Enzalutamide in Combination with Abiraterone Acetate in Bone Metastatic Castration-resistant Prostate Cancer Patients

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Abstract

Background: It is hypothesised that cotargeting the androgen receptor (AR) and paracrine androgen biosynthesis with enzalutamide and abiraterone acetate in metastatic castration-resistant prostate cancer (mCRPC) will dissipate adaptive feedback loops observed with either agent alone.

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Objective: To assess the safety, efficacy, androgen signalling/metabolome, and drug-drug interactions (DDIs) of enzalutamide with abiraterone acetate in progressive bone mCRPC (bmCRPC).

Design, setting, and participants: This open-label, single-centre interventional study was conducted in bmCRPC patients.

Intervention: Enzalutamide 160 mg and abiraterone acetate 1000 mg once daily; prednisone 5 mg twice daily.

Outcome measurements and statistical analysis: Adverse events (AEs), prostate-specific antigen (PSA) response, progression-free survival (PFS), tumour biomarker/metabolite expression, and C_{min} plasma concentrations were evaluated.

Results and limitations: Sixty patients were enrolled. Common AEs independent of grade/causality included fatigue (72%), hyperglycaemia (67%), alkaline phosphatase (ALP) elevation (53%), and hot flush (43%). Grade 3 AEs included hypertension (17%), alanine aminotransferase elevation (12%), ALP elevation (5%), and arthralgia (5%). No treatment-related grade 4 AEs or deaths were reported. Median treatment-discontinuation time was 312 d (95% confidence interval [CI] 196.0–483.0). Maximal PSA decline 50% and 90% occurred in 46 (77%) and 29 (48%) patients, respectively. Median PFS was 251 d (95% CI 147–337). At week 9, median tumour microenvironment androgens, precursors, and nuclear AR expression decreased ($p < 0.001$). The baseline tumour AR C/N terminal ratio of 80% was associated with treatment benefit. At enzalutamide steady state, abiraterone acetate C_{min} was ~23% lower (range 14.05–200.5 ng/ml) than when given alone.

Conclusions: Enzalutamide combined with abiraterone acetate has a manageable safety profile, without a meaningful DDI. Both agents are pharmacodynamically active with no feedback. Efficacy findings do not support significant benefit of combined treatment for unselected bmCRPC.

Patient summary: This is the first study combining enzalutamide plus abiraterone in bone metastatic castration-resistant prostate cancer. Results show that this combination is safe.

1. Introduction

Enzalutamide, a potent second-generation androgen receptor (AR) antagonist, and abiraterone acetate plus prednisone (henceforth referred to as "abiraterone"), a first-generation androgen biosynthesis inhibitor, individually prolong the lives of men with metastatic castration-resistant prostate cancer (mCRPC) [1–5]. These findings have informed the initial hypothesis that intracrine androgen biosynthesis [6] and alterations in the AR, such as amplification, mutation, and potentially splice variants [7], remain drivers of castration-resistant disease progression and suitable therapy targets.

As anticipated, not all patients benefit equally [1–5] and progression patterns differ. Our correlative clinical studies demonstrate that the clinical efficacy of enzalutamide and abiraterone may depend on, or vary according to, pretreatment AR signalling [8,9]. These observations are indicative of interpatient, intrapatient, and temporal tumour heterogeneity [10], allowing for the determination of two broad groups of prostate cancer: one group is primarily resistant to enhanced androgen deprivation with no benefit from further suppression of androgen signalling with existing agents and in the other group androgen signalling remains a meaningful, though not exclusive, "driver". We hypothesised that within the latter group, the combination of enzalutamide and abiraterone may inhibit androgen signalling more completely than either agent alone. The rationale for the combination derives from previous single-agent studies with enzalutamide or abiraterone, pointing to a two-compartment, potentially adaptive, feedback loop [8,9]. The hypothesis tested is that the combination will dissipate the adaptive response observed with each agent alone. That may contribute to improved efficacy in a subset of patients if observed feedbacks are implicated in secondary resistance to androgen signalling inhibition.

This first reported combinatorial phase 2 study [11] evaluated the safety, efficacy, tumour microenvironment effects on androgen signalling/metabolome, and potential drug-drug interactions (DDIs) of cotargeting AR and androgen biosynthesis with enzalutamide and abiraterone in patients with progressive bone metastatic castration-resistant prostate cancer (bmCRPC).

2. Patients and methods

2.1. Study design

This was a phase 2, open-label, single-centre interventional study. Key inclusion and exclusion criteria are included in the Supplementary material.

Oral enzalutamide 160 mg once daily, abiraterone 1000 mg once daily, and prednisone 5 mg twice daily were administered until disease progression (a composite endpoint comprising radiographic (per RECIST 1.1), prostate-specific antigen (PSA; per Prostate Cancer Working Group 2), and/or clinical disease progression (PSA progression alone was not sufficient), physician discretion, or patient withdrawal. This included discontinuation of any study drug or occurrence of an adverse event (AE), whereby continued treatment was not in the patient's best interest.

Disease evaluations were performed every three cycles. Patients underwent bone marrow biopsy (BMB) and bone marrow aspirate (BMA) prior to treatment initiation, at week 9, and upon treatment discontinuation. Optional pharmacokinetic predosing blood draws were performed on cycle (C) 1on day (D) 4 and C2D1 for abiraterone, on C2D1 for enzalutamide, and on C3D1 for BMBs and BMAs.

2.2. Endpoints

2.2.1. Primary endpoints—Safety and tolerability were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE), version 4.03, per 28-d cycles.

2.2.2. Secondary endpoints—Efficacy was assessed by PSA decline from baseline (30%, 50%, and 90%), and progression-free survival (PFS) was defined as the time from treatment initiation until progression, study withdrawal, or death.

Changes in AR signalling, androgen levels, and other pathways of interest and proliferation within the tumour microenvironment were also evaluated.

2.2.3. Exploratory endpoints—DDIs were determined by assessment of plasma concentrations of enzalutamide and its metabolite M2, and abiraterone.

Nuclear expression of AR N and C terminals, ARV7, CYP17, NKX3.1, and other markers (not shown) was assessed in tumour infiltrate bone marrow samples by immunohistochemistry (Supplementary material) [8,9].

Androgen precursor and other associated metabolite concentrations in BMA and peripheral blood were assessed using liquid chromatography mass spectrometry.

2.3. Statistical analyses

Statistical analyses are outlined in the Supplementary material.

3. Results

3.1. Baseline patient and tumour characteristics

Sixty bmCRPC patients were enrolled between June 2012 and August 2015 (Supplementary Fig. 1). Baseline patient and tumour characteristics are presented in Table 1.

3.2. Safety and tolerability

All patients reported one or more AEs, independent of causality. The most frequent any-grade AEs (40% incidence) were fatigue (43 patients; 72%), hyperglycaemia (40 patients; 67%), blood alkaline phosphatase increase (32 patients; 53%), and hot flush (26 patients; 43%; Supplementary Table 1). Grade 3 AEs occurring in more than one patient are reported in Table 2. One patient (2%) reported grade 3 fatigue. One patient (2%) reported a grade 4 event (elevated creatinine level) that was considered unrelated to treatment. Ten serious AEs were reported in eight (13%) patients, two of which were considered treatment related (femur fracture and urosepsis). There were no grade 5 AEs and no deaths occurred.

Two (4%) patients had liver function AEs classified as potential drug-induced liver injury (two times the upper limit of normal range for alanine aminotransferase [ALT] and/or two times the upper limit of normal range for aspartate aminotransferase in combination with two times the upper limit of normal range for total bilirubin). One patient discontinued treatment, while the other continued with a reduced dose of abiraterone (750 mg). Overall, combination treatment revealed no new safety concerns.

3.3. Exposure and discontinuation

Median time to treatment discontinuation was 312 d (95% confidence interval [CI] 196.0–483.0; range 0–1134 d; Fig. 1A). Ten patients were still on treatment at the data cut-off date,

while 40 discontinued (Supplementary Fig. 1). Forty-one (68%) patients experienced radiographic or clinical disease progression: 16 (39%) experienced radiographic progression only, nine (22%) clinical progression only, and 16 (39%) more than one definition of progression. Three (5%) patients discontinued, as per physician decision, for PSA increase only. Five (8%) patients withdrew for one of the following reasons: grade 3 ALT and aspartate aminotransferase increases, withdrawal of consent, physician decision, intervention, and sponsor decision. Of note, 11 (18%) patients exhibited primary resistance with progression within 4 mo, as previously defined [8]. Associations between pretreatment patient and tumour characteristics and time to treatment discontinuation were observed. Prior chemotherapy, tumour-infiltrated lymph nodes, tumour-infiltrated biopsy, and time to castration-resistant prostate cancer <1 yr were associated with primary resistance (Supplementary Fig. 2).

3.4. Efficacy

A maximal decline from baseline in PSA level of 50% occurred in 46 (77%) patients, with 52 (87%) having a 30% decline and 29 (48%) having a 90% decline. Six (10%) patients did not experience a decrease in PSA level (Fig. 1B). Median PFS was 251 d (95% CI 147–337; Fig. 1C).

Of the 16 patients with measurable soft tissue disease at screening and one or more postbaseline assessments, 11 (69%) had partial response, three (19%) had stable disease, and two (13%) had progressive disease as the best overall response per RECIST, version 1.1.

Mean and median urine *N*-telopeptide increased from baseline to week 9 (mean [standard deviation]: 72% [151%]; median: 38%) and at the end of treatment visit (mean [standard deviation]: 79% [78%]; median: 80%).

3.5. Effect of treatment on AR signalling and androgen levels

Twenty (33%) patients had bone marrow infiltration at pretreatment BMBs and 16 (27%) in subsequent C3D1 BMBs. Paired tumour-infiltrated specimens amenable to molecular characterisation (ie, tumour infiltration >10%) were available for 11 patients. Six (55%) tumours were primarily resistant to treatment (ie, progressed within 4 mo of treatment initiation per prior definition) [8], while five (45%) experienced confirmed treatment benefit and serum PSA decline. Reductions in tumour AR N/C terminal nuclear expression and downstream NKX3.1 expression were observed in these latter samples (Fig. 2).

Fifteen pretreatment tumour samples were evaluable for further molecular characterisation, including expression of AR (AR-N/AR-C), CYP17, and ARV7, and AR C/N terminal ratio and association with primary resistance. The combination of AR N terminal overexpression and expression of an AR C/N terminal ratio of 80% was significantly associated with treatment benefit ($p = 0.0002$; Supplementary Table 2 and Fig. 3). Two of six (33%) baseline tumour specimens with primary resistance, and none of those exhibiting benefit, had nuclear ARV7 expression.

There was a statistically significant decrease ($p < 0.001$) in median BMA and plasma testosterone, cortisol, and androstenedione levels from baseline to week 9 (Supplementary

Table 3 and Fig. 4). Conversely, median BMA, and plasma progesterone and pregnenolone levels increased significantly ($p < 0.001$) from baseline to week 9 (Supplementary Table 3).

No monotonic correlation was established between any of the androgens or other associated metabolites and blood PSA levels at baseline or week 9: bone marrow and plasma testosterone ($r = -0.1$ and -0.2, respectively), cortisol ($r = -0.3$ and -0.1, respectively), androstenedione ($-r = 0.1$ and -0.2, respectively), progesterone ($r = -0.02$ and -0.01, respectively), and pregnenolone ($r = -0.08$ and 0.08, respectively).

3.6. Predose concentrations of enzalutamide and its metabolite M2, and abiraterone

Enzalutamide mean steady-state C_{min} on C2D1 for patients in the current study (9785-CL-0011; $n = 15$) was similar to that observed for castration-resistant prostate cancer patients in the AFFIRM trial ($n = 704$; Astellas Pharma, Inc., Northbrook, IL, USA; data on file), suggesting that coadministration of enzalutamide and abiraterone has no influence on the exposure of enzalutamide (Supplementary Fig. 3A).

The least squares mean abiraterone concentrations indicate that C_{min} of abiraterone was approximately 23% lower on C2D1 (37.9 ng/ml; range 14.09–200.5 ng/ml), when both enzalutamide and abiraterone were at steady state, compared with C1D4 (48.8 ng/ml; range 14.39–172.22 ng/ml), when abiraterone was given alone ($n = 14$; least squares mean ratio 77.7%; 90% CI 47.5–127.0; Supplementary Fig. 3B). The observed data do not suggest a significant DDI when the treatments are given in combination, considering the large intrasubject variability, with approximately 31% for area under the curve and 42% for C_{max}.

4.   Discussion

The goal of this study was to assess safety of the combination and build on previously reported pharmacodynamics and efficacy results of enzalutamide and abiraterone in bmCRPC [1–5].

Based on the results of this study, cotargeting the AR and androgen biosynthesis with enzalutamide and abiraterone is feasible. The safety profile of the combination did not differ significantly from that reported for either drug alone, as it pertains to AEs of grade 3 severity. However, 72% of patients experienced fatigue of grade 1–2 severity that may impact quality of life and 67% of patients experienced hyperglycaemia. Additionally, grade 3 ALT increase was reported in seven patients, with liver function AEs classified as potential drug-induced liver injury in two patients.

Though no objective, direct comparisons can be made with reported phase 3 outcomes for each agent alone, time to progression in COU-AA-302 [2] and PREVAIL [4] appears longer than that reported in this study, while PSA declines are similar. The median radiographic PFS in COU-AA-302 was 16.5 mo with abiraterone-prednisone and 8.3 mo with prednisone alone (hazard ratio for abiraterone-prednisone vs prednisone alone, 0.53; 95% CI 0.45–0.62; $p < 0.001$). In PREVAIL study, the rate of radiographic PFS at 12 mo was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo

(81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% CI 0.15–0.23; $p <$ 0.001).

This may be due partly to enrolling some chemotherapytreated individuals with more advanced disease and differences in study design, specifically as it relates to assessment of disease progression. The variable treatment-discontinuation time and PFS response may still suggest that enzalutamide and abiraterone in combination may offer benefit in a subset of patients who remain to be identified.

A nuclear to cytoplasmic AR shift and a corresponding rise in tumour-associated testosterone following enzalutamide [9], and depletion of tumour-associated androgens with increased nuclear AR expression and AR copy numbers following abiraterone [8], have previously been reported. This agent-specific androgen signalling modulation indicates a two-compartment adaptive loop. Our findings demonstrate that in men with "androgen signalling–responsive" mCRPC, simultaneous inhibition of AR signalling and biosynthesis avoids the adaptive response of either agent alone, and may more completely suppress androgen signalling. Based on this, we hypothesise that more complete suppression of androgen signalling may more effectively control a subset of prostate cancer as compared with delivering either agent alone. A recent report of a phase 4 study comparing sequential versus combinatorial strategy has not identified differences in efficacy, though the design may have hindered addressing the specific question [12].

Primary resistance occurred in 11/60 (18%) patients treated, which is in line with single-agent phase 2 and 3 experience, hence supporting our hypothesis that primary resistant tumours are not driven by androgen signalling, and should be identified a priori and treated with a different strategy.

This study allowed us to further investigate the predictors of outcome. Our first report of an association between the presence of nuclear ARV7 in tumour biopsy specimens and primary resistance to enzalutamide [9] was explored; however, nuclear ARV7 expression was found only in two baseline specimens of primary resistant tumours. In an attempt to detect AR C terminal loss as a potential contributor to primary resistance, we utilised an AR C/N terminal ratio [13] and found a strong association ($p = 0.0002$) between pretreatment AR N terminal overexpression with an AR-C/AR-N expression ratio of 80% and treatment benefit in this limited sample size ($n = 9$). Other markers of interest were investigated (data not shown) without findings of any correlation, possibly due to the availability of a limited number of samples ($n = 15$). This is in line with the understanding that robust androgen signalling axis is a requirement for efficient tumour targeting in mCRPC. Our methodology differs from those employed by others as it is biopsy based and identifies nuclear protein expression, which might account for more limited incidence than ribonucleic acid and circulating tumour cell assays [14–16]. Taken together, these "by-association" findings regarding the presence of AR variants suggest a deficit in "wild-type" androgen signalling that may be an epiphenomenon and not necessarily a driver of primary or secondary resistance. Importantly, methodologies employed are not validated with recent controversial results, adding to the complexity. Based on the reports suggestive of an association between glucocorticoid receptor overexpression and resistance to enzalutamide [17] and inclusion of prednisone in

therapy schema, we assessed the expression of glucocorticoid receptor (data not shown) and identified no associations.

Given the potential for enzalutamide to induce CYP3A4 [18,19], pharmacokinetic assessments were an important component of our investigation. No significant DDIs that would limit this combination strategy were observed. Pharmacokinetic measurements were performed on C1D4 and C2D1. The latter measurement was consistent with enzalutamide steady state, though follow-up measurements may have provided more confidence in this finding.

Ongoing studies should test the hypothesis that cotargeting both AR and androgen biosynthesis inhibition in AR-responsive prostate cancer may further prolong survival in some mCRPC patients by delaying the emergence of resistance. This is an approach currently excluded from the treatment paradigm driven by a drug development strategy imposed by a lack of selection criteria. This is of particular relevance given the recent data supportive of a significant survival benefit by introducing androgen biosynthesis inhibition in the hormone-sensitive setting [20,21].

5. Conclusions

In this study conducted in bmCRPC patients, enzalutamide and abiraterone were used safely without adverse pharmacologic or pharmacodynamic interactions, differentiating patients into those with primary resistance and those who benefit from combination treatment. Our findings indicate that enzalutamide and abiraterone in combination prevent the "adaptive response" observed with either agent alone. However, we did not see an alteration in the incidence of primary resistance. Although it is hypothesised that treatment combination may contribute to increased efficacy in a subset of patients with bmCRPC, employing this adaptive feedback loop in treatment resistance warrants further investigation and validation of predictive markers that will help in the identification of these patients. We are looking forward to ongoing phase 3 study results interrogating the efficacy of enzalutamide and abiraterone in combination in bmCRPC to provide further insight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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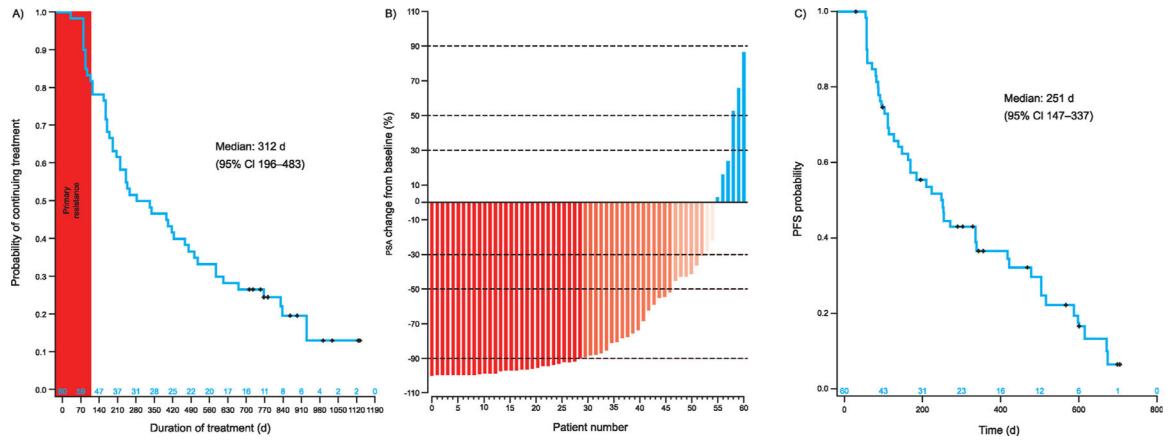
Fig. 1 –.
(A) Kaplan-Meier plot of time to treatment discontinuation, (B) waterfall plot of prostate-specific antigen change from baseline at nadir, and (C) Kaplan-Meier plot of progression-free survival. CI = confidence interval; PFS = progression-free survival; PSA = prostate-specific antigen.
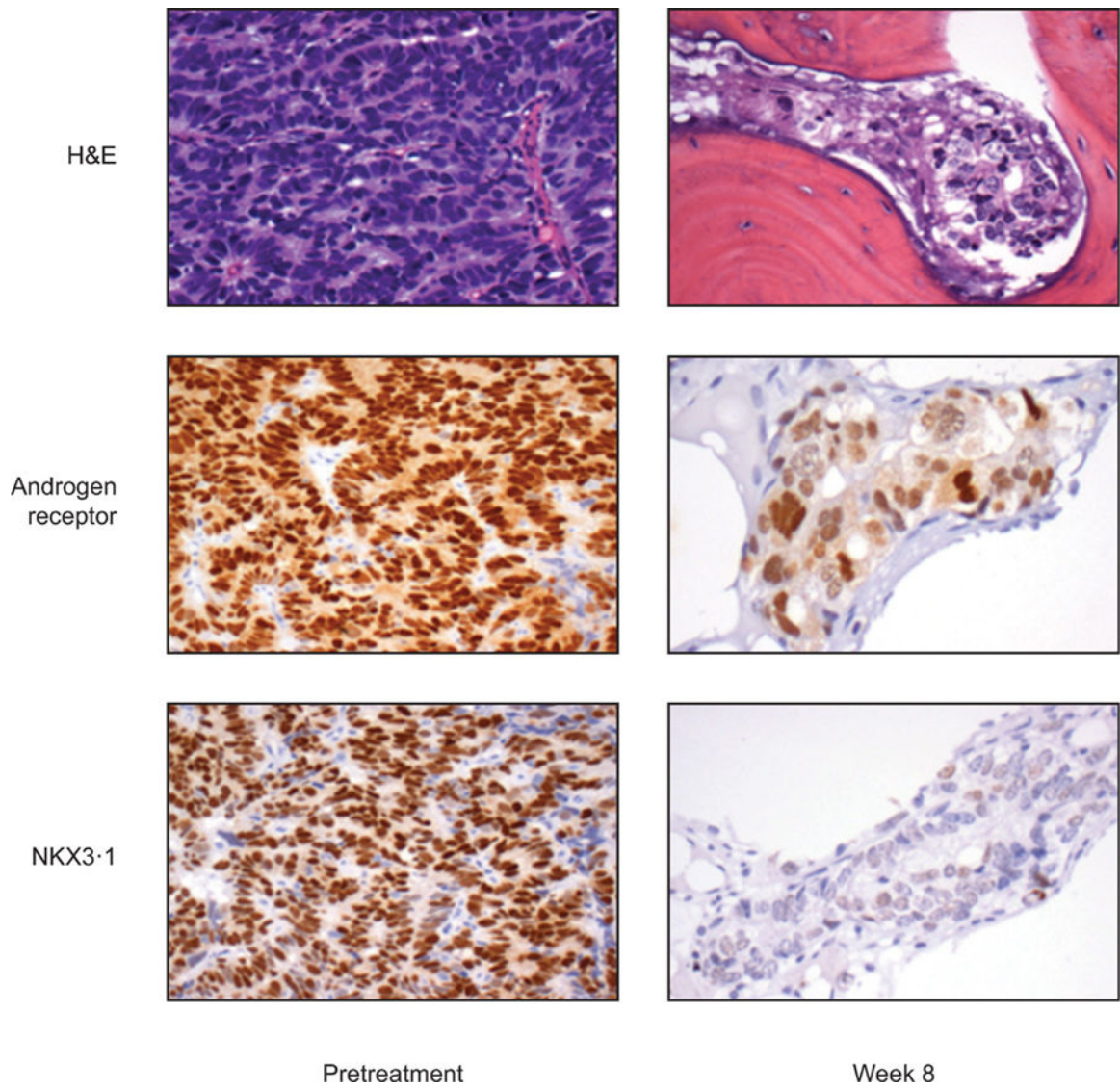
H&E

Androgen receptor

NKX3·1

Pretreatment   Week 8

Fig. 2 –.
Tumour AR-N terminal nuclear expression and downstream NKX3.1 expression using immunohistochemistry. AR = androgen receptor; H&E = haematoxylin and eosin stain.
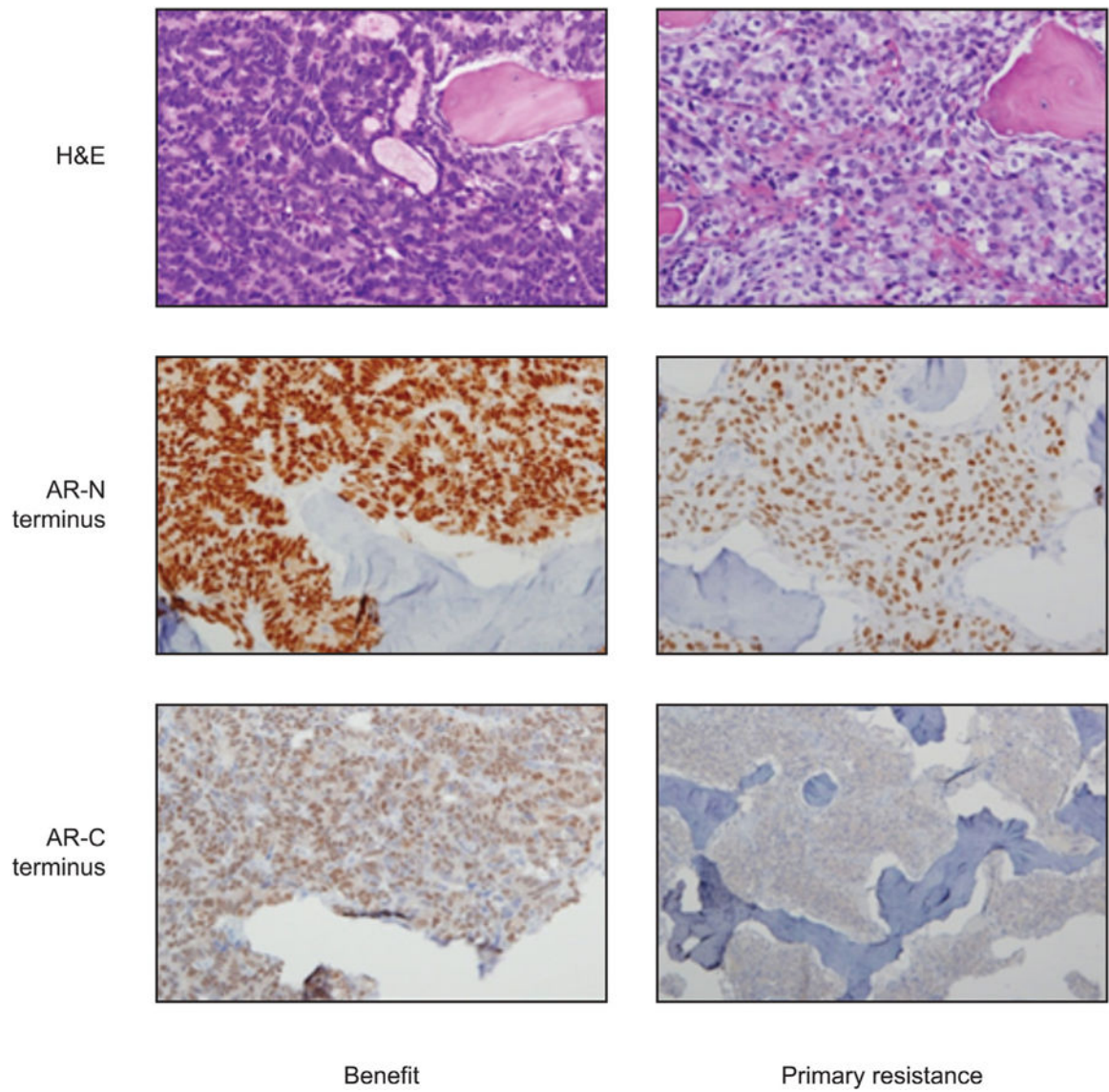
Fig. 3 –.

Ratio of AR-C/AR-N terminal expression and association with treatment benefit/primary resistance. AR = androgen receptor; H&E = haematoxylin and eosin stain.
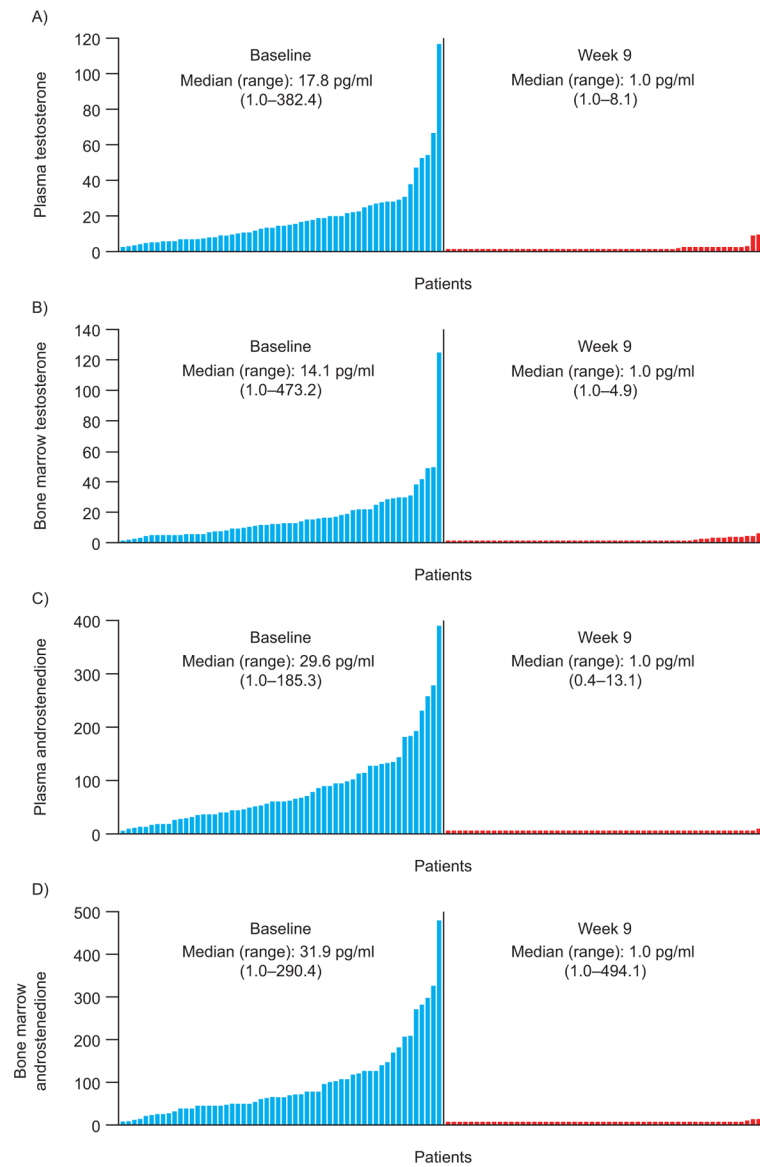
Fig. 4 –.
Waterfall plots of changes in (A and B) plasma and bone marrow testosterone and (C and D) plasma and bone marrow androstenedione at baseline and following 9 wk of treatment.

Table 1 –

Summary of demographic and baseline patient and tumour characteristics

Parameter	Patient number ($n = 60$)
Race, n (%)	
White	51 (85.0)
Black or African American	6 (10.0)
Asian	2 (3.3)
Other	1 (1.7)
Median age, yr (range)	66 (40–82)
Age category (yr), n (%)	
<55	7 (11.7)
55 to <75	44 (73.3)
75	9 (15.0)
Body mass index (kg/m^2), mean (±SD)	31.1 (±4.7)
Baseline PSA (μg/l), median (range)	20.7 (1.0–670.2)
Duration of prostate cancer (yr), median (range)	4.0 (0–19)
Prior treatments	
Median hormonal treatment lines (range)	1 (1–4)
Antiandrogens, n (%)	24 (40)
Oestrogens/prednisone, n (%)	5 (8)
Chemotherapy, n (%)	8 (13)
Other therapies, n (%)	6 (10)
ECOG PS, n (%)	
0	21 (35.0)
1	35 (58.3)
2	4 (6.7)
Gleason score at initial diagnosis,[a] n (%)	
7	14 (23.3)
8–10	39 (65.0)
Unknown/missing[a]	7 (11.7)
Distribution of disease at screening,[b] n (%)	
Bone	60 (100.0)
Lymph node	10 (16.7)
Visceral metastases[c]	6 (10.0)
Number of bone lesions at screening,[d] n (%)	
3–5	6 (10.0)
6–9	12 (20.0)
10–20	11 (18.3)
>20	31 (51.7)
Bone marrow infiltration, n (%)	
Baseline	19 (31.2)

Parameter	Patient number (n = 60)
Any time point	23 (38.4)

ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; SD = standard deviation.

[a] Primary and secondary Gleason grades were not available.

[b] Patients can be included in more than one category.

[c] Adrenal gland, one patient; prostate, one patient; lung, two patients; and right pelvic mass, two patients.

[d] Includes metastatic lesions per bone lesion.

Table 2 –

Summary of NCI CTCAE grade 3 adverse events occurring in more than one patient

Adverse event	Patient number ($n = 60$), n (%)
Hypertension	10 (16.7)
Alanine aminotransferase increase	7 (11.7)
Arthralgia	3 (5.0)
Alkaline phosphatase increase	3 (5.0)
Aspartate aminotransferase increase	2 (3.3)
Lymphocyte count decrease	2 (3.3)
Bone pain	2 (3.3)
Hypokalaemia	2 (3.3)
Syncope	2 (3.3)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.