Impact of Bone-targeted Therapies in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients Treated with Abiraterone Acetate: Post Hoc Analysis of Study COU-AA-302

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Abstract

Background—Metastatic castration-resistant prostate cancer (mCRPC) often involves bone, and bone-targeted therapy (BTT) has become part of the overall treatment strategy.

Objective—Investigation of outcomes for concomitant BTT in a post hoc analysis of the COU-AA-302 trial, which demonstrated an overall clinical benefit of abiraterone acetate (AA) plus prednisone over placebo plus prednisone in asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC patients.

Design, setting, and participants—This report describes the third interim analysis (prespecified at 55% overall survival [OS] events) for the COU-AA-302 trial.

Intervention—Patients were grouped by concomitant BTT use or no BTT use.

Outcome measurements and statistical analysis—Radiographic progression-free survival and OS were coprimary end points. This report describes the third interim analysis (prespecified at 55% OS events) and involves patients treated with or without concomitant BTT during the COU-AA-302 study. Median follow-up for OS was 27.1 mo. Median time-to-event variables with 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. Adjusted hazard ratios (HRs), 95% CIs, and p values for concomitant BTT versus no BTT were obtained via Cox models.

Results and limitations—While the post hoc nature of the analysis is a limitation, superiority of AA and prednisone versus prednisone alone was demonstrated for clinical outcomes with or without BTT use. Compared with no BTT use, concomitant BTT significantly improved OS (HR 0.75; $p = 0.01$) and increased the time to ECOG deterioration (HR 0.75; $p < 0.001$) and time to opiate use for cancer-related pain (HR 0.80; $p = 0.036$). The safety profile of concomitant BTT with AA was similar to that reported for AA in the overall intent-to-treat population. Osteonecrosis of the jaw (all grade 1/2) with concomitant BTT use was reported in <3% of patients.

Conclusions—AA with concomitant BTT was safe and well tolerated in men with chemotherapy-naïve mCRPC. The benefits of AA on clinical outcomes were increased with concomitant BTT.

Patient summary—Treatment of advanced prostate cancer often includes bone-targeted therapy. This post hoc analysis showed that in patients with advanced prostate cancer who were treated with abiraterone acetate and prednisone in combination with bone-targeted therapy, there was a continued trend in prolongation of life when compared with patients treated with prednisone alone.

Trial registration—ClinicalTrials.gov NCT00887198.

1. Introduction

Prostate cancer is the second most commonly diagnosed malignancy in men, with a 5-yr prevalence estimate of 3 200 000 men worldwide [1]. In the USA, prostate cancer is the second leading cause of cancer-related death in men [2]. Most patients who present with metastatic disease at diagnosis or with disease recurrence after potentially curative therapy with prostatectomy or radiation therapy respond to castration with androgen deprivation therapy [3]; however, progression to castration-resistant disease usually occurs within 2–3 yr [3,4]. Ultimately, almost all patients who progress after androgen deprivation therapy develop metastatic castration-resistant prostate cancer (mCRPC) [3,4], and more than 90% of patients with mCRPC develop bone metastases, which produces significant morbidity in many men and is associated with increased mortality [5,6].

Bone-targeted therapy (BTT) delays the development of symptoms and reduces the risk of bone-specific morbidities [7–10]. The BTT agents bisphosphonates and denosumab inhibit osteoclast-mediated bone resorption and can prevent bone loss and increase bone mineral density in patients with prostate cancer receiving androgen deprivation therapy [10–12]. Zoledronic acid and denosumab are effective for the prevention of skeletal-related events in patients with metastatic prostate cancer [13]. Historically, bone-seeking radiopharmaceuticals have been used as a palliative treatment for pain in patients with metastatic prostate cancer [14]. Radium-223 was the first radiopharmaceutical agent shown to improve survival for symptomatic patients with mCRPC and no visceral disease, and was recently approved for this indication [15].

Abiraterone acetate is converted in vivo to abiraterone, which inhibits the enzyme 17α-hydroxylase/C17,20-lyase and blocks extragonadal and testicular androgen biosynthesis, a key target for blocking tumor growth in mCRPC [16,17].

Study COU-AA-302 compared the efficacy and safety of abiraterone acetate plus low-dose prednisone (hereafter referred to as abiraterone) compared to prednisone alone in asymptomatic or mildly symptomatic men with chemotherapy-naïve mCRPC [20]. Abiraterone doubled time to radiographic progression-free survival (rPFS) compared to prednisone alone (median 16.5 vs 8.3 mo). All secondary endpoints significantly favored abiraterone over prednisone alone [20].

The third interim analysis (IA3) of study COU-AA-302 (56% of expected death events) confirmed that patients treated with abiraterone had a statistically significant improvement in rPFS (HR 0.52; $p < 0.0001$), The overall survival (OS) analysis favored abiraterone over prednisone alone (median 35.3 vs 30.1 mo, HR 0.79; $p = 0.0151$; prespecified statistical boundary $\alpha = 0.0035$), and the OS benefit of abiraterone was supported in an exploratory multivariate analysis (HR 0.74; $p = 0.0017$) that adjusted for baseline prognostic factors [22]. In addition, analyses of prespecified measures of patient-reported outcomes confirmed that abiraterone treatment delayed pain progression and deterioration in functional status compared with prednisone alone [21,22]. The objective of the present post hoc analysis of

study COU-AA-302 was to evaluate the clinical benefits and safety of abiraterone and concomitant BTT in chemotherapy-naïve mCRPC patients.

2. Patients and methods

Study COU-AA-302 (NCT00887198) is a phase 3, multinational, randomized, double-blind, placebo-controlled study being conducted at 151 sites in 12 countries. Patients were enrolled from April 2009 to June 2010, and the study is ongoing. The ethics review boards at all participating institutions approved the study, and all patients gave written informed consent.

2.1 Study design

The study design and the primary and secondary efficacy endpoints have been described previously [20]. The study included male patients with mCRPC aged 18 yr who were medically or surgically castrated, had tumor progression, and were asymptomatic or mildly symptomatic. Patients with visceral metastases were excluded, as were patients who had received previous therapy with ketoconazole for >7 d.

Patients were randomized at a 1:1 ratio to receive abiraterone acetate 1 g daily and prednisone 5 mg twice daily (abiraterone group) or placebo and prednisone 5 mg twice daily (prednisone alone group) via a centralized interactive web/voice response system in this double-blind, placebo-controlled multinational study. A permuted block randomization was used. The treatment was in continuous 28-d cycles [20]. Patients were stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score (0 vs 1). Concomitant BTT use was defined as the use of at least one of the following classes of bone drugs during the study: bisphosphonate, RANKL inhibitor, radiopharmaceutical, or other bone-targeted agent. Patients had the first recorded dose of BTT in the study after randomization, and although new BTT was not allowed per protocol, 7% of patients treated with BTT were actually treated after study entry. The primary end point of rPFS was defined as time from randomization to radiographic progression, as previously described [20]. Secondary endpoints were time to prostate-specific antigen (PSA) progression according to Prostate Cancer Working Group 2 criteria, time to initiation of cytotoxic chemotherapy, time to opiate use for cancer-related pain, and time to deterioration in ECOG PS score by 1 point [23]. Adverse events (AEs) of special interest included events related to mineralocorticoid excess (hypertension, hypokalemia, fluid retention).

2.2. Statistical analyses

The present analyses represent IA3 data at 56% of expected death events. The medians for time-to-event variables with 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. Patients were grouped by concomitant BTT use or no BTT use. Since most patients who used concomitant BTT received it from study start (336/353, 95%), concomitant BTT use was treated as a baseline covariate. However, sensitivity analyses treating concomitant BTT use as time-dependent were also conducted and showed similar results. The adjusted HRs, 95% CIs, and p values for concomitant BTT use versus no BTT use were obtained through Cox models that also included treatment and key baseline factors (PSA, lactate dehydrogenase, alkaline phosphatase, hemoglobin, and whether a patient had

bone metastases only at entry) as covariates. The treatment effect on all endpoints within each subgroup was assessed using a stratified Cox regression model, and p values were determined by stratified log-rank test. No adjustment for multiple testing was made for this post hoc analysis; significance was declared for p 0.05.

3. Results

A total of 353 patients (34% [184/546] of the abiraterone group, 31% [169/542] of the prednisone group) were receiving concomitant BTT. Of these 353 patients, 93% were treated with zoledronic acid, 6% with denosumab, and the remaining 1% with other BTT. Among the 353 patients who received concomitant BTT, 336 (95%) were receiving BTT at baseline. Another 17 (5%) patients started BTT during the study. Baseline patient characteristics were generally similar among the treatment arms (Table 1). As expected, there was a higher prevalence of bone disease and a higher percentage of patients with a baseline Gleason score   8 among patients with BTT use. In the BTT group, 93% (329/353) of patients had bone disease at study entry, with a median time of 4 yr from the time of initial diagnosis to first dose of the study drug. In the group without BTT use, 76% (555/735) of patients had bone disease at study start, with a median time of 6 yr from the time of initial diagnosis to first dose of study drug. BTT use in patients without bone disease at study start was compatible with the dosing used for bone loss prevention, not the level used for bone metastases. The primary and secondary endpoint results obtained at the time of the IA3 have been described in detail previously [22].

3.1. Effect of concomitant BTT use versus no BTT use

The effect of concomitant BTT use on clinical endpoints was evaluated using data from both treatment arms. The interaction effects of concomitant BTT use and treatment group were not statistically significant for any of the endpoints (Table 2; p = 0.13–1.0). Point estimates of HRs for all efficacy endpoints were <1.0. BTT use was associated with significantly longer OS ($p = 0.012$; risk reduction 25%), longer time to deterioration in ECOG PS ($p < 0.001$, risk reduction 25%), and longer time to opiate use for cancer-related pain ($p = 0.036$, risk reduction 20%; Table 2). BTT use was not associated with significantly longer time to chemotherapy initiation or to PSA progression.

3.2. Subgroup analysis

Exploratory associations with clinical outcomes were evaluated within the subgroups of patients with and without BTT use. Favorable results for abiraterone were observed for all endpoints with or without BTT use, although statistical significance was not consistently achieved because of the reduced sample size in each subgroup (Table 3). The Kaplan-Meier data for time-to-event outcomes stratified by BTT use in each of the treatment arms illustrate the effect of BTT use and beneficial effects on OS, time to opiate use, and ECOG PS deterioration (Fig. 1).

3.3. Safety

As expected given the mechanisms of action of the drugs, the incidence of AEs observed for concomitant BTT was similar to that observed in the overall population [20] and in patients

without concomitant BTT (Table 4). Grade 3/4 AEs with or without BTT in the abiraterone and prednisone treatment subgroups were similar to those reported previously [20,22]. AEs of special interest were similar among treatment subgroups. In addition, grade 3 or 4 mineralocorticoid-related AEs were similar across treatment subgroups. Increases in alanine aminotransferase were more common with abiraterone. Osteonecrosis of the jaw with concomitant BTT use was reported in <3% of patients across the treatment groups; all cases were grade 1/2. Hypocalcemia was observed in 12 patients across the treatment groups, including one report each of grade 3 or 4 hypocalcemia in the prednisone with BTT group and abiraterone without BTT.

4. Discussion

This post hoc analysis is the first to evaluate the association between BTT and clinical outcomes in patients receiving abiraterone versus prednisone alone for mCRPC. We demonstrate that concomitant administration of abiraterone and BTT appears to be safe and well tolerated, and that the efficacy of abiraterone is maintained with concomitant BTT, with a possible added benefit of delaying the need for opiates to control pain. Delaying symptoms from bone metastases as mCRPC progresses is central to therapeutic management [24]. Prostate cancer patients with bone metastases have a greater risk of skeletal morbidity, which can impair quality of life (QoL) [25]. The findings that concomitant BTT use was associated with improvements in OS, time to opiate use for cancer-related pain, and time to ECOG PS deterioration are clinically relevant in the context of the mCRPC patient population. In the present analysis, all treatment group comparisons favored abiraterone over prednisone alone, and concomitant BTT was associated with increased effectiveness of abiraterone regarding clinical outcomes. Abiraterone with or without BTT was associated with a beneficial effect on survival, time to opiate use for cancer-related pain, and time to ECOG PS deterioration. These findings support and corroborate the patient-reported QoL outcomes from study COU-AA-302, in which abiraterone delayed pain progression, pain interference, and health-related QoL degradation compared with prednisone alone [22,26], and the outcomes from study COU-AA-301, in which abiraterone delayed pain progression and time to the first skeletal-related event in men with mCRPC previously treated with docetaxel [27].

Among patients treated with abiraterone, BTT was associated with a longer time to ECOG PS deterioration. Compared with prednisone with BTT, abiraterone in combination with BTT delayed the median time to deterioration in ECOG PS by 3.9 mo. Patients receiving abiraterone in combination with BTT also had a longer time to treatment with cytotoxic chemotherapy, an observation that supports the findings of previous reports [20,22]. These associations are consistent with an interaction between abiraterone and BTT use that may benefit clinical outcomes. In fact there is accumulating preclinical and clinical evidence of a potential anticancer effect of bisphosphonates [13]. In a retrospective analysis of a phase 3 clinical trial on zoledronic acid versus placebo, zoledronic acid–mediated normalization of bone markers was associated with improved survival in men with bone metastases from CRPC [28].

A limitation of our post hoc analysis is that as a retrospective analysis it may not account for unknown variables that may have had an impact on outcomes. Among the 353 patients who received BTT, 93% were treated with zoledronic acid. Furthermore, BTT use was not randomized, and the treatment effect was evaluated in subgroups, resulting in smaller sample sizes. Thus, these results are hypothesis-generating and may not represent the effects or interactions of abiraterone and other types of BTT, such as RANKL inhibitors. However, this post hoc analysis was conducted from a prespecified interim analysis, and the association between BTT use and outcomes was evaluated in patient subgroups that were well balanced among treatment arms. Moreover, the sample size in the current analysis is similar to that reported in a retrospective analysis showing a significant delay in the median time to a second skeletal-related event with zoledronic acid versus placebo in 422 men with advanced prostate cancer [29].

Safety data indicate that, as expected, there was no additional toxicity associated with abiraterone in combination with BTT compared to abiraterone without BTT. AEs that were mechanism-based and secondary to mineralocorticoid excess resulting from 17α-hydroxylase/C17,20-lyase blockade occurred at similar rates in patients with or without concomitant BTT. Moreover, treatment-emergent AEs, including those leading to treatment discontinuation or death, were similar across treatment subgroups.

5. Conclusions

The results of this post hoc analysis of study COU-AA-302 show that the safety profile of treatment with abiraterone plus prednisone or prednisone alone with concomitant BTT is similar to that without concomitant BTT in chemotherapy-naïve patients with mCRPC. Concomitant BTT use was associated with longer OS, time to opiate use for cancer-related pain, and time to ECOG PS deterioration. The abiraterone treatment effect was maintained with or without concomitant BTT use for all endpoints. Moreover, this post hoc analysis suggests an added clinical benefit of abiraterone in combination with BTT in reducing symptomatic progression.

Acknowledgments

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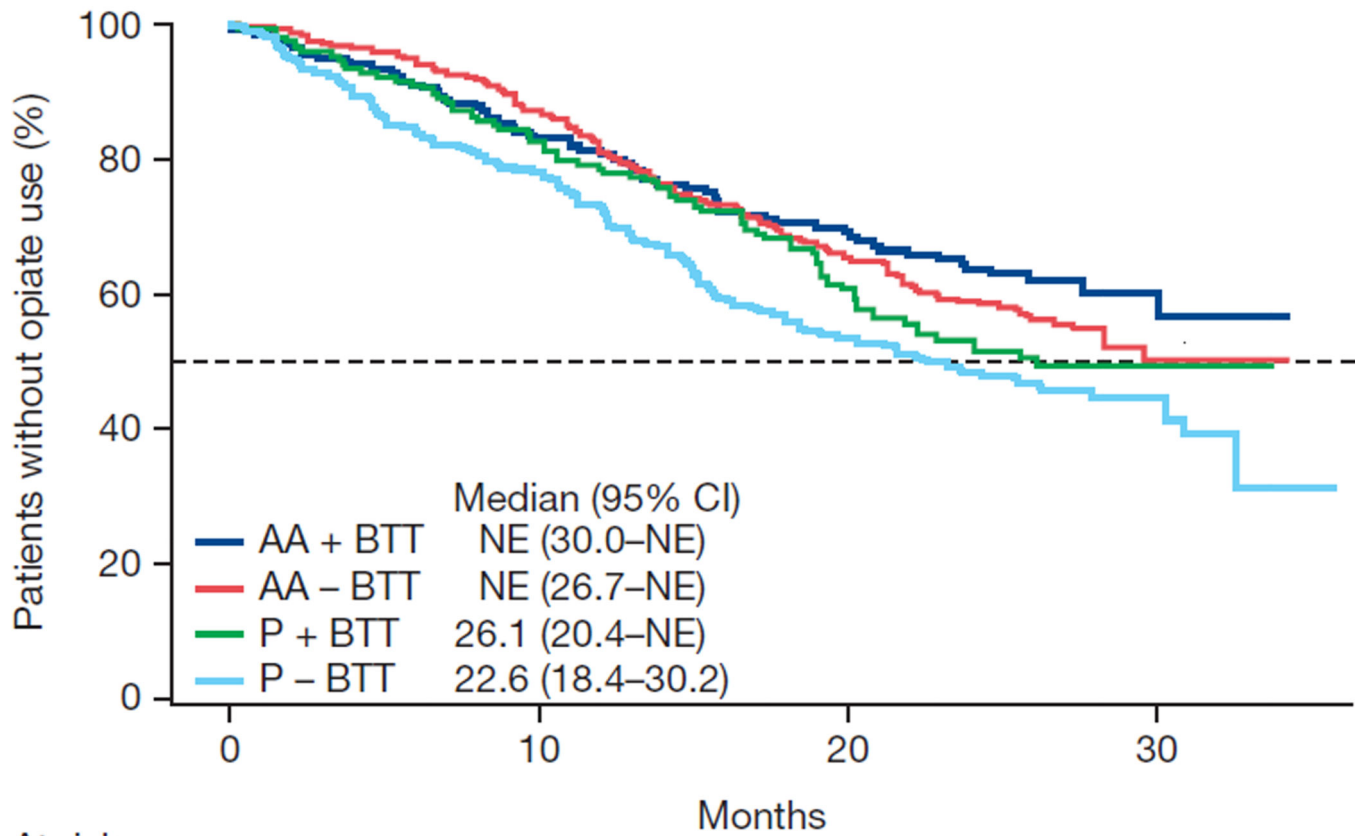
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In patients with metastatic castration-resistant prostate cancer, treatment with abiraterone acetate and prednisone with concomitant bone-targeted therapy showed improved clinical benefit compared to prednisone alone, as measured by overall survival, time to deterioration of Eastern Cooperative Oncology Group performance status, and time to opiate use for cancer-related pain.
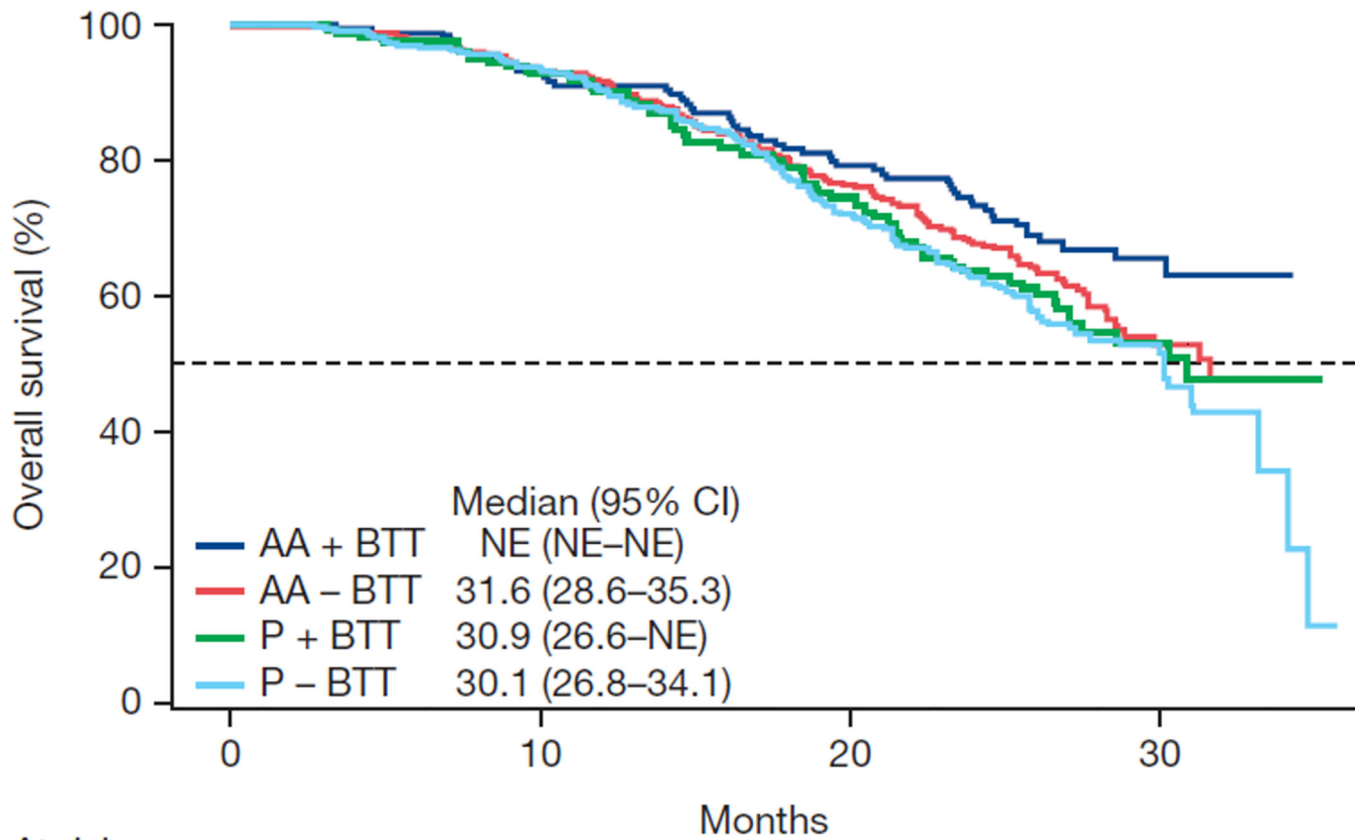
The chart shows "Patients without opiate use (%)" on the y-axis (0 to 100) versus "Months" on the x-axis (0 to 30).

Legend:

	Median (95% CI)
AA + BTT	NE (30.0–NE)
AA – BTT	NE (26.7–NE)
P + BTT	26.1 (20.4–NE)
P – BTT	22.6 (18.4–30.2)

At risk

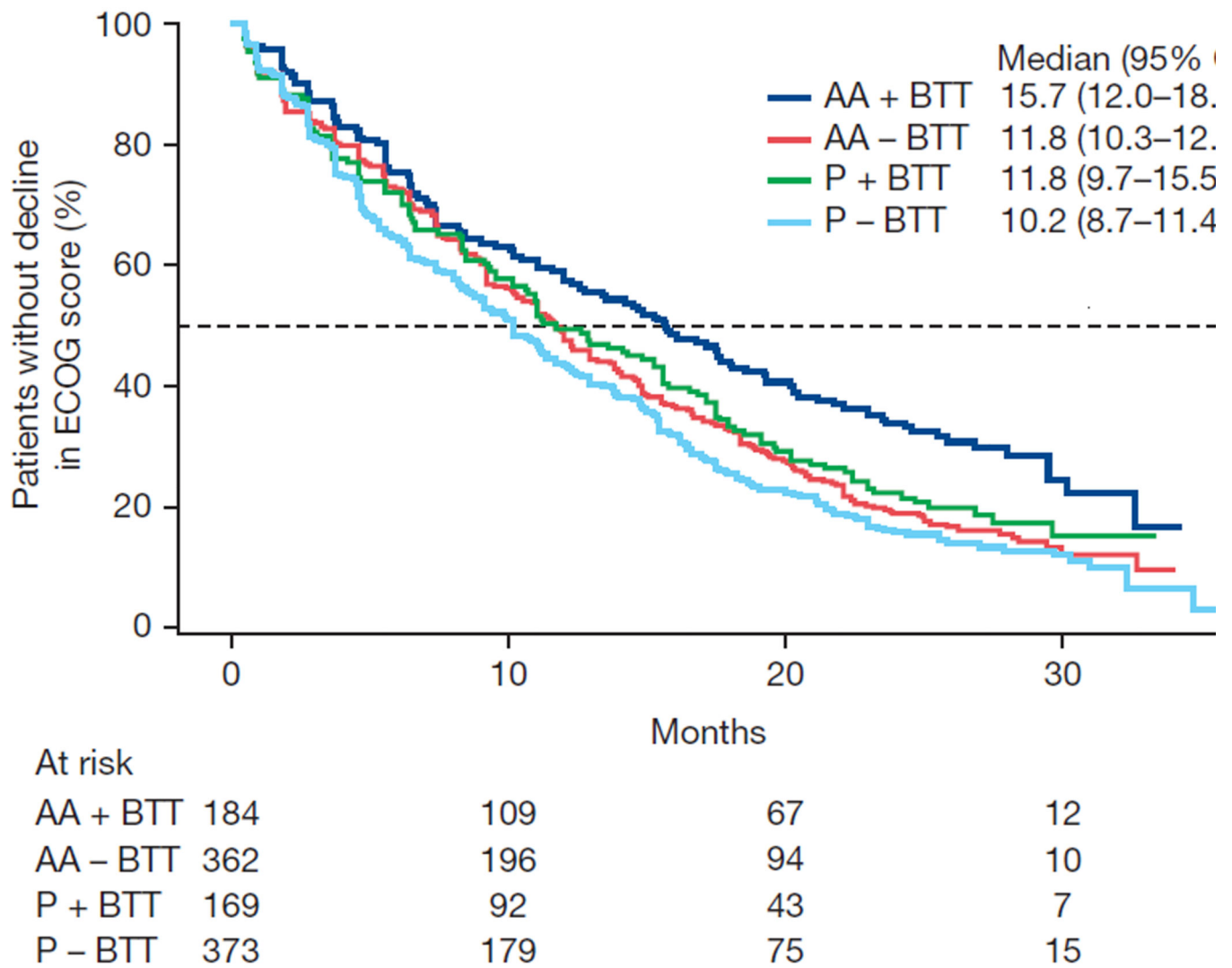|				
AA + BTT	184	140	104	18
AA – BTT	362	295	198	24
P + BTT	169	126	83	16
P – BTT	373	272	165	30

Fig. 1.
Kaplan-Meier estimates of (A) overall survival, (B) time to opiate use for cancer-related pain, and (C) time to deterioration in Eastern Cooperative Oncology Group (ECOG) performance status score by 1 point. AA = abiraterone acetate; BTT = bone-targeted therapy; CI = confidence interval; NE = not estimable; P = prednisone.

Table 1

Baseline patient characteristics and covariates (intent-to-treat population)

Characteristic	Abiraterone (*n* = 546)		Prednisone (*n* = 542)	
	BTT (*n* = 184)	No BTT (*n* = 362)	BTT (*n* = 169)	No BTT (*n* = 373)
Median age, yr (IQR)	70.0 (64.0–76.0)	71.0 (65.0–78.0)	70.0 (65.0–76.0)	70.0 (63.0–76.0)
Gleason score 8 at initial diagnosis, *n/N* (%)	95/167 (57)	168/321 (52)	89/157 (57)	165/351 (47)
Median PSA at study entry, ng/ml (IQR)	42.5 (16.4–128.2)	41.5 (16.1–110.4)	34.2 (11.3–91.9)[a]	39.1 (18.2–98.1)[b]
ECOG PS at study entry, *n* (%)				
0 or 1	184 (100)	361 (100)	169 (100)	373 (100)
2	0	1 (0.3)	0	0
Extent of disease, *n* (%)				
Bone	172 (94)	280 (78)	157 (93)	275 (74)
Soft tissue or node[c]	76 (41)	191 (53)	58 (34)	213 (57)
Other	2 (1)	2 (0.6)	1 (0.6)	6 (2)
Bone metastasis only at study entry, *n* (%)	100 (54)	138 (38)	95 (56)	147 (39)
Median alkaline phosphatase, IU/l (IQR)	91.5 (66.0–140.5)	94.0 (72.0–133.0)	91.0 (65.5–137.0)[d]	89.0 (69.0–139.0)[e]
Median lactate dehydrogenase, U/l (IQR)	192.0 (164.0–223.0)[f]	184.5 (160.0–207.5)[g]	187.0 (161.0–222.0)[h]	183.0 (165.0–210.0)[i]
BTT use, *n* (%)				
At baseline	170 (31)	NA	157 (29)	NA
New starts during study	14 (3)	NA	12 (2)	NA
Type of BTT, *n* (%)[j]				
Zoledronic acid	172 (32)	NA	158 (29)	NA
Other bisphosphonates	7 (1)	NA	8 (2)	NA
Denosumab	16 (3)	NA	6 (1)	NA
Other[k]	2 (0.4)	NA	3 (0.6)	NA

BTT = bone-targeted therapy; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; NA = not applicable; PSA = prostate-specific antigen.

[a] *n* = 167;

[b] *n* = 372.

[c] Metastatic lesions other than liver or visceral metastases on computed tomography or magnetic resonance imaging. If lymph node metastasis was the only evidence of metastasis, it must be ?2 cm in diameter. Patients with visceral metastases were excluded.

[d] *n* = 168;

[e] *n* = 371;

[f] *n* = 183;

[g] *n* = 360;

[h] *n* = 166;

[i] *n* = 370.

[j]Patients could receive more than one BTT at the same time.

[k]Methylsulfonylmethane, strontium ranelate.

Table 2

Clinical outcomes for treatment with and without concomitant bone-targeted therapy (BTT)

	BTT	No BTT	HR (95% CI)[a]	p value
Median rPFS (mo)	13.6	11.0	0.86 (0.72–1.02)	0.08
Median overall survival (mo)	NE	30.3	0.75 (0.60–0.94)	0.012
Median time to opiate use for CaRP (mo)	NE	27.9	0.80 (0.65–0.99)	0.036
Median time to chemotherapy initiation (mo)	22.4	21.1	0.92 (0.76–1.10)	0.4
Median time to ECOG PS deterioration (mo)	14.3	11.1	0.75 (0.64–0.87)	<0.001
Median time to PSA progression (mo)	8.3	8.3	0.88 (0.75–1.03)	0.11

CaRP = cancer-related pain; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NE = not estimable; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

[a]Stratified Cox model with concomitant BTT use, treatment, and key baseline parameters (PSA, lactate dehydrogenase, alkaline phosphatase, hemoglobin, and whether a patient had bone metastases only at entry) as factors. When the interaction effect of treatment and BTT use was included in the models, the p values were not significant (rPFS, $p = 0.18$; OS, $p = 0.13$; time to opiate use for Ca-RP, $p = 1.0$; time to chemotherapy initiation, $p = 0.9$; time to ECOG PS deterioration, $p = 0.18$; time to PSA progression, $p = 0.8$).

Table 3

Comparison of clinical outcomes for different treatments within bone-targeted therapy subgroups using a stratified Cox model

	Bone-target therapy		No bone-targeted therapy	
	Abiraterone	Prednisone	Abiraterone	Prednisone
Median rPFS (mo)	16.6	10.4	16.3	8.2
Adjusted HR (95% CI)		0.63 (0.48–0.84)		0.48 (0.40–0.58)
p value[a]		0.001		<0.0001
Median overall survival (mo)	NE	30.9	31.6	30.1
Adjusted HR (95% CI)		0.71 (0.50–1.00)		0.84 (0.67–1.05)
p value		0.050		0.13
Median time to opiate use for CaRP (mo)	NE	26.1	NE	22.6
Adjusted HR (95% CI)		0.74 (0.53–1.04)		0.70 (0.56–0.87)
p value[a]		0.078		0.001
Median time to chemotherapy initiation (mo)	27.1	17.5	26.1	16.7
Adjusted HR (95% CI)		0.66 (0.49–0.89)		0.59 (0.48–0.72)
p value[a]		0.006		<0.0001
Median time to ECOG PS deterioration (mo)	15.7	11.8	11.8	10.2
Adjusted HR (95% CI)		0.76 (0.59–0.97)		0.87 (0.74–1.02)
p value[a]		0.025		0.086
Median time to PSA progression (mo)	11.1	5.6	11.0	5.6
Adjusted HR (95% CI)		0.54 (0.42–0.70)		0.50 (0.42–0.60)
p value[a]		<0.0001		<0.0001

CaRP = cancer-related pain; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NE = not estimable; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

[a] Stratified log-rank test.

Table 4

Treatment-emergent adverse events by treatment subgroup

	Abiraterone		Prednisone	
	BTT (n = 183)	No BTT (n = 359)	BTT (n = 168)	No BTT (n = 372)
TE AEs, n (%)	181 (99)	357 (99)	163 (97)	361 (97)
Grade 3/4 TE AEs, n (%)	85 (46)	182 (51)	68 (41)	167 (45)
TE serious AEs, n (%)	62 (34)	126 (35)	45 (27)	101 (27)
Grade 3/4 AEs, n (%)	47 (26)	109 (30)	37 (22)	86 (23)

	Abiraterone				Prednisone			
	BTT (n = 183)		No BTT (n = 359)		BTT (n = 168)		No BTT (n = 372)	
	Total	Grade 3/4	Total	Grade 3/4	Total	Grade 3/4	Total	Grade 3/4
TE AEs leading to treatment discontinuation, n (%)	15 (8)		43 (12)		16 (10)		37 (10)	
TEAE leading to death, n (%)	6 (3)		15 (4)		6 (4)		10 (3)	
Osteonecrosis of the jaw, n (%)[a]	5 (3)		1 (<1)		4 (2)		0 (0)	
AEs of special interest, n (%)								
Fluid retention/edema[b]	47 (26)	2 (1)	111 (31)	3 (<1)	37 (22)	5 (3)	93 (25)	4 (1)
Hypertension[b]	44 (24)	10 (5)	74 (21)	13 (4)	26 (15)	6 (4)	47 (13)	11 (3)
Cardiac disorders[b]	32 (17)	10 (5)	81 (23)	26 (7)	38 (23)	9 (5)	57 (15)	10 (3)
Hypokalemia[b]	32 (17)	3 (2)	61 (17)	11 (3)	21 (13)	3 (2)	48 (13)	7 (2)
ALT increased[b]	18 (10)	9 (5)	1 (<1)	1 (<1)	8 (5)	0	19 (5)	4 (1)

BTT = bone-targeted therapy; TE = treatment-emergent; AE = adverse event; ALT = alanine aminotransferase.

[a] All events were grade 1/2.

[b] Reflects collection of terms based on specific Standardized Medical Dictionary for Regulatory Activities queries.