ALTERNATIVE STEROID STUDY

A Randomized Trial of Abiraterone Acetate Administered With 1 of 4 Glucocorticoid Regimens in Metastatic Castration-Resistant Prostate Cancer

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INTRODUCTION

- Abiraterone acetate (AA) is a prodrug of abiraterone, a potent and specific inhibitor of CYP17, indicated for metastatic castration-resistant prostate cancer (mCRPC).
- Prednisone (P) coadministration resulted in reduced mineralocorticoid excess (ME)-associated adverse events (AEs). The efficacy of this regimen was demonstrated in randomized, double-blind, placebo-controlled phase 3 studies,[1-3] and the AEs associated with ME were shown to be manageable over longer-term treatment.[3]

Study Aim

- To determine whether a lower dosage of P (ie, 5 mg once daily [QD] or 2.5 mg twice daily [BID]), or low-dose dexamethasone (DEX; 0.5 mg QD), coadministered with AA, prevents ME-associated AEs.

METHODS

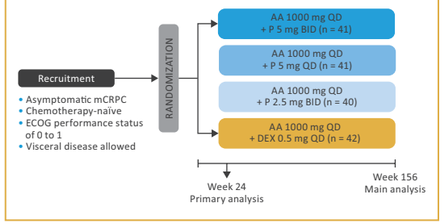
Study Population

- Asymptomatic, chemotherapy-naïve mCRPC patients with disease progression following withdrawal of antiandrogen therapy (Figure 1).
- Patients with diabetes mellitus, and those with prior corticosteroid treatment for prostate cancer or previous ketoconazole therapy for > 7 days, were excluded.

Study Design

- Open-label, multicenter, phase 2 study (ClinicalTrials.gov identifier: NCT01867710).

Figure 1. Study Design



ECOG, Eastern Cooperative Oncology Group.

Primary Endpoint

- Lack of ME, defined as patients experiencing neither hypokalemia nor hypertension treatment-emergent adverse events (TEAEs) during the first 24 weeks of treatment.
  - ME-associated TEAEs were classed as single events of National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) and included grade ≥ 1 hypokalemia and/or grade ≥ 2 hypertension.
    - Hypertension was assessed based on 3 consecutive blood pressure measurements using an automated device; the lowest of the 3 consecutive readings was reported.

METHODS (continued)

- The threshold percentage of patients experiencing neither hypokalemia nor hypertension during the first 24 weeks at which the treatment was considered not to sufficiently prevent ME was 50%.
- N (%) and 95% confidence intervals (CIs) are reported in evaluable patients (completed 24 weeks of treatment or discontinued early and experienced either hypertension or hypokalemia).
- Secondary parameters include laboratory tests to assess insulin resistance, impact on lipids, and prostate-specific antigen (PSA) response rate (≥ 50% PSA decline from baseline; confirmed after 4 weeks).

BASELINE CHARACTERISTICS

Patients

- Patients were enrolled between July 2013 and October 2014 at 23 sites in 5 countries; 164 patients were randomized; 163 received treatment and 133 (81.6%) completed 24 weeks of treatment.

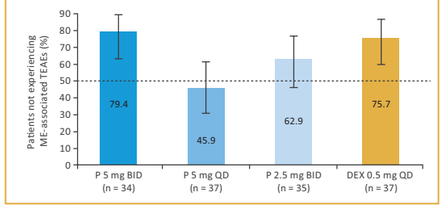
Table 1. Baseline Characteristics

	Experimental arms			
	P 5 mg BID (n = 41)	P 5 mg QD (n = 41)	P 2.5 mg BID (n = 40)	DEX 0.5 mg QD (n = 42)
Median (range) age, years	68.0 (50-88)	69.0 (54-88)	70.0 (53-83)	71.0 (54-90)
≥ 75 years, n (%)	11 (26.8)	10 (24.4)	11 (27.5)	15 (35.7)
Median (range) time from diagnosis to randomization, months	42.3 (1.6-268.6)	45.8 (11.0-215.2)	44.3 (9.6-144.3)	101.1 (1.3-246.4)
Bone metastases, n (%)	[a]	[a]	[b]	
None	8 (20.0)	10 (25.0)	6 (15.8)	9 (21.4)
1-10	17 (42.5)	15 (37.5)	17 (44.7)	20 (47.6)
> 10	15 (37.5)	15 (37.5)	15 (39.5)	13 (31.0)
Extent of disease, n (%)			[a]	[a]
Bone	33 (80.5)	32 (78.0)	34 (87.2)	33 (80.5)
Lymph node	19 (46.3)	24 (58.5)	16 (41.0)	21 (51.2)
Visceral (liver or lung)[c]	0 (0.0)	2 (4.9)	0 (0.0)	3 (7.3)
Prior therapy for prostate cancer, n (%)				
Radiotherapy	23 (56.1)	23 (56.1)	25 (62.5)	26 (61.9)
Surgery	19 (46.3)	17 (41.5)	22 (55.0)	25 (59.5)
Systemic therapy	41 (100.0)	41 (100.0)	39 (97.5)	42 (100.0)
GnRH agonist	39 (95.1)	38 (92.7)	37 (94.9)	38 (90.5)
Antiandrogen	40 (97.6)	40 (97.6)	36 (92.3)	41 (97.6)
Bone-targeted agent	6 (14.6)	8 (19.5)	5 (12.8)	5 (11.9)
Median (range) BMI, kg/m²	27.8 (19-38)	26.6 (17-37)	27.8 (21-41)	27.4 (19-41)
Hypertension at baseline according to medical history, n (%)	18 (43.9)	17 (41.5)	20 (50.0)	24 (57.1)
Hypertension at baseline according to BP, n (%)			[a]	
Grade 2[d]	9 (22.0)	18 (43.9)	9 (23.1)	13 (31.0)
Grade 3[e] or higher	2 (4.9)	1 (2.4)	2 (5.1)	1 (2.4)

BMI, body mass index; BP, blood pressure; GnRH, gonadotropin-releasing hormone.
[a]Missing data for 1 patient. [b]Missing data for 2 patients. [c]Patients with visceral metastases were originally excluded from the study, but later included as part of a protocol amendment. [d]Systolic BP ≥ 140 and < 160 mm Hg or diastolic BP ≥ 90 and < 100 mm Hg. [e]Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg at baseline.

PRIMARY ENDPOINT: ME-ASSOCIATED TEAEs

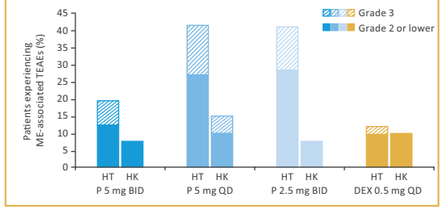
Figure 2. Primary Endpoint: Patients Not Experiencing TEAEs Associated With ME



Error bars represent Wilson's 95% CI. Dotted line signifies the threshold percentage of patients experiencing neither hypokalemia nor hypertension during the first 24 weeks at which the treatment was considered not to sufficiently prevent ME.

- The lowest proportion of patients free from ME-associated TEAEs was seen in the P 5 mg QD group; however, this group contained the highest proportion of patients with grade 2 hypertension at baseline, which might have biased the results.

Figure 3. Patients Experiencing ME-Associated TEAEs: Hypertension and Hypokalemia Incidence by Grade



HK, hypokalemia; HT, hypertension. HT as assessed at 1 or more visits.
2 patients who experienced grade 3 HK had prior HK during the screening period; 1 patient was normalized before the start of treatment.

- Hypertension was the most frequent ME-associated TEAE in all treatment groups.
- No grade 4 hypokalemia or hypertension was reported and no patients discontinued treatment because of grade 4 HK or HT.

Table 2. Post Hoc Multivariate Logistic Regression Analysis: Best Model

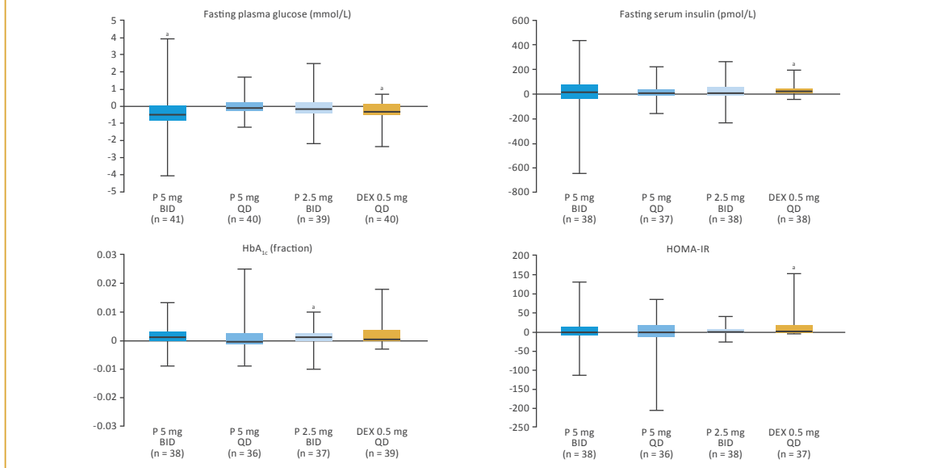
	Effect estimate	OR (95% CI)	*p* value
Treatment (vs P 5 mg BID)			
P 5 mg QD	-1.33	0.26 (0.09-0.80)	0.019
P 2.5 mg BID	-0.76	0.47 (0.15-1.47)	0.192
DEX 0.5 mg QD	-0.01	0.99 (0.30-3.24)	0.985
Systolic BP at baseline	-0.04	0.96 (0.93-0.99)	0.009
Sodium at baseline	-0.15	0.86 (0.75-0.99)	0.029
Pre-existing hypertension[a] ongoing at baseline (yes/no)	-0.79	0.46 (0.21-0.99)	0.048

OR, odds ratio.
[a]Based on patient medical history. The post hoc analysis considered 19 baseline variables including age, BMI, systolic and diastolic BP, glucose, potassium, sodium, creatinine, HbA_{1c}, number of hypertension treatments and hypertension (based on either BP or medical history). At first, all factors were considered separately for their potential to predict 'no ME'; the strongest predictors were primarily selected for multivariate modelling with a maximum of 4 or 5 factors per model, including treatment. The table presents the results of the most optimal model when running backward and forward selection models with these predictors.

- A post hoc predictor analysis suggested that higher systolic BP, pre-existing hypertension and higher sodium at baseline best predict a higher probability of experiencing ME.

METABOLIC EFFECTS

Figure 4. Changes in Glucose, Insulin, HbA_{1c} and HOMA-IR from Baseline to Endpoint (LOCF) of 24 Weeks of Treatment

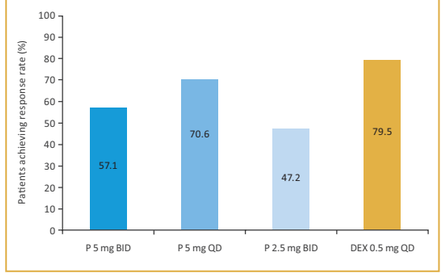


HbA_{1c}, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment–insulin resistance; LOCF, last observation carried forward.
Boxes represent median (horizontal bar) with 95% CIs and whiskers show minimum and maximum values.
[a]Statistically significant change from baseline.

- Changes in HbA_{1c} values were minimal and observed in 16/150 (10.7%) patients.

PSA

Figure 5. Confirmed PSA Response Rate (≥ 50%) After 12 Weeks



CONCLUSIONS

- During 24 weeks of treatment with AA, P 5 mg BID and DEX 0.5 mg QD both adequately controlled ME-associated TEAEs.
- P 2.5 mg BID and 5 mg QD require adequate monitoring, especially for patients with high systolic BP or pre-existing hypertension at baseline.
- A post hoc predictor analysis suggested that higher systolic BP, pre-existing hypertension and higher sodium at baseline best predict a higher probability of experiencing ME.
- These initial results and conclusions will be re-evaluated after longer-term treatment data (up to 3 years) are obtained.

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