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Clinical Trial Results

A Phase I Study of Abiraterone Acetate Combined with BEZ235, a Dual PI3K/mTOR Inhibitor, in Metastatic Castration Resistant Prostate Cancer

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01717898
- **Sponsor(s)**: Charles J. Ryan
- **Principal Investigator**: Charles J. Ryan
- **IRB Approved**: Yes

Lessons Learned

- The combination of standard dose abiraterone acetate and BEZ235, a pan-class I PI3K and mTORC1/2 inhibitor, was poorly tolerated in men with progressive mCRPC.
- Although the clinical development of BEZ235 has been discontinued in prostate cancer, agents that more selectively target PI3K-AKT-mTOR signaling may have a more favorable therapeutic index and should continue to be explored.

Abstract

Background. Androgen receptor (AR) and phosphatidylinositol-3 kinase (PI3K) signaling are two commonly perturbed pathways in prostate cancer. Preclinical data have shown that the two pathways compensate for each other when one is inhibited, and combined inhibition of AR and PI3K signaling may be a viable strategy to prevent or overcome castration resistance.

Methods. This phase I study evaluated the safety and tolerability of abiraterone acetate and prednisone combined with BEZ235, a dual PI3K and mTORC1/2 inhibitor, in men with progressive metastatic castration resistant prostate cancer (mCRPC) who have not received prior chemotherapy.

Results. Six patients ($n = 6$) were treated at the starting dose level of abiraterone acetate 1,000 mg with prednisone 5 mg twice daily and BEZ235 200 mg twice daily in a 3 + 3 dose escalation design. The study was terminated early because three of the six patients (50%) experienced dose-limiting toxicities: grade 3 mucositis, grade 3 hypotension, and grade 4 dyspnea and pneumonitis. All six patients had previously progressed on abiraterone/prednisone. The median treatment duration was 27 days (range: 3–130 days). No prostate-specific antigen (PSA) decline or objective response were observed.

Conclusion. The combination of standard-dose abiraterone/prednisone with BEZ235 200 mg twice daily was poorly tolerated in patients with mCRPC. The on-target and off-target effects of dual PI3K and mTORC inhibition likely contributed to the unacceptable toxicity profile. ***The Oncologist*** 2017; 22:503–e43

Discussion

AR signaling and PI3K-AKT-mTOR signaling are among the most common aberrant pathways found in advanced prostate cancer and are implicated in the development and maintenance of castration resistant disease. Preclinical prostate cancer models have shown crosstalk and cross-regulation between the two pathways, and enhanced tumor control with combination strategies that co-inhibit AR and PI3K-AKT-mTOR signaling.

We report results of a phase I study evaluating the safety and tolerability of standard dose abiraterone acetate (1,000 mg daily with prednisone 5 mg b.i.d.) combined with BEZ235, a potent dual pan-class I PI3K and mTORC1/2 inhibitor, in patients with progressive mCRPC. The original study design planned to determine the maximum tolerated dose (MTD) of the combination during 3 + 3 dose escalation, followed by a dose expansion phase to assess efficacy. The study protocol specified that if >1 of 3 or >2 of 6 patients experience a dose-limiting toxicity (DLT) at dose level 1, the study would be terminated. One of the first three patients accrued experienced a DLT at dose level 1 (abiraterone/prednisone plus BEZ235 200 mg b.i.d.), and three more patients were accrued at dose level 1 (Table 1). Two of the last three patients also experienced DLT, and the study was terminated

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Table 1. Dose-limiting toxicities

Dose level	Dose of drug: abiraterone acetate	Dose of drug: BEZ235	Number of patients enrolled	Number of patients evaluable for toxicity	Number of patients with a dose-limiting toxicity	Dose-limiting toxicities information
1	1,000 mg daily	200 mg twice daily	6	6	3	Grade 3 mucositis (patient 1) Grade 3 hypotension (patient 5) Grade 4 dyspnea and pneumonitis (patient 6)

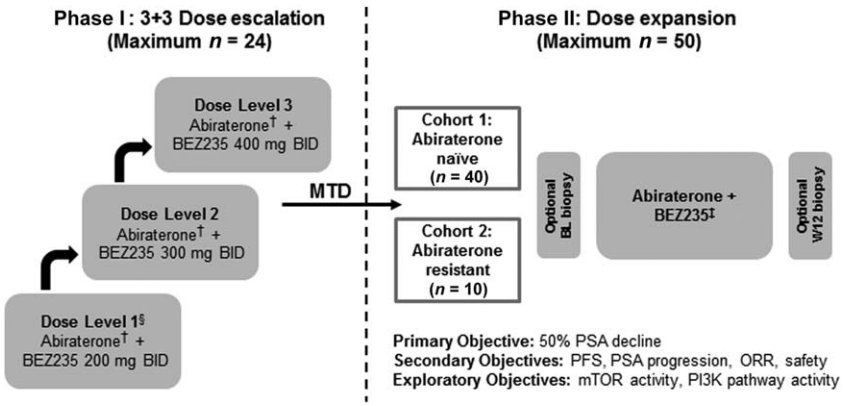

Figure 1. Study schema. †, Phase 1 abiraterone dose was 1,000 mg daily with prednisone 5 mg b.i.d. and BEZ235 at MTD. ‡, Phase 2 starting dose was abiraterone 1,000 mg daily with prednisone 5 mg b.i.d. and BEZ235 at MTD. §, If >1 of 3 or ≥ 2 of 6 patients experienced a dose-limiting toxicity at dose level 1, the study would be terminated.

Abbreviations: BL, baseline; BID, twice daily; MTD, maximum tolerated dose; mTOR, mechanistic target of rapamycin; ORR, objective response rate; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PSA, prostate-specific antigen; W12, week 12.

due to lack of safety as specified by study protocol. The median age of the patients was 71 years (range: 59–75 years). The majority of patients (83.3%) had Gleason 8–10 disease. All patients had bone metastases with or without nodal metastasis; no patients had visceral metastases. All patients had previously progressed on abiraterone.

The combination of standard dose abiraterone acetate and BEZ235 200 mg b.i.d. was poorly tolerated. The median treatment duration was 27 days (range: 3–130 days). The most common adverse events were oral mucositis (83.4%), diarrhea (66.7%), nausea (50.0%), anorexia (50.0%), weight loss (50.0%), and musculoskeletal pain (50.0%). The DLTs experienced by patients ($n = 3$, 50%) were grade 3 mucositis, grade 3 hypotension, and grade 4 dyspnea and pneumonitis. Five patients (83%) came off study because of study-related adverse events, and one patient came off study due to disease progression. No patient achieved any level of PSA decline (Fig. 1). The best radiographic response in two patients was stable disease. The clinical development of BEZ235 as a potential therapy for prostate cancer has been discontinued.

Trial Information	
Disease	Prostate Cancer
Stage of disease/treatment	Metastatic/Advanced
Prior Therapy	No designated number of regimens
Type of study	Phase I/II
Primary Endpoint	Safety and feasibility
Secondary Endpoint	Pharmacokinetics studies were not performed because the study was terminated early.
Additional Details of Endpoints or Study Design	
The original study design planned to determine the MTD of the combination of abiraterone acetate and BEZ235 during 3 + 3 dose escalation (phase I), followed by a dose expansion phase to assess efficacy (phase II). The primary endpoint of the phase I study was to determine the safety and feasibility of combining BEZ235 and abiraterone acetate. The primary endpoint of the phase II study was PSA response rate, by >50%, at 12 weeks. The study protocol specified that if >1 of 3 patients or >2 of 6 patients experience a dose-limiting toxicity (DLT) at dose level 1, the study would be terminated (Fig. 2).	
Investigator's Analysis	Poorly tolerated/not feasible

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Drug Information	
Drug 1	
Generic/Working name	Abiraterone acetate
Trade name	Zytiga
Company name	Janssen Biotech
Drug type	Small molecule
Dose	milligrams (mg) per flat dose
Route	oral (p.o.)
Schedule of Administration	1,000 mg daily (given with prednisone 5 mg twice daily)
Drug 2	
Generic/Working name	BEZ235
Trade name	N/A
Company name	Novartis
Drug type	Small molecule
Drug class	PI3 kinase
Dose	milligrams (mg) per flat dose
Route	oral (p.o.)
Schedule of Administration	200 mg twice daily

Patient Characteristics	
Number of patients, male	6
Number of patients, female	0
Stage	Metastatic, castration resistant
Age	Median (range): 71 years (59–75 years)
Number of prior systemic therapies	Median (range): 2 (1–3)
Performance status: ECOG	0 — 4 1 — 2 2 — 3 — unknown —
Cancer types or histologic subtypes	Prostate 6

Primary Assessment Method	
Control Arm: Prostate	
Number of patients screened	13
Number of patients enrolled	6
Number of patients evaluable for toxicity	6
Number of patients evaluated for efficacy	2
Evaluation method	RECIST v1.1 and PCWG2
Response assessment SD	$n = 2$ (100%)
(Median) duration assessments duration of treatment	27 days

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Adverse Events

	All Cycles						
Name	***NC/NA**	**1**	**2**	**3**	**4**	**5**	**All Grades**
Mucositis oral	16%	17%	50%	17%	0%	0%	84%
Diarrhea	33%	50%	17%	0%	0%	0%	67%
Nausea	50%	33%	17%	0%	0%	0%	50%
Anorexia	50%	17%	33%	0%	0%	0%	50%
Weight loss	50%	50%	0%	0%	0%	0%	50%
Investigations - Musculoskeletal pain	50%	17%	33%	0%	0%	0%	50%
Fatigue	67%	33%	0%	0%	0%	0%	33%
Rash maculopapular	66%	17%	17%	0%	0%	0%	34%
Hypotension	83%	0%	0%	17%	0%	0%	17%
Dyspnea	83%	0%	0%	0%	17%	0%	17%
Pneumonitis	83%	0%	0%	0%	17%	0%	17%
Investigations - Malaise	83%	17%	0%	0%	0%	0%	17%
Dyspepsia	83%	17%	0%	0%	0%	0%	17%
Investigations - Abdominal bloating	83%	17%	0%	0%	0%	0%	17%
Vomiting	83%	17%	0%	0%	0%	0%	17%
Dysgeusia	83%	17%	0%	0%	0%	0%	17%
Anal mucositis	83%	17%	0%	0%	0%	0%	17%
Investigations - Sore throat	83%	17%	0%	0%	0%	0%	17%
Epistaxis	83%	17%	0%	0%	0%	0%	17%
Skin hyperpigmentation	83%	17%	0%	0%	0%	0%	17%
Investigations - Extremity weakness	83%	17%	0%	0%	0%	0%	17%
Photosensitivity	83%	17%	0%	0%	0%	0%	17%
Investigations - Hemoptysis	83%	17%	0%	0%	0%	0%	17%
Platelet count decreased	83%	17%	0%	0%	0%	0%	17%
Serum amylase increased	83%	17%	0%	0%	0%	0%	17%
Hypocalcemia	83%	17%	0%	0%	0%	0%	17%

Adverse Events Legend
*No Change from Baseline/No Adverse Event
All adverse events that are at least probably related to study therapy, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Serious Adverse Events

Name	**Grade**	**Attribution**
Dyspnea	4	Possible
Pneumonitis	4	Possible

Serious Adverse Events Legend
Grade 4 dyspnea and pneumonitis occurred in the same patient.

Dose-Limiting Toxicities

Dose level	**Dose of drug: abiraterone acetate**	**Dose of drug: BEZ235**	**Number of patients enrolled**	**Number of patients evaluable for toxicity**	**Number of patients with a dose-limiting toxicity**	**Dose-limiting toxicities information**
1	1,000 mg daily	200 mg twice daily	6	6	3	Grade 3 mucositis (patient 1) Grade 3 hypotension (patient 5) Grade 4 dyspnea and pneumonitis (patient 6)

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Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Toxicity
Pharmacokinetics/Pharmacodynamics	Not collected—pharmacokinetics studies were not performed because the study was terminated early.
Investigator's Assessment	Poorly tolerated/not feasible

In this phase I study of the combination of abiraterone/prednisone plus BEZ235, combination therapy was found to be intolerable. The PI3K (phosphoinositide 3-kinase) pathway is a major driver of cancer progression in different malignancies. Genomic aberrancy in the PI3K pathway is present in approximately 60% of mCRPC, and PI3K signaling has been identified as a major mechanism of resistance in mCRPC [1, 2]. Preclinical work from different groups has shown cross-regulation between AR signaling and PI3K-AKT-mTOR signaling [3–5]. Furthermore, combined inhibition of AR signaling and PI3K-AKT-mTOR signaling has been shown to augment anti-cancer activity, particularly in models of prostate cancer with PTEN-loss [3–5]. This led to the hypothesis that co-inhibition of these two interconnected pathways may be a viable strategy to prevent or overcome resistance in patients with CRPC.

Clinical trials of allosteric mTOR inhibitors in men with advanced prostate cancer have demonstrated limited clinical activity [6, 7]. This was thought to be due in part to the activation of AKT and led to the development of strategies that target upstream of PI3K-AKT-mTOR signaling. Here, we report the first study designed specifically to target androgen synthesis inhibition in combination with targeting PI3K signaling in mCRPC. In this study, the combination of standard dose abiraterone acetate (1,000 mg daily with prednisone 5 mg b.i.d.) with BEZ235, a potent dual pan-class I PI3K and mTORC1/2 inhibitor was evaluated (Figure 1). The combination was found to be poorly tolerated, and dose escalation and cohort expansion was not possible.

Six patients were accrued at dose level 1. The median age of the patients was 71 years. The majority of patients (83.3%) had Gleason 8–10 disease (Table 2). All patients had bone metastasis with or without nodal metastasis; no patients had visceral metastasis. The median number of prior therapy for mCRPC was 2 (range: 1–3). All patients had previously progressed on abiraterone and were abiraterone-resistant. All patients were chemotherapy-naive (Table 1).

The median treatment duration was 27 days (range: 3–130 days). The most common adverse events were grade 1–2 oral mucositis (66.7%), diarrhea (66.7%), nausea (50.0%), anorexia (50.0%), weight loss (50.0%), and musculoskeletal pain (50.0%). Three patients (50%) experienced DLT: grade 3 mucositis, grade 3 hypotension, and grade 4 dyspnea and pneumonitis (Table 3). Five patients (83%) came off study due to study-related adverse events, and one patient came off study due to disease progression (Table 4). Of the three patients who received study therapy for at least 1 month (range: 38–130 days), none achieved any level of PSA decline (Figure 2). The best radiographic response in two patients was stable disease.

Mucositis, anorexia, and weight loss are adverse events previously observed with PI3K-AKT-mTOR pathway inhibition and may represent a class effect of targeting the PI3K pathway. These adverse events were observed to a greater extent than anticipated. BEZ235 was administered in suspension, after sachets of the drug were dissolved in approximately 200 mL of water; therefore, the increased rate of mucositis observed may be related to higher drug exposure and absorption in the oral mucosa. All patients enrolled received maximal supportive care; therefore, our findings demonstrate an extremely low likelihood that pan-PI3K and mTORC1/2 inhibition can be achieved at the dose administered. It is likely that adverse events were contributed by off-target effects as well as on-target effects from inhibiting all class I PI3K isoforms in addition to mTORC1/2 inhibition, irrespective of their role in tumorigenesis. Based on these findings as well as findings from another study with this agent (NCT01634061, unpublished, but registered at ClinicalTrials.gov), clinical development of BEZ235 as a potential therapy for prostate cancer was discontinued. Of note, the development of BEZ235 has also been discontinued for renal cell carcinoma (RCC) due to high incidence of DLTs seen in a phase Ib study of BEZ235 monotherapy in advanced RCC patients [8].

Metastatic castration resistant prostate cancer that has progressed despite abiraterone therapy is a challenge for drug development as no agent other than docetaxel chemotherapy has shown consistent clinical activity in this setting [9]. The rationale for targeting the PI3K-AKT-mTOR pathway in mCRPC remains sound, however, and distinct agents that may have a more favorable therapeutic index should continue to be explored. Agents targeting specific PI3K isoforms may be better tolerated and achieve greater therapeutic efficacy [10], and several isoform-specific PI3K inhibitors are currently under investigation as monotherapy or as combination therapy in advanced solid tumors in early phase clinical trials [11]. Furthermore, mTOR inhibitors that compete with the ATP-binding site are currently under clinical development, including the combination of enzalutamide with a dual ATP-competitive mTOR and DNA-PK inhibitor, CC-115 in men with abiraterone- and enzalutamide-naive progressive mCRPC (NCT02833883) [12].

It remains to be determined what combination of AR and PI3K pathway inhibition will be both tolerable and clinically active. The combination of enzalutamide with BKM120, a pan-class I PI3 kinase inhibitor, was investigated in a phase II nonrandomized study of BKM120 with or without enzalutamide in men with progressive mCRPC who failed or were not candidates for docetaxel chemotherapy [13]. Thirteen of 30 (43%) patients received BKM120 while continuing enzalutamide. Of all patients treated, treatment was not well tolerated (47% of patients experienced grade 3 adverse events), and no patient achieved >50% PSA response or objective response

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[13]. More recently, results of a randomized phase II study of ipatasertib (GDC-0068), an AKT inhibitor, combined with abiraterone/prednisone in men with docetaxel-pretreated mCRPC, were presented [14]. In this study, 253 patients were randomized to ipatasertib 200 mg daily, ipatasertib 400 mg daily, or placebo in combination with standard dose abiraterone. A trend toward improved radiographic progression-free survival (hazard ratio (HR) = 0.75, $p = .17$) and overall survival (HR = 0.72, $p = .22$) was observed with ipatasertib 400 mg daily plus abiraterone, but not ipatasertib 200 mg daily plus abiraterone, indicating a dose response. Importantly, adverse events were also dose dependent, and this combination was well tolerated with manageable side effects. AKT inhibitors lie at an important signaling junction—downstream of PI3K and upstream of mTOR—and may have a better therapeutic index compared with agents such as BEZ235.

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Disclosures

Andrew C. Hsieh: Revolution Medicines (C/A); **Won Kim:** Genentech (C/A); **Terence Friedlander:** MedBioGene (E), Genentech, AstraZeneca, Clovis Oncology, Pfizer (C/A), Dendreon, Astellas, Sanofi-Genzyme (H), Janssen, Novartis (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Robinson D, Van Allen EM, Wu YM et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–1228.

2. Taylor BS, Schultz N, Hieronymus H et al. Integrative genomic profiling of human prostate cancer. Cancer Cell 2010;18:11–22.

3. Carver BS, Chapinski C, Wongvipat J et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 2011;19:575–586.

4. Thomas C, Lamoureux F, Crafter C et al. Synergistic targeting of PI3K/AKT pathway and androgen receptor axis significantly delays castration-resistant prostate cancer progression in vivo. Mol Cancer Ther 2013;12:2342–2355.

5. Marques RB, Aghai A, de Ridder CM et al. High efficacy of combination therapy using PI3K/AKT inhibitors with androgen deprivation in prostate cancer preclinical models. Eur Urol 2015;67:1177–1185.

6. Nakabayashi M, Werner L, Courtney KD et al. Phase II trial of RAD001 and bicalutamide for castration-resistant prostate cancer. BJU Int 2012; 110:1729–1735.

7. Templeton AJ, Dutoit V, Cathomas R et al. Phase 2 trial of single-agent everolimus in chemotherapy-naïve patients with castration-resistant prostate cancer (SAKK 08/08). Eur Urol 2013;64:150–158.

8. Carlo MI, Molina AM, Lakhman Y et al. A phase Ib study of BEZ235, a dual inhibitor of phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR), in patients with advanced renal cell carcinoma. ***The Oncologist*** 2016;21:787–788.

9. de Bono JS, Smith MR, Saad F et al. Subsequent chemotherapy and treatment patterns after abiraterone acetate in patients with metastatic castration-resistant prostate cancer: Post hoc analysis of COU-AA-302. Eur Urol 2016 [Epub ahead of print].

10. Thorpe LM, Yuzugullu H, Zhao JJ et al. PI3K in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer 2015; 15:7–24.

11. Edlind MP and Hsieh AC. PI3K-AKT-mTOR signaling in prostate cancer progression and androgen deprivation therapy resistance. Asian J Androl 2014; 16:378–386.

12. Munster PN, Mahipal A, Nemunaitis JJ et al. Phase I trial of dual TOR kinase and DNA-PK inhibitor (CC-115) in advanced solid and hematologic cancers. J Clin Oncol 2016;34(suppl):abstract 2505.

13. Armstrong AJ, Halabi S, Healy P et al. Phase II trial of the PI3 kinase inhibitor BKM120 with or without enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol 2015:33(suppl):abstract 5025.

14. De Bono JS, Giorgi UD, Massard C et al. Randomized phase II study of AKT blockade with ipatasertib (GDC-0068) and abiraterone (Abi) vs. abi alone in patients with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel chemotherapy (A. MARTIN Study). J Clin Oncol 2016;34(suppl); abstract 5017.

Figures and Tables

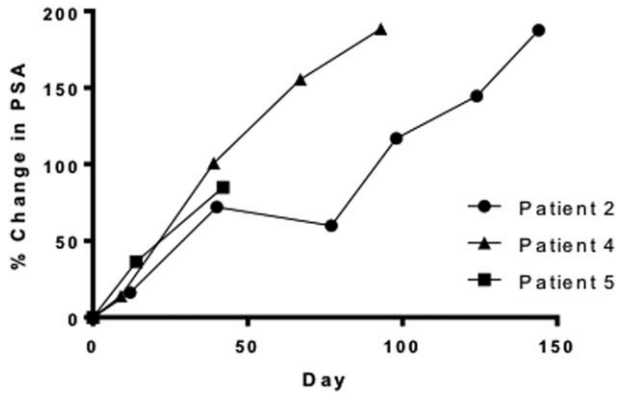

Figure 2. Percentage PSA change from baseline during study period for patients who received at least 1 month of study treatment. The longest treatment break was 12 days in patient 2.

Abbreviation: PSA, prostate-specific antigen.

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Table 2. Baseline demographic and disease characteristics

Characteristic	Abiraterone/Prednisone[a] + BEZ235 200 mg b.i.d. ($n = 6$)
Patients, no.	6
Age, year	
Median (range)	71 (59–75)
Race, no. (%)	
White	4 (66.7)
Black	1 (!6.7)
Asian	1 (16.7)
ECOG performance status, no. (%)	
0	4 (66.7)
1	2 (33.3)
Gleason score, no. (%)	
4–6	1 (16.7)
7	0 (0)
8–10	5 (83.3)
Site of metastasis, no. (%)	
Node only	0 (0)
Bone only	4 (66.7)
Bone + node	2 (33.3)
Visceral	0 (0.0)
Prior treatment for mCRPC, no. (%)	
Abiraterone acetate	6 (100.0)
Ketoconazole	4 (66.7)
Sipuleucel-T	1 (16.7)
Enzalutamide	0 (0.0)
Radium-223	0 (0.0)
Chemotherapy	0 (0.0)
PSA, ng/mL	
Median (range)	110.5 (26.7–233.6)
LDH, U/L	
Median (range)	218.5 (171.0–345.0)
Hematocrit, g/dL	
Median (range)	36.6 (31.8–39.6)
Alkaline phosphatase, U/L	
Median (range)	86.5 (51.0–493.0)

[a]Abiraterone dose: 1,000 mg daily with prednisone 5 mg b.i.d.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mCRPC, metastatic castration resistant prostate cancer; PSA, prostate specific antigen.

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Table 3. Treatment-related adverse events

	Abiraterone/Prednisone* + BEZ235 200 mg b.i.d. ($n = 6$)		
Adverse events	**Grade 1–2, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
Any event	6 (100.0)	2 (33.3)	1 (16.7)
Oral mucositis	4 (66.7)	1 (16.7)	0 (0.0)
Diarrhea	4 (66.7)	0 (0.0)	0 (0.0)
Nausea	3 (50.0)	0 (0.0)	0 (0.0)
Anorexia	3 (50.0)	0 (0.0)	0 (0.0)
Weight loss	3 (50.0)	0 (0.0)	0 (0.0)
Musculoskeletal pain	3 (50.0)	0 (0.0)	0 (0.0)
Fatigue	2 (33.3)	0 (0.0)	0 (0.0)
Rash	2 (33.3)	0 (0.0)	0 (0.0)

Adverse events were graded by CTCAE v4.0. Patients were classified according to the worst grade of adverse event(s) reported. Adverse events occurring in more than 1 patient (>16.7%) are shown. *Abiraterone dose: 1,000 mg daily with prednisone 5 mg b.i.d.

Table 4. Treatment duration and reason off study

Patient no.	Treatment duration	Off study reason	Patient withdrawal
1	3 days	AEs, including grade 3 oral mucositis and grade 1 diarrhea	Yes
2	130 days	Disease progression	No
3	7 days	AEs, including grade 2 oral mucositis and grade 1 anal mucositis	Yes
4	112 days	AEs, including grade 1 anorexia, grade 1 dyspepsia, and grade 1 emesis	Yes
5	38 days	AEs, specifically grade 4 dyspnea and pneumonitis requiring hospitalization (resolved after steroids)	Yes
6	16 days	AEs, including grade 3 hypotension, grade 2 anorexia, grade 2 oral mucositis, and grade 2 diarrhea	Yes

Abbreviation: AE, adverse event.

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