduced PSA mRNA and AR protein in both sub clones [15].

The primary objectives of the studies described here (study 1 and study 2) were to evaluate the safety and tolerability of AZD3514, and define dose-limiting toxicities (DLTs), maximum-tolerated dose (MTD), and recommended phase II dose (RP2D) of AZD3514 when administered orally to patients with advanced metastatic castrate-resistant prostate cancer (CRPC). Although both studies were initiated with once daily (QD) dosing, a switch to twice daily (BID) dosing was pursued to increase drug exposure. In expansion cohorts, the anti-tumour activity in patients naïve to and progressing whilst taking abiraterone was investigated. Secondary objectives included the pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of AZD3514, as well as preliminary assessment of anti-tumour efficacy according to PCWG2 and RECIST 1.1 [17, 18]. Putative predictive tumour biomarkers were also evaluated.

Patients and methods

Clinical studies

Two independent phase I clinical trials of AZD3514 were performed. The first study (study 1; NCT01162395) was an open-label, dose-escalation study of continuous oral treatment with AZD3514, conducted at five centres (The Christie National Health Service (NHS) Foundation Trust, Manchester, UK; The Royal Marsden NHS Foundation Trust, London, UK; the Beatson West of Scotland Cancer Centre, Glasgow, UK; The Netherlands Cancer Institute NKI, Amsterdam, Netherlands; and Oregon Health & Science University, Portland, OR, USA). The second study was an open-label dose-escalation study (study 2; NCT01351688) performed at two sites in Japan (Kitasato University Hospital, Sagamihara, Kanagawa; and Shizuoka Cancer Center Hospital, Sunto-gun, Shizuoka). Both studies were performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and approved by relevant regulatory and independent ethics committees.

Inclusion/exclusion criteria

Both trials used the same inclusion and exclusion criteria. Study inclusion criteria included written informed consent; males aged 20 years or older; histologically or cytologically confirmed metastatic prostate cancer for which no standard therapy was considered appropriate. Disease progression was defined as either one or more of 1) biochemical progression with at least 2 stepwise increases in a series of any 3 PSA values collected while patient was castrate; 2) malignant soft tissue disease progression by RECIST 1.1; or 3) two or more new metastatic bone lesions from bone scans from a previous assessment. Other inclusion criteria included serum testosterone ≤50 ng/dL; life expectancy≥12 weeks; and Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less. Exclusion criteria included major surgery or radiotherapy within 4 weeks, or chemotherapy within 3 weeks before start of study; hormonal therapy with the exception of ongoing luteinizing-hormone releasing hormone (LHRH) analogue treatment within 4 weeks of the first dose of study treatment (6 weeks for anti-androgens); prior treatment with a selective AR down-regulator; residual toxicity≥CTCAE grade 2 from prior treatment (acceptable is grade 1 or lower); inadequate bone marrow reserve or function, or inadequate renal or hepatic function; severe or uncontrolled systemic disease; uncontrolled brain metastases or untreated spinal cord compression; any relevant cardiac abnormalities including mean resting corrected QT interval (QTc)>470 msec obtained from 3 electrocardiograms (ECGs); conditions that would impede drug ingestion or absorption; potent inhibitors or inducers of

cytochrome P450 3A4 (CYP3A4); and other significant coexisting medical conditions. For the abiraterone expansion cohorts in study 1, the same inclusion criteria were applied; for cohort 9, where AZD3514 was added to abiraterone in patients at the time of progression on abiraterone alone, prior evidence of a PSA decline of ≥50 % maintained for 4 months while on abiraterone monotherapy was required.

DLT definition

A DLT was defined as any toxicity not attributable to the disease or disease-related processes under investigation and considered to be related to AZD3514 therapy during the single-dose period and the first 21-days of multiple dosing (i.e., by study day 29), which includes: haematological toxicity≥CTCAEv4 grade 4 present for more than 4 days; non-haematological toxicity≥CTCAEv4 grade 3 including febrile neutropenia and QTc prolongation (>500 msec); any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of dosing schedule of more than 14 days; and any event, including significant dose reductions or omissions, judged to be a DLT by the safety review committee (SRC).

Study design

For both studies, a single-dose of AZD3514 was administered to fasting patients on cycle 1 day 1, with a 7 day washout to collect single-dose PK samples. Continuous once daily (QD) dosing (schedule A) started from cycle 1 day 8 in 28 day cycles to fasting patients in 50 mg and 75 mg capsules. The formulation was switched to 250 mg tablets from cohort 5 (1000 mg QD) onwards in study 1; in study 2, only the tablet formulation was used (see Table 1). The reason for the formulation switch was that capsules were only available at 50 and 75 mg doses, which limited total daily dose due to the number of capsules patients were required to take. PK assessments led to a change to BID dosing (schedule B) to increase exposure from cohort 6 in study 1 and cohort 3 in study 2.

A cohort size of 3 to 6 patients ('rolling-six design') was employed to improve the rate of accrual of patients to cohorts nearer the presumed therapeutic dose by reducing the need for late replacement of patients who become non-evaluable [19]. To further characterize safety and anti-tumour activity, four expansion cohorts in study 1 were opened, where cohort 3 (500 mg QD) was expanded to 12 patients; cohort 6 (1000 mg BID) expanded to 9 patients; and two abiraterone acetate combination cohorts were opened (cohorts 8 and 9).

Safety

Safety assessments were conducted at baseline; days 1, 2, 8, 15, and 28 of cycle 1 and subsequently every 28 days. All patients had a medical history taken, underwent physical examination and had an ECG, as well as haematology and chemistry profiling. Adverse events (AEs) and laboratory variables were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

PK analyses

PK profiling from patients was undertaken to guide the optimal selection of dose and schedule of AZD3514. Single-dose PK was determined from blood samples collected pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 24, 48, 72, 96 h after a single-dose of AZD3514 on day 1. Steady state PK was performed using blood samples collected on day 29 at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 24 h after dosing. Urine samples for the determination of AZD3514 concentration were taken pre-dose and 10 h post-dose on days 1 and 29 of cycle 1. For BID dosing cohorts, the 10 h blood and 0–10 h urine samples were not taken and instead replaced by 12 h and 0–12 h samples (on day 1 and before the second dose on day 29), respectively. Plasma and urine concentrations were analysed by high performance liquid chromatography with tandem mass spectroscopy (HPLC-MS/MS) at PRA Health Sciences Bio-analytical Laboratory (USA). Plasma PK parameters were derived by non-compartmental analysis.

Pharmacodynamic biomarker studies

PSA as readout of AR-signalling was obtained from patients at screening, day 8, 15 and 29 of cycle 1 and thereafter every 28 days. Circulating tumour cells (CTCs) were measured by the CellSearch™ system [20] and assessed at day 1, 15, and 29 of cycle 1, and days 57 and 85 and at treatment discontinuation.

Radiological response

Radiologic assessment of disease status was performed at baseline and every 12 weeks. For soft tissue disease, RECIST (Response Evaluation Criteria in Solid Tumours version 1.1) [18] was applied. Bone lesions were assessed by bone scans and progressive disease was defined as the appearance of 2 or more new bone metastases detected on a follow-up bone scan [17]. If only 2 new bone lesions were present on the bone scan, a confirmatory scan (CT, MRI or plain X-ray) was required to confirm that both lesions were metastases.

Table 1 Patient disposition for study 1 and study 2

Cohort #	Treatment	No of patients	Number of patients in expansion	AZD3514 formulation	[a]Dose interruptions N (%)	[b]Dose reduction N (%)
Study 1						
1	100 mg QD	5	NA	Capsules	1 (20)	0
2	250 mg QD	6	NA	Capsules	0	0
3	500 mg QD	6	6	Capsules	2 (17)	0
4	1000 mg QD	6	NA	Capsules	1 (17)	0
5	1000 mg QD	6	NA	Tablets	1 (17)	0
6	1000 mg BID	6	3	Tablets	2 (22)	3 (33)
7	2000 mg BID	5	NA	Tablets	2 (40)	3 (60)
8	[c]500 mg BID+AA 1000 mg QD	3	NA	Tablets	2 (66)	0
9	[d]500 mg BID+AA 1000 mg QD	5	NA	Tablets	0	0
Study 2						
1	250 mg QD	4		Tablets	0	0
2	500 mg QD	4		Tablets	3 (75)	0
3	500 mg BID	5		Tablets	3 (60)	3 (60)

NA not applicable, *AA* abiraterone acetate

[a] Number of patients who had dose interruptions due to an adverse event

[b] Number of patients who had dose reductions due to an adverse event

[c] Abiraterone acetate (AA) naïve patients

[d] Patients whose disease had progressed on abiraterone acetate

Results

Patient characteristics

Fifty-seven patients were enrolled in study 1 between August 2010 and December 2012. Twenty-nine patients received the capsule formulation of AZD3514 and 28 patients received the tablet formulation of AZD3514 (see Table 1 for disposition of patients). A total of eight patients received AZD3514 either in combination with concurrently initiated abiraterone acetate (abiraterone; $n=3$) or AZD3514 was added to abiraterone in patients progressing on abiraterone alone ($n=5$). Thirteen Japanese patients received the tablet formulation of AZD3514 in study 2. The patient demographics, clinical characteristics and details of prior anti-tumour therapies are given in Table 2.

Dose-escalation, DLT, MTD and RP2D

Pre-clinical efficacy studies suggested that an AZD3514 target concentration of 2410 ng/ml for 18 h was required for efficacy. However, human exposure was much less than predicted by preclinical species, and QD dosing failed to reach the required target level. The summary statistics for the PK non-compartmental analysis are given in Table 3. At 1000 mg OD, the unbound drug concentration was at or above target for only 6.5 h in a 24 h period. This led to a change to twice-daily dosing and an unexpected time-dependent change in exposure that was observed at 1000 mg BID. The highest explored dose of AZD3514 at 2000 mg BID was deemed intolerable based on multiple grade 2 toxicities (chiefly nausea and vomiting, see below) although none of the AEs reached pre-specified DLT criteria.

Systems pharmacology modelling (described elsewhere) and preclinical data suggested that greatest efficacy with AZD3514 would be achieved at minimal dihydrotestosterone (DHT) levels. Thus, a combination expansion cohort with abiraterone was opened, initially in patients who were abiraterone naïve (cohort 8), and later in patients whose disease had progressed while on abiraterone monotherapy (cohort 9). However, an insufficient number of responses in cohort 9 were observed and the trial was terminated. A recommended phase II dose was not identified.

PK analysis of AZD3514

For study 1, patients received 100–1000 mg QD and 1000–2000 mg BID of AZD3514. The 2000 mg BID dose was not tolerated so no steady-state PK data are available at this dose level. In study 1, a formulation switch from capsules to tablets occurred at the 1000 mg QD dose. The mean C_{max} and AUC were similar between the two formulations at this dose (<10 % difference), hence the combined PK, safety and efficacy data from the capsule and tablet are reported (Table 3). The PK parameters for abiraterone acetate in the combination cohorts are described in Supplementary Materials. In study 2, patients

Table 2 Demographics and clinical characteristics of the patients

Characteristic	Unit/detail	Study 1 (n=57)	Study 2 (n=13)
Age (y)	Median	69	66
	Range	45–86	56–80
ECOG	0	35 (61 %)	8 (62 %)
	1	22 (39 %)	5 (38 %)
Sites of metastatic disease	Bone	48 (84 %)	11 (85 %)
	Lymph node	28 (49 %)	3 (23 %)
	Visceral	7 (12 %)	6 (46 %)
	Other (skin)	1 (2 %)	1 (8 %)
PSA ng/ml	Median	97.15	12.55
	Range	6.54–5408.01	0.90–818.00
CTC count CTC/7.5 ml	n with no CTC; n with <5 CTC n with ≥5 CTC	11 (20 %) 17 (31 %) 26 (48 %)	N/A
CTC in patients with ≥5 CTC/7.5 ml	Median	33	N/A
	Range	5–712	N/A
Prior hormonal therapies	LHRH	57	13
	Orchiectomy[a]	0	1
	Anti-androgen	54 (95 %)	13 (100 %)
	Diethylstilboestrol	8 (14 %)	0
	Single-agent corticosteroids	9 (16 %)	5 (38 %)
Prior chemotherapy	Docetaxel	23 (40 %)	10 (26 %)
	Cabazitaxel	2 (4 %)	0
	Mitoxantrone	1 (2 %)	0
	Estramustine	0	5 (38 %)
	Tegafur-uracil	0	1 (8 %)
Prior novel hormonal therapies	Abiraterone discontinued before study start	4	1
	Enzalutamide	0	0
	Abiraterone continued and AZD3514 added on progression	5	0

[a] one patient started on LHRH analogues and later had orchiectomy

were administered AZD3514 tablets at doses of 250–500 mg QD and 500 mg BID.

AZD3514 was rapidly absorbed with median time to peak plasma concentration between 1 to 3 h following oral administration, after which plasma levels declined in a bi-phasic manner with the majority of AZD3514 eliminated by 24 h post-dose. The geometric mean plasma concentration vs. time profiles following a single-dose of AZD3514 and at steady state for study 1 are shown in Fig. 1. Similar plasma concentration vs. time profiles were observed in study 2 (data not shown).

Safety and tolerability

Overall, treatment with AZD3514 was safe at doses below 2000 mg BID with mainly grade 1 to 2 AEs observed across both studies (Table 4). The most common treatment-related AEs (>10 %) were grade 1 to 2 nausea (n=55; 79 %), vomiting (n=34; 49 %); fatigue (n=16; 23 %), lethargy (n=16; 23 %), anorexia (n=15; 21 %), dysgeusia (n=11; 16 %),

diarrhoea (n=10; 14 %) and constipation (n=8; 11 %). The frequency of AEs was generally greater in patients who received larger doses of AZD3514; 38/39 (97 %) patients who received ≥1000 mg QD AZD3514 experienced any grade nausea, while 18/31 (58 %) patients who received <1000 mg QD experienced nausea. Notable differences between studies 1 and 2 included lethargy (14 % vs. 0 %), abdominal discomfort (2 % vs. 15 %) and fatigue (32 % vs. 8 %). Four patients (6 %) experienced grade 1/2 thrombocytopenia and a further 2 patients grade 3/4 thrombocytopenia. Four of the six patients with any grade thrombocytopenia were dosed with ≥1000 mg QD AZD3514. A total of 54 patients (n=46 (81 %) study 1; and n=8 (62 %) study 2) required 5-HT3 antagonist treatment to control AZD3514-related nausea and vomiting. Dose reductions due to AEs occurred in 9 (13 %) patients and dose interruptions in 17 (24 %) (Table 1). Neither nausea nor vomiting was considered by the SRC to be a DLT as these AEs were not deemed of sufficient severity and could in most cases be controlled by anti-emetics including metoclopramide, domperidone or 5-HT3 antagonists.

Table 3 Study 1 & study 2 steady state AZD3514 PK parameters

Parameter	Study 1						Study 2		
	Monotherapy					Combination with abiraterone	Monotherapy		
	100 mg QD (N=5)	250 mg QD (N=6)	500 mg QD (N=12)	1000 mg QD (N=12)	1000 mg BD (N=9)	500 BD (N=5)	250 mg QD (N=4)	500 mg QD (N=4)	500 mg BD (N=5)
AUC_{ss}[a] (ng.h/ml)	6662 (8.9)	15640 (35)	27180 (29)	55830 (25)	36890 (23)	20650 (30)	16180 (34)	41330 (15)	23320 (20)
$C_{ss\,max}$[a] (ng/ml)	1059 (4.9)	3054 (40)	5086 (27)	9194 (24)	9750 (36)	4914 (19)	3218 (17)	6809 (10)	5099 (26)
$t_{ss\,max}$[n] (h)	1.0 (0.9–1.0)	2.0 (1.0–2.1)	2.0 (1.0–4.0)	2.0 (1.0–3.3)	1.0 (1.0–2.2)	2.1 (2.0–2.3)	1.5 (0.5–3.0)	1.5 (0.5–2.0)	2.9 (1.9–3.0)
CL_{ss}/F[o] (L/T)	15 (1.3)	17 (5.0)	19 (6.0)	18 (4.3)	25 (4.9)	25 (7.8)	16 (5.0)	12 (2.0)	22 (4.2)
Accumulation ratio[c]	1.05 (0.05)	0.96 (0.25)	0.93 (0.20)	0.91 (0.19)	0.75 (0.08)	NC	0.91 (0.06)	1.07 (0.20)	NC
Temporal change parameter[c]	0.91 (0.08)	0.86 (0.23)	0.87 (0.19)	0.85 (0.16)	0.70 (0.07)	NC	0.86 (0.08)	1.00 (0.18)	NC
$C_{ss\,min}$[d] (ng.mL)	38.9 (45)	8.74 (32)	112 (31)	219 (41)	519 (29)	324 (55)	67 (94)	189 (33)	535 (32)
Time above target concentration i 24 h period[b] (h)	<1	1.5 (<1.0–2.5>)	1.3 (1.0–5.5)	6.5 (4.5–10.0)	10.5 (4.0–12.0)	6.5 (3.0–10.0)	1.0 (1.0–2.0)	1.8 (4.0–6.0)	7.0 (6.0–10.0)

AUC_{ss} area under the plasma concentration-time curve at steady state, $C_{ss\,max}$ maximum observed plasma concentration at steady state, $C_{ss\,min}$ minimum observed plasma concentration the end of the dosing interval, $t_{ss\,max}$ time to $C_{ss\,max}$, CL_{ss}/F apparent clearance at steady state, *NC* Not calculable

[a] Geometric mean (%CV)

[b] Median (min max)

[c] Arithmetic mean (SD)

## PSA, CTC enumeration, and radiologic evidence for antitumor activity

In study 1, a decline in PSA (at any time) of ≥50 % was observed in 9/57 (16 %) patients; 15/57 (26 %) patients had a decline in PSA of ≥30 % (Table 5). Excluding the patients who received a combination with abiraterone (*n*=49), a decline in PSA of ≥50 % was observed in 7 (14 %) patients and a ≥30 % decline in 12 (24 %) patients. The change in PSA from baseline at 12 weeks and the maximal change at any time on study are presented in Fig. 2. Of the 9 patients with PSA decline ≥50 % at any time on study, 5 received ≥1000 mg QD AZD3514 and a further two received combination therapy with abiraterone; both of the abiraterone combination patients were abiraterone-naïve at study entry. A total of 9 patients had prior exposure to abiraterone (4 in the dose escalation cohorts, 5 in the expansion cohort); none of the 9 patients had a ≥50 % PSA decline on AZD3514 at any time on study and only 1 of these patients had a ≥30 % PSA decline. In study 2, a ≥30 % PSA decline at any time was observed in 4 (31 %) patients (Supplementary Figure S1 and Table 5).

Counts of CTCs were available for patients in study 1 only (Table 5). A total of 25 patients (44 %) had baseline CTC counts of ≥5/7.5 ml and biomarker data available for time on treatment. In these patients, a decline in CTC count from ≥5 to less than 5/7.5 ml was documented in 9/25 (36 %), and 16/25 (64 %) patients had a decline of ≥30 % (at any time) after starting treatment with AZD3514 (Fig. 3).

By RECIST criteria, 24 patients had measurable disease on CT scan in study 1. Thirty-three patients had no target lesions or had non-evaluable follow up assessments. Significant tumour shrinkage by RECIST criteria was noted in 4 patients; 3 partial responses (PRs) and 1 complete response (CR). The CR was a patient with nodal disease and this patient, together with one of the PRs, received the up-front combination of AZD3514 plus abiraterone. The two remaining PRs were patients who were on AZD3514 monotherapy at 1000 mg QD (Fig. 4). In study 2, 3 patients were evaluable and the best objective response was stable disease for all 3 patients. For studies 1 and 2 combined, 30 patients (43 %) had no evidence of progression and remained on study at 6 months, and 15 patients (21 %) at 12 months.

Discussion

These two phase I studies evaluated the safety and tolerability of continuous oral AZD3514, a selective AR down-regulator. AZD3514 had significant issues with long-term tolerability, namely nausea and vomiting. No DLTs were identified in this trial but chronic dosing was associated with high rates of mainly grade 1–2 nausea and vomiting despite standard supportive measures. A significant proportion of patients required
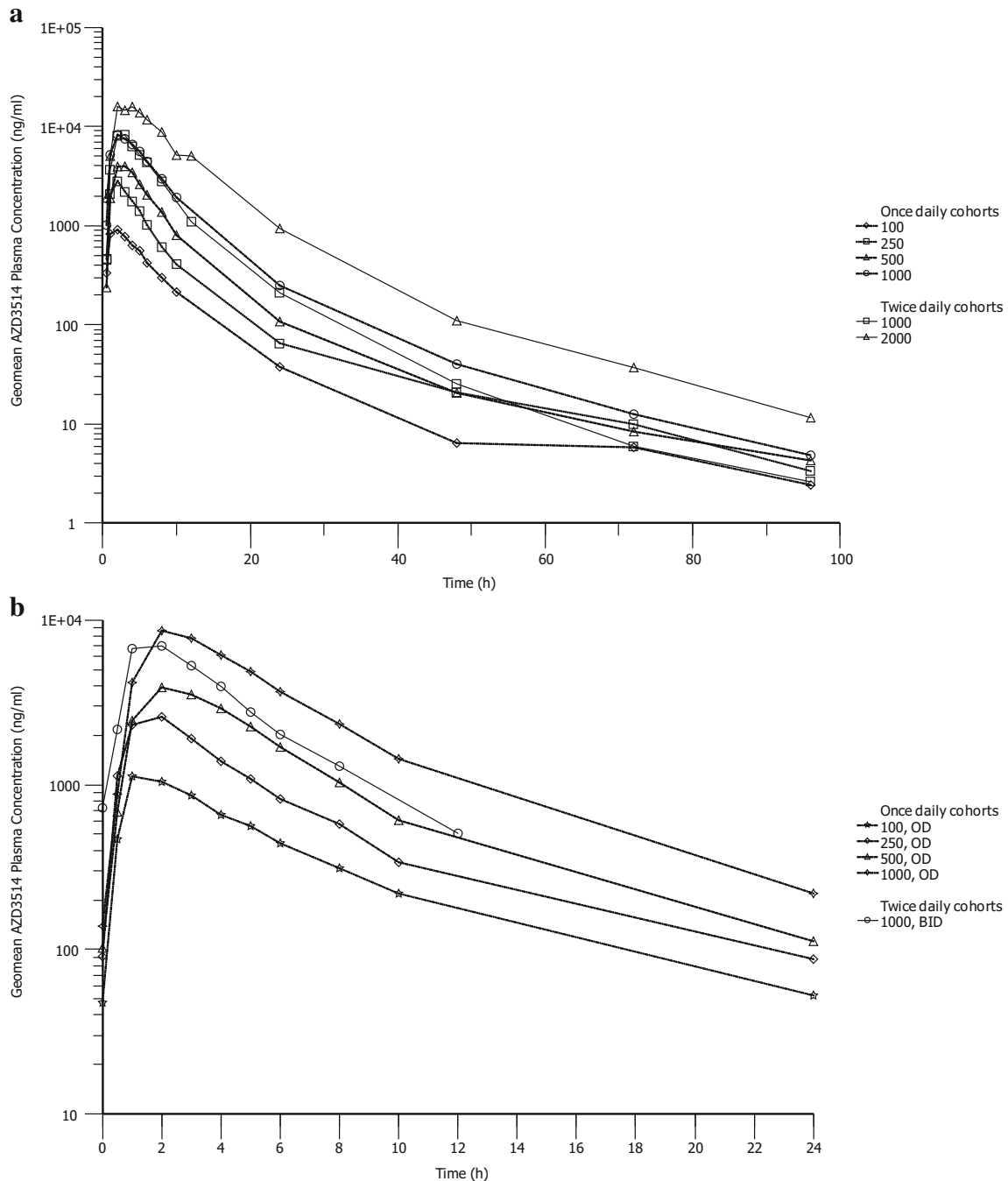
Fig. 1 **a**. Study 1 single-dose geometric mean AZD3514 monotherapy plasma concentration vs. time (Day 1). **b**. Study 1 steady state geometric mean AZD3514 monotherapy plasma concentration vs. time (Day 29)

long-term prophylactic dosing with 5-HT3 antagonists. The aetiology of the observed nausea and vomiting could not be fully elucidated in the trial. Pre-clinical data had suggested the drug may produce some gastric irritation, but the fact that a large number of patients required centrally acting anti-emetics suggests perhaps a central mechanism. Another compound, which seems to have AR-degrading properties is galeterone and preliminary activity and safety data have been recently presented [21]. Treatment related nausea and vomiting (all

grades) occurred in 33.6 and 12.1 % of patients respectively, however grade 3/4 nausea and vomiting were uncommon (<1 %) [22]. For the potent AR-antagonist enzalutamide, nausea and vomiting have not been reported at relevant frequencies both in the pre- and post-chemotherapy phase III clinical trials [6, 5].

AZD3514 monotherapy demonstrated moderate anti-tumour activity with documented PSA declines, conversions of CTC counts and RECIST responses at the plasma

Table 4 Adverse events causally-related to AZD3514 observed at frequency ≥10 % in study 1 or study 2

Adverse event[a]	Study 1 (monotherapy only, n=49)			Study 1 (all cohorts, n=57)			Study 2 (n=13)			Total study 1 and 2 (n=70)		
	Grades 1–2	Grades 3–4	All grades (%)	Grades 1–2	Grades 3–4	All grades	Grades 1–2	Grades 3–4	All grades (%)	Grades 1–2	Grades 3–4	All grades (%)
Nausea	39		39 (79.6)	46	1	47 (82.5)	9		9 (69.2)	55	1	56 (80)
Nausea <1000 mg AZD3514 TDD	14		14 (60.9)	14		14 (60.9)	4		4 (50.0)	18		18 (58.1)
Nausea ≥1000 mg AZD3514 TDD[b]	25		25 (96.2)	32	1	33 (97.1)	5		5 (100)	37	1	38 (97.4)
Vomiting	24	1	25 (51.0)	30	1	31 (54.4)	4		4 (30.8)	34	1	35 (50)
Vomiting <1000 mg AZD3514 TDD	9		9 (39.1)	9		9 (39.1)	1		1 (12.5)	10		10 (32.3)
Vomiting ≥1000 mg AZD3514 TDD[b]	15	1	16 (61.5)	21	1	22 (64.7)	3		3 (60)	24	1	25 (64.1)
Fatigue	11	2	13 (26.5)	15	3	18 (31.6)	1		1 (7.7)	16	3	19 (27.1)
Decreased appetite	8	1	9 (18.4)	11	1	12 (21.1)	4		4 (30.8)	15	1	16 (22.9)
Dysgeusia	6		6 (12.2)	9		9 (15.8)	2		2 (15.4)	11		11 (15.7)
Diarrhoea	7		7 (14.3)	9		9 (15.8)	1		1 (7.7)	10		10 (14.3)
Constipation	6		6 (12.2)	6		6 (10.5)	2		2 (15.4)	8		8 (11.4)
Lethargy	8		8 (16.3)	8		8 (14.0)	0		0	16		8 (11.4)
Dizziness	5	1	6 (12.2)	5	1	6 (10.5)	1		1 (7.7)	6	1	7 (10)
Platelet count decreased	4		4 (8.2)	4		4 (7.0)	0	2	2 (15.4)	4	2	6 (8.6)
Abdominal discomfort	1		1 (2.0)	1		1 (1.8)	2		2 (15.4)	3		3 (4.3)

TDD total daily dose

[a] Numbers of patients with a specific AE are for all cohort doses unless stated

[b] Includes 500 mg BID AZD3514 with abiraterone in study 1 and 500 mg BID AZD3514 monotherapy in study 2

Table 5 PSA and circulating tumour cells (CTCs) on AZD3514 treatment

	PSA ≥50 % decline	PSA ≥50 % decline confirmed ≥3 weeks later	PSA ≥30 % decline	CTC conversion to <5 from a baseline ≥5[a]	CTC ≥30 % decline[a]
Study 1					
AZD3514 monotherapy n=49	7 (14 %)	6 (12 %)	12 (24 %)	8/23 (35 %)	15/23 (65 %)
AZD3514 & abiraterone; AA naive n=3	2 (66 %)	2 (66 %)	2 (66 %)	1/1 (100 %)	1/1 (100 %)
All study 1 patients post-abiraterone n=9	0/9	0/9	1/9 (11 %)	1/4 (25 %)	2/4 (50 %)
All study 1 cohorts n=57	9 (16 %)	8 (14 %)	15 (26 %)	9/25 (36 %)	16/25 (64 %)
Study 2					
AZD3514 monotherapy n=13	2 (15 %)	1 (8 %)	4 (31 %)	N/A	N/A

N/A data not available

[a] Only in patients with baseline ≥5 CTC/7.5 ml

exposures achieved in the studies. The PK of AZD3514 was sub-optimal and the target of 18 h over the IC_{50} of 2410 ng/ml predicted to be required for efficiency from preclinical models was not achieved due to the combination of adverse events and the PK properties of the drug. Anti-tumour activity was poor in patients who had previously discontinued abiraterone or who were progressing on abiraterone at the time of study entry. Furthermore, in light of the already available AR-

targeting treatment options in CRPC and the array of experimental compounds in late stage development, the activity of AZD3514 in patients that were mostly abiraterone- and enzalutamide-naive was considered insufficient to warrant further development of this experimental drug.

The concept of targeting the AR in CRPC is valid and supported by the fact that even in patients progressing after abiraterone or enzalutamide the disease is still AR driven.

Fig. 2 **a**. PSA decline on treatment with AZD3514 at 12 weeks in study 1 by dose cohort. In patients with no decline on treatment maximum PSA increase is captured and capped at 50 %. **b**. PSA decline on treatment with AZD3514 at any time in study 1. Asterisked columns indicate patients who received prior abiraterone acetate
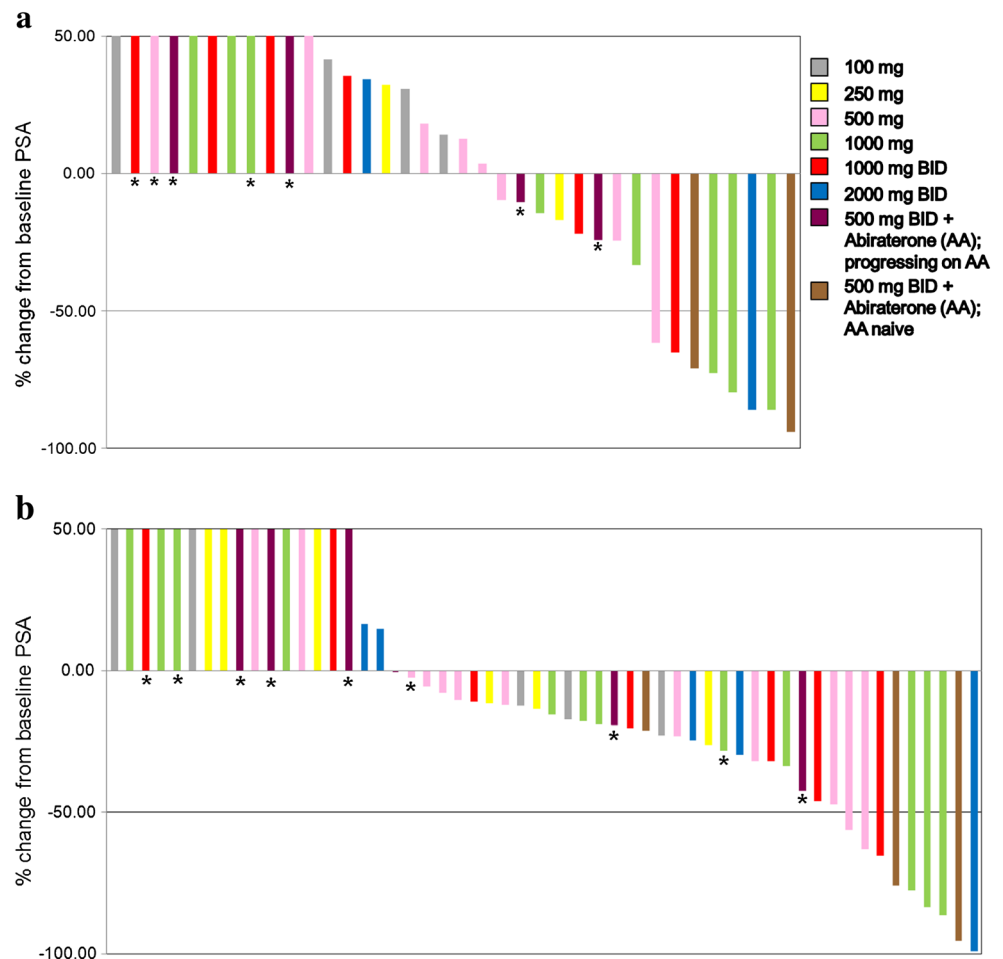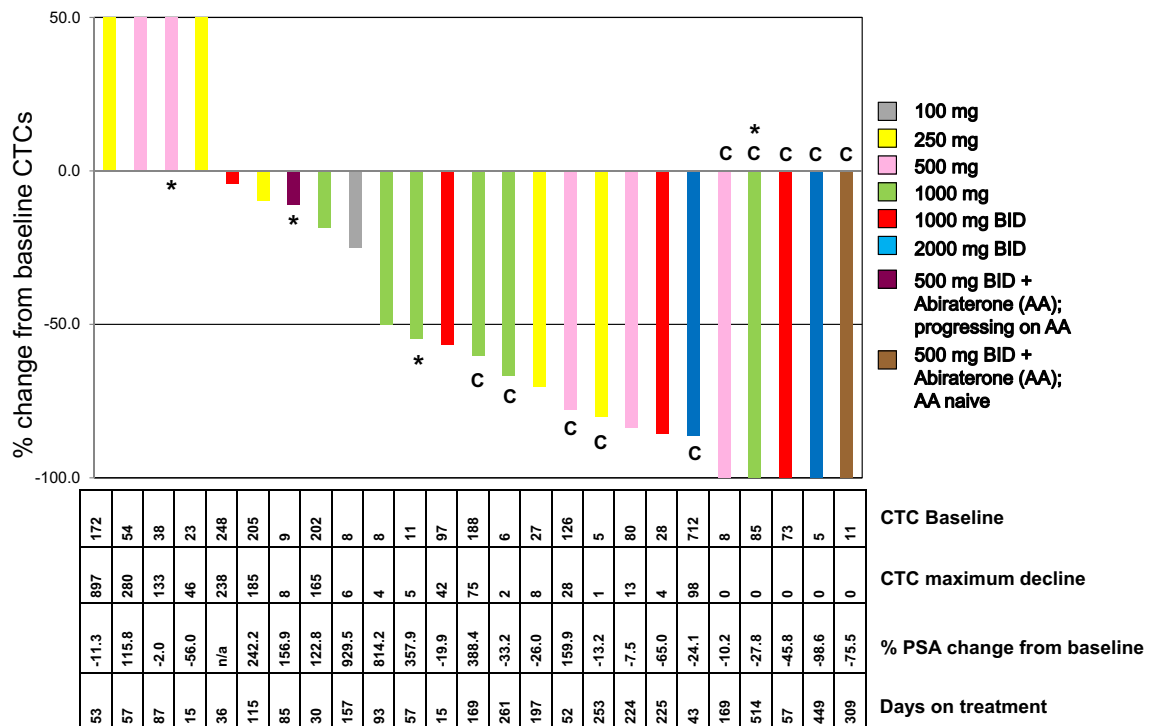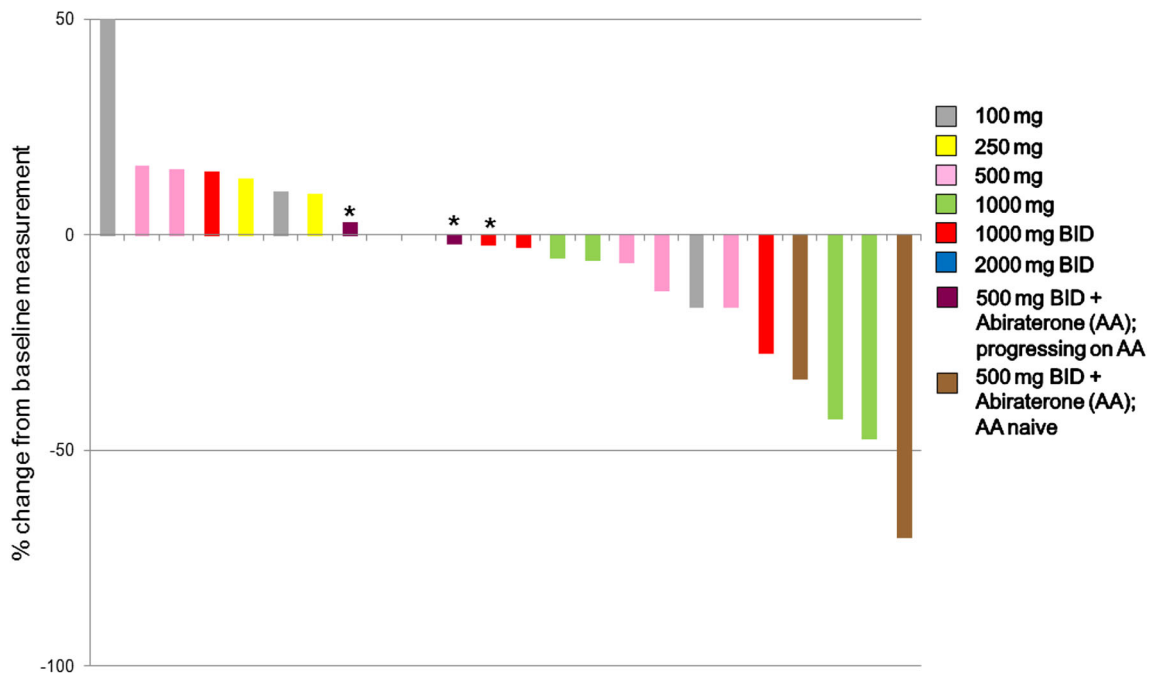
Fig. 3 Maximum CTC decline at any time on treatment in study 1 by dose cohort. Each bar in the figure represents an individual patient. For patients with no declines the figure shows maximum increase capped at 50 %. Only patients with ≥5 CTCs/7.5 ml blood at baseline are included. *Asterisks* indicate patients who had received prior abiraterone acetate and "c" patients who had a≥50 % CTC decline that was confirmed from a separate blood sample collected 3–4 weeks later. The *numbers below the figure* show the CTC counts for patients represented by the *bar* directly above, and include baseline CTCs (*top row*), CTCs at maximum decline (*2nd row*), maximal PSA decline from baseline (*3rd row*) and total number of days receiving AZD3514 (*bottom row*)

Recent data suggest that progression following abiraterone or enzalutamide is mediated by AR-splice variants (AR-sv) [23, 24]. Selective AR-down-regulating compounds (SARDs) could potentially be important if their mechanism of

Fig. 4 Maximum tumour shrinkage of target lesions in study 1 at any time on treatment. *Asterisks* indicate patients who had received prior abiraterone acetate. In patients with no decline on treatment maximum PSA increase is captured and capped at 50 %

action is independent of the presence of the AR ligand binding domain. Pre-clinical data suggested that AZD3514 inhibited AR-signalling through two distinct mechanisms: inhibition of ligand-driven nuclear transloca-tion of AR and down-regulation of receptor levels, both of which were observed in vitro and in vivo. In the described clinical studies, attempts were made to collect paired tu-mour biopsies but were unsuccessful. Thus, we were not able to evaluate AZD3514-driven AR knock-down in pa-tients, as had been observed in prostate models. Reasons for not seeing greater clinical benefit even at the highest dose levels may be due to a number of reasons, including lack of sufficient target cover and inability to engage and deplete AR-sv.

However, these studies lend support to the hypothesis that down-regulating AR is associated with anti-tumour activity, and further research into this class of compounds is ongoing. There is an unmet need for AR inhibitors that also block AR-sv. We hypothesize that the treatment-associated nausea and vomiting observed in these studies was mediated by central mechanisms. Therefore, more effective AR inhibitors may also be associated with increased toxicity (especially if they potentially penetrate the blood-brain barrier). Novel com-pounds (e.g., EPI-001) that bind to the N-terminal domain of the AR and interfere with protein-protein interaction may be promising new approaches [25, 26].

In conclusion, dosing with AZD3514 was associated with moderate anti-tumour activity in CRPC patients but was not well tolerated at biologically active doses, with nausea and vomiting being the main toxicities. However, antitumor activ-ity with significant PSA declines, objective responses and durable disease stabilisations provide a rationale for further development of AR-targeting compounds.

Conflict of interest vdNR, JHMS, RR, N-R D, JJA, AZ, MC, MO, JG, CD, RS, DM, MN: no conflict of interest.

TE: Advisory role for Astellas, AstraZeneca, Janssen, Sanofi.

AO: Advisory role for Pfizer, Janssen, Bayer, Sanofi, Astellas, AstraZeneca.

RJJ: Consultancy for Janssen, Astellas, Sanofi, Dendreon; speaker honoraria for Astellas, Janssen, Sanofi, Ferring. Research funding from AstraZeneca, Janssen, Astellas, Medivation, Sanofi.

MR: Advisory role for AstraZeneca.

SAS, GC, PD, AD, MM, RDF: (1) AstraZeneca stock ownership; (2) AstraZeneca employee at the time of this study.

JDB: has received consulting fees and travel support from AstraZeneca, and grant support from AstraZeneca

TS: Speaking fees from Daiichi Sanko, AstraZeneca, Astellas, Janssen

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