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Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer

Gerhardt Attard, **Alison H.M. Reid**, **Roger A'Hern**, **Christopher Parker**, **Nikhil Babu Oommen**, **Elizabeth Folkerd**, **Christina Messiou**, **L. Rhoda Molife**, **Gal Maier**, **Emilda Thompson**, **David Olmos**, **Rajesh Sinha**, **Gloria Lee**, **Mitch Dowsett**, **Stan B. Kaye**, **David Dearnaley**, **Thian Kheoh**, **Arturo Molina**, and **Johann S. de Bono**
Royal Marsden National Health Service Foundation Trust; The Institute of Cancer Research, Sutton, Surrey, United Kingdom; and Cougar Biotechnology, Los Angeles, CA

Abstract

Purpose—It has been postulated that castration-resistant prostate cancer (CRPC) commonly remains hormone dependent. Abiraterone acetate is a potent, selective, and orally available inhibitor of CYP17, the key enzyme in androgen and estrogen biosynthesis.

Patients and Methods—This was a phase I/II study of abiraterone acetate in castrate, chemotherapy-naive CRPC patients (n = 54) with phase II expansion at 1,000 mg (n = 42) using a two-stage design to reject the null hypothesis if more than seven patients had a prostate-specific

Corresponding author: Johann S. de Bono, MB ChB, FRCP, MSc, PhD, Section of Medicine, The Institute of Cancer Research, the Royal Marsden National Health Service Foundation Trust, Downs Rd, Sutton, Surrey SM2, 5PT, United Kingdom; johann.de-bono@icr.ac.uk..

AUTHOR CONTRIBUTIONS

Financial support: Gloria Lee

Conception and design: Gerhardt Attard, Johann S. de Bono
Administrative support: Gal Maier, Gloria Lee, Thian Kheoh, Arturo Molina
Provision of study materials or patients: Gerhardt Attard, Alison H.M. Reid, Christopher Parker, Nikhil Babu Oommen, L. Rhoda Molife, Emilda Thompson, David Olmos, Rajesh Sinha, Stan B. Kaye, David Dearnaley, Johann S. de Bono
Collection and assembly of data: Gerhardt Attard, Elizabeth Folkerd, Nikhil Babu Oommen, Christina Messiou, Gal Maier, Emilda Thompson
Data analysis and interpretation: Gerhardt Attard, Elizabeth Folkerd, Roger A'Hern, Mitch Dowsett, Johann S. de Bono
Manuscript writing: Gerhardt Attard, Roger A'Hern, Johann S. de Bono
Final approval of manuscript: Gerhardt Attard, Alison H.M. Reid, Roger A'Hern, Christopher Parker, Elizabeth Folkerd, Nikhil Babu Oommen, Christina Messiou, L. Rhoda Molife, Gal Maier, Emilda Thompson, David Olmos, Rajesh Sinha, Gloria Lee, Mitch Dowsett, Stan B. Kaye, David Dearnaley, Thian Kheoh, Johann S. de Bono

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antigen (PSA) decline of ≥ 50% (null hypothesis = 0.1; alternative hypothesis = 0.3; α = .05; β = .14). Computed tomography scans every 12 weeks and circulating tumor cell (CTC) enumeration were performed. Prospective reversal of resistance at progression by adding dexamethasone 0.5 mg/d to suppress adrenocorticotropic hormone and upstream steroids was pursued.

Results—A decline in PSA of ≥ 50% was observed in 28 (67%) of 42 phase II patients, and declines of ≥ 90% were observed in eight (19%) of 42 patients. Independent radiologic evaluation reported partial responses (Response Evaluation Criteria in Solid Tumors) in nine (37.5%) of 24 phase II patients with measurable disease. Decreases in CTC counts were also documented. The median time to PSA progression (TTPP) on abiraterone acetate alone for all phase II patients was 225 days (95% CI, 162 to 287 days). Exploratory analyses were performed on all 54 phase I/II patients; the addition of dexamethasone at disease progression reversed resistance in 33% of patients regardless of prior treatment with dexamethasone, and pretreatment serum androgen and estradiol levels were associated with a probability of ≥ 50% PSA decline and TTPP on abiraterone acetate and dexamethasone.

Conclusion—CYP17 blockade by abiraterone acetate results in declines in PSA and CTC counts and radiologic responses, confirming that CRPC commonly remains hormone driven.

INTRODUCTION

Prostate cancer mortality is invariably a result of what has been described as hormone-refractory or androgen-independent disease. Patients who experience relapse despite castration can respond to further hormonal treatments, but these have been modestly effective to date.1,2 Evidence is accumulating that the more appropriately named castration-resistant prostate cancer (CRPC) frequently remains hormone driven, by using adrenal hormones or through intracrine synthesis.3-7

CYP17 is key to androgen and estrogen synthesis. The nonspecific weak inhibitor of CYP17, ketoconazole, has modest antitumor activity in CRPC,8 and its utility has been limited by its toxicities. Furthermore, an increase in androgenic steroids at disease progression on this agent indicates incomplete target blockade.8 Chemists at our institution used testicular extracts and radiolabeled CYP17 steroid substrates to screen for small-molecule inhibitors of this enzyme.9-12 This led to the design of a potent, selective, and irreversible inhibitor of CYP17, abiraterone,13,14 which we have shown to be safe, with promising antitumor activity in chemotherapy-naive patients with CRPC.15 In these studies, concomitant castration was continued to prevent a compensatory luteinizing hormone surge that can overcome CYP17 blockade.16 Continuous CYP17 inhibition results in raised levels of adrenocorticotropic hormone (ACTH) that increase steroid levels upstream of CYP17, including corticosterone and deoxycorticosterone. These raised upstream steroids prevent adrenocortical insufficiency but can result in a syndrome of secondary mineralocorticoid excess characterized by fluid retention, hypertension, and hypokalemia. This can be ameliorated by mineralocorticoid antagonists or low-dose glucocorticoids, which decrease ACTH and steroids upstream of the CYP17 blockade. This may be of relevance to antitumor activity because these upstream steroids are implicated in activating a promiscuous androgen receptor (AR).17 To rapidly evaluate the antitumor activity of abiraterone acetate, this phase I study seamlessly expanded15 into a two-stage, single-arm, phase II trial; we now present data of the antitumor activity of abiraterone acetate administered at 1,000 mg, once daily, continuously in chemotherapy-naive CRPC patients who experienced progression on multiple treatments.

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PATIENTS AND METHODS

Patients

All of the patients enrolled onto this study were castrate, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had progressive disease as defined by Prostate-Specific Antigen Working Group (PSAWG) I.18 This was a single-center study conducted at the Royal Marsden Hospital (London, United Kingdom). Patients were required to have a minimum washout period of 4 weeks after the use of prostate cancer therapy except luteinizing hormone–releasing hormone (LHRH) agonists and 6 weeks after stopping the antiandrogens bicalutamide or nilutamide. Patients who had previously received cytotoxic chemotherapy or a radiopharmaceutical for their prostate cancer were excluded. Other eligibility criteria included castrate serum testosterone levels (< 50 ng/dL), normal serum potassium, and adequate bone marrow, renal, and hepatic function. Patients were excluded if they had brain metastases or spinal cord compression, active autoimmune disease requiring corticosteroid therapy, uncontrolled hypertension, a history of class III or IV cardiac failure, or a serious concurrent medical illness. This phase I/II study was approved by the Ethics Review Committees of the Royal Marsden Hospital, and informed consent was obtained from all patients.

Treatment and Procedures

Four capsules (250 mg each) of abiraterone acetate powder were administered once daily, continuously, to fasted patients in 28-day cycles. Toxicity related to elevated mineralocorticoid levels was managed with a mineralocorticoid receptor antagonist (eplerenone 50 to 200 mg/d); treatment with glucocorticoids to suppress ACTH was only used if mineralocorticoid antagonism did not reverse these toxicities. Spironolactone was not used because it has been reported to bind and activate the AR.19

Safety evaluations were conducted at baseline, weekly for the first two cycles, and every cycle thereafter. All patients had a physical examination, CBC, international normalized ratio, partial thromboplastin time, serum creatinine, electrolytes, AST, ALT, and bilirubin. All adverse events were graded according to the US National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0). Prostate-specific antigen (PSA), lactate dehydrogenase, and alkaline phosphatase were measured at baseline and at the end of every cycle. High-resolution computed tomography (CT) scans were performed on all patients at baseline and every 12 weeks, and bone scans were performed at baseline and every 24 weeks. A 7.5-mL blood sample was collected into CellSave tubes (Immunicon, Huntingdon Valley, PA) from consenting patients at baseline and on the first day of every cycle for the enumeration of circulating tumor cells (CTCs) using the CellSearch system (Immunicon) as described previously.20,21 Circulating dehydroepiandrostenedione (DHEA), DHEA-sulfate (DHEA-S), androstenedione, testosterone, and estradiol were evaluated at baseline.

Study

This was an open-label, single-arm study of abiraterone acetate. The phase I, dose-escalation portion of the study, which has been reported previously,15 recruited 21 patients and identified 1,000 mg as the recommended phase II dose. The primary end point was a ≥ 50% PSA decline at any time after 12 weeks of treatment confirmed by a second PSA 4 weeks later (PSAWG I) in patients treated at 1,000 mg. PSA progression was as defined by PSAWG I. Because a PSA decline of ≥ 30% was associated with improved survival in patients treated with docetaxel,22 the rate of PSA declines ≥ 30% was a secondary end point. Declines in PSA by ≥ 90% were also reported. However, in the absence of PSA being a surrogate for survival in CRPC, we have included waterfall plots of PSA decrements as

recommended by Prostate Cancer Clinical Trials Working Group II23 (published after the start of this study), which although not originally specified in the protocol, are not a violation of protocol design. Moreover, other intermediate end points were used, namely radiologic assessments and changes in CTC counts. Measurable target lesions were monitored by CT scans using Response Evaluation Criteria in Solid Tumors (RECIST)24 and reported by a radiologist blinded to clinical outcome. Patients with ≥ 5 CTCs/7.5 mL before treatment were classified as having a decline in CTCs to less than 5 CTCs/7.5 mL and/or by ≥ 30% or neither; these declines have been previously shown to correlate with an improvement in overall survival.25-27

The median time to PSA progression (TTPP) was calculated using the Kaplan-Meier product-limit method and was defined as the time elapsed from the start of therapy until PSA progression after ≥ 12 weeks as defined by PSAWG I criteria. This required an increase in PSA of more than 25% greater than baseline or nadir for patients whose PSA did not decrease or decreased by less than 50%, respectively, and an increase in PSA of more than 50% above nadir and an absolute increase of 5 ng/mL for patients whose PSA had decreased by ≥ 50%. A second confirmatory value was required. The date of data cutoff was July 28, 2008. Median follow-up time was calculated using the reverse Kaplan-Meier method; patients were censored if they had reached the end of their participation in the trial but were otherwise considered as events.

Addition of Corticosteroids at Progression on Abiraterone Acetate

Preclinical models report that hormones upstream of CYP17 that are increased as a result of high ACTH levels in patients receiving abiraterone acetate could activate a promiscuous AR.17,28 Promiscuous AR activation by antiandrogens is observed in up to 30% of CRPC patients and manifests clinically as a withdrawal response.8 This study was prospectively designed to allow addition of dexamethasone 0.5 mg daily to abiraterone acetate to all patients at progression. Dexamethasone 0.5 mg/d is the standard corticosteroid treatment for CRPC at our institution29 and was thus used in preference to another corticosteroid. In the phase I study, addition of dexamethasone suppressed ACTH and steroids upstream of CYP17 and reversed resistance to abiraterone acetate.15 To confirm these preliminary observations, tumor responses (defined earlier) on addition of dexamethasone in the 1,000-mg abiraterone acetate population were assessed and reported (separate to the abiraterone acetate alone response data) based on whether patients had previously experienced progression on the same dose and schedule of dexamethasone (group I) or not (group II). The median TTPP from start of abiraterone acetate until PSA progression on dexamethasone and abiraterone acetate (or on abiraterone acetate alone if dexamethasone was not added), as defined by PSAWG I, was calculated using the Kaplan-Meier method. The median TTPP from start of dexamethasone until PSA progression on dexamethasone and abiraterone acetate is also reported. In keeping with the CONSORT statement on transparency in clinical trials, all relevant additional details of these patients are listed in Appendix Table A1 (online only).

Statistical Considerations

The primary objective was to determine the rate of patients demonstrating a ≥ 50% decline in PSA after 12 weeks of treatment with single-agent abiraterone acetate 1,000 mg. A two-stage, attained phase II trial design was used30 in the phase II component of the study. The null hypothesis was a ≥ 50% PSA decline rate in 10% of patients; a decline in 30% of patients was the alternative hypothesis. With 42 assessable phase II patients, this study had an 86% power to detect a ≥ 50% decline in PSA in 30% of patients, with a one-sided α level of 5%. The first stage ended after the evaluation of 20 patients, with continued accrual to the second stage if more than one patient had a ≥ 50% decline in PSA.

RESULTS

Patient Characteristics

Fifty-four CRPC patients were recruited to this phase I/II trial between December 13, 2005 and November 28, 2007,15 and six patients continue on single-agent abiraterone acetate. Forty-two patients were treated at 1,000 mg (including nine patients in the phase I portion of the study treated at 1,000 mg); the other 12 patients were treated at 250, 500, 750, and 2,000 mg (three patients at each dose level). As defined a priori in this phase I/II trial protocol, all patients treated at 1,000 mg were included in this phase II antitumor activity analysis. Table 1 lists the demographics and clinical characteristics of the 42 patients treated at 1,000 mg. The median number of lines of prior hormonal treatments was three. All patients had experienced progression on LHRH analogs, and 41 of 42 patients had experienced progression on antiandrogens; one patient had experienced progression on LHRH analogs and diethylstilboestrol but had not received an antiandrogen. Fourteen (33%) of 42 patients had experienced progression on dexamethasone, and 20 (48%) of 42 patients had experienced progression on diethylstilboestrol, including seven (17%) of 42 patients on both. Two patients had experienced progression on ketoconazole. Twenty-four patients (57%) had measurable disease on CT scan at baseline, and 32 (76%) of 42 patients had bone metastasis on bone scan; 17 (40%) of 42 patients had ≥ 5 CTCs/7.5 mL at baseline.

PSA, CTC Count, and Radiologic Evidence for Antitumor Activity

A decline in PSA of ≥ 50% was observed in 28 (67%) of 42 patients, and 30 (71%) of 42 and eight (19%) of 42 patients had a decline in PSA of ≥ 30% and ≥ 90%, respectively. The change in PSA from baseline at 12 weeks and the maximal change at any time point after 12 weeks are presented in Figure 1. One of the two patients who had previously experienced progression on ketoconazole and hydrocortisone had a decline in PSA from 79 to 10.9 ng/mL, which is ongoing after 230 days of treatment. By RECIST criteria, 24 patients had measurable disease on CT scan, with nine patients (37.5%) having tumor regression that constituted a partial response (Fig 2); overall, 16 patients (66%) had no evidence of progression at 6 months. Furthermore, 10 (59%) of 17 patients had a decline in CTC count from ≥ 5to less than 5/7.5 mL, and 12 (70%) of 17 patients had a decline of ≥ 30% after starting treatment with abiraterone acetate.

Safety Profile

A syndrome of secondary mineralocorticoid excess characterized by hypokalemia (37 of 42 patients; 88%), hypertension (17 of 42 patients; 40%), and fluid overload (13 of 42 patients; 31%) was reported. This was managed by eplerenone 50 to 200 mg daily except in three patients who required glucocorticoid replacement for symptomatic fluid overload; in two patients, this was associated with migrainous headaches. Magnetic resonance imaging of the brain was normal in both patients. Another patient with a prior history of asthma required high-dose corticosteroids for worsening asthma and was subsequently maintained on dexamethasone 0.5 mg daily. Hot flushes developed in four of 42 patients; venlafaxine was required to control symptoms in two patients. Two patients (5%) developed asymptomatic grade 3 transaminase elevation 10 weeks and 27 weeks after starting abiraterone acetate. Interruption of treatment resulted in complete resolution. One patient was rechallenged with abiraterone acetate 750 mg, and the transaminase elevation recurred, suggesting that this event was secondary to study treatment. Another patient suffered grade 2 asymptomatic transaminase elevation 16 weeks after starting abiraterone acetate 1,000 mg, but this resolved after temporary discontinuation of treatment, and a dose of 750 mg was then administered uneventfully. Four patients developed grade 1 headaches, and five patients complained of grade 1 joint aches; these symptoms occurred intermittently on abiraterone acetate and did not necessitate treatment interruption. No other adverse events considered

related to abiraterone acetate of grade ≥ 2 severity or occurring in two or more patients were reported.

TTPP

The median follow-up time for the 42 patients treated at 1,000 mg was 505 days (95% CI, 457 to 552 days), with a median TTPP on abiraterone acetate alone of 225 days (95% CI, 162 to 287 days; Fig 3A). The median TTPP for the patients treated at 1,000 mg who had a ≥ 50% decline in PSA was 253 days (95% CI, 122 to 383 days), and the median TTPP for the patients who had a ≥ 90% decline in PSA was 393 days (95% CI, 252 to 533 days). Fourteen patients were censored for this analysis; five patients continued on single-agent abiraterone acetate at the date of data cutoff, and nine patients started dexamethasone or stopped abiraterone acetate without confirmed PSA progression after 12 weeks (Appendix Table A1). The median follow-up time for all 54 phase I/II patients who received any amount of study medication was 588 days (95% CI, 409 to 767 days), with a median TTPP on abiraterone acetate alone of 229 days (95% CI, 157 to 301 days) and median TTPP for patients who had a ≥ 50% and ≥ 90% decline in PSA of 339 days (95% CI, 136 to 542 days) and 477 days (95% CI, 350 to 604 days), respectively. Sixteen patients were censored for this analysis; six patients continued on single-agent abiraterone acetate at the date of data cutoff, and 10 patients started dexamethasone or stopped abiraterone acetate without confirmed PSA progression after 12 weeks (Appendix Table A1).

Addition of Corticosteroids at Progression on Abiraterone Acetate Alone

To date, 39 of 54 patients in this phase I/II study have received abiraterone acetate in combination with dexamethasone 0.5 mg daily; 14 continued on this combination at date of data cutoff (Appendix Table A1). The median TTPP from addition of dexamethasone until stopping both abiraterone acetate and dexamethasone (n = 39) was 151 days (95% CI, 117 to 185 days). Thirty patients received the combination for ≥ 12 weeks after progression on abiraterone acetate alone and were thus assessable for magnitude of PSA decline; 24 patients experienced progression on the combination (Appendix Table A1). Eleven of these 30 patients had previously experienced progression on dexamethasone (group I), and 19 of 30 were dexamethasone naive (group II); four (36%) of 11 patients in group I and six (32%) of 19 patients in group II had ≥ 50% declines in PSA (Appendix Fig A1, online only). The median TTPP for all 54 patients from start of abiraterone acetate until PSA progression on the combination (n = 25) or on abiraterone acetate alone if dexamethasone was not used (n = 3) was 420 days (95% CI, 259 to 580 days; Fig 3B); the median TTPP was 372 days (95% CI, 55 to 688 days) for patients who previously experienced progression on dexamethasone (group I) and 361 days (95% CI, 241 to 480 days) for dexamethasone-naive patients (group II). The remaining 26 patients were censored at the date of data cutoff either because they continued on treatment (n = 20) or they had stopped treatment without confirmed criteria for PSA progression (n = 6; Appendix Table A1).

Predictors of Response to Abiraterone Acetate

All 54 patients who received any amount of single-agent abiraterone acetate were included in this analysis. Pretreatment levels of DHEA, DHEA-S, androstenedione (continuous variable), and estradiol were associated with increased probability of a ≥ 50% PSA decline on abiraterone acetate and with median TTPP calculated from start of abiraterone acetate until PSA progression on dexamethasone and abiraterone acetate (or on abiraterone acetate alone if dexamethasone was not added; Tables 2 and 3).

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DISCUSSION

This study confirms that selective inhibition of CYP17 with abiraterone acetate results in declines in PSA, radiologic responses, and declines in CTC counts in patients with hormone-dependent CRPC. Abiraterone acetate 1,000 mg was administered daily continuously to 42 patients in this study, resulting in ≥ 50% PSA declines in 67% of patients. The rates of ≥ 50% PSA declines in prospective phase II studies of ketoconazole in chemotherapy-naive patients ranged from 31% to 62%, and the median duration of response was up to 7.7 months.31-35 All of the ketoconazole studies required hydrocortisone replacement therapy, which may have contributed to the antitumor activity36 and described grade ≥ 3 toxicities in up to 30% of patients. Although it is difficult to make any comparisons, the patients in our study had received more lines of hormone treatment and had more advanced disease. Furthermore, abiraterone acetate administered without concomitant glucocorticoids can be well tolerated, although monitoring and immediate treatment of secondary mineralocorticoid excess is important. Androstenedione is the sole hormone reported to significantly predict a decline in PSA by ≥ 50% in a series of 103 patients treated with ketoconazole.38 We report that DHEA, DHEA-S, and estradiol, in addition to androstenedione, were associated with ≥ 50% declines in PSA and TTPP, although the relatively small size of this study implies that only strong relationships would be identified, and none of the outcomes evaluated is significant if a correction for multiple testing, requiring $P < .006$, is used.

We have not previously observed and, to our knowledge, there are no published reports of secondary responses to reinstitution of single-agent dexamethasone in patients who had previously experienced progression on this therapy. In this trial, 33% of patients had a secondary ≥ 50% PSA decline on addition of dexamethasone to abiraterone acetate regardless of prior dexamethasone exposure. These data suggest that AR may be activated by elevated hormone levels upstream of CYP17 and supports the future evaluation of a combination of abiraterone acetate with low-dose corticosteroids to maximize efficacy and minimize toxicity. Abiraterone acetate is now being evaluated in combination with corticosteroids in a 1,180-patient, multicenter, double-blind, randomized phase III study comparing abiraterone acetate plus prednisone versus prednisone plus placebo in CRPC patients who have previously received docetaxel. The primary end point of this study is overall survival. This phase III study incorporates the prospective evaluation of whether CTC counts after treatment can serve as a robust intermediate end point for overall survival to accelerate new drug approval for CRPC. Phase III studies in the prechemotherapy setting are also planned. Overall, these data suggest that abiraterone acetate is an effective, well-tolerated treatment and confirm that a subgroup of CRPC patients continue to have hormone-driven disease.

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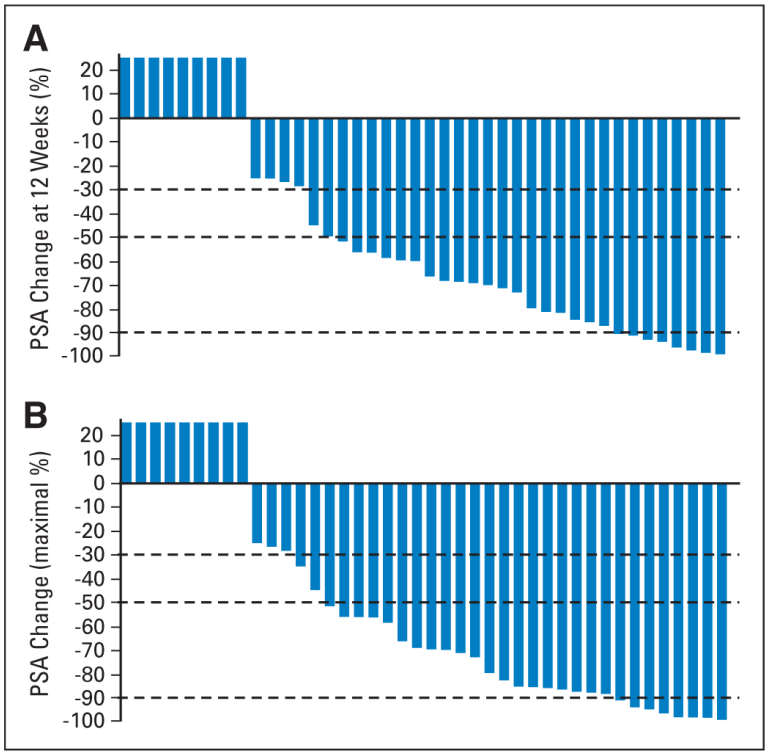

Fig 1.

Changes in prostate-specific antigen (PSA) with abiraterone acetate. Waterfall plot showing maximal percentage change in PSA from baseline with single-agent abiraterone acetate 1,000 mg at (A) 12 weeks and (B) any time point after 12 weeks. The dashed lines indicate PSA declines of 30%, 50%, and 90%.

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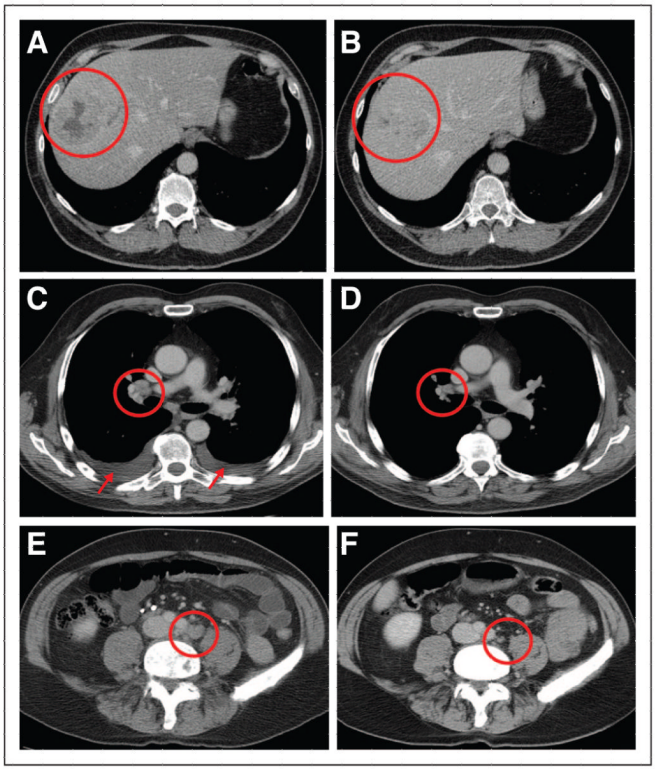

Fig 2.

Radiologic responses to abiraterone acetate. (A) Patient 203 had previously experienced progression on luteinizing hormone–releasing hormone (LHRH) agonists, bicalutamide, diethylstilboestrol, and the histone deacetylase inhibitor FK228. Before starting treatment with abiraterone acetate, he had a prostate-specific antigen (PSA) level of 200 ng/mL and multiple liver metastases but no bone metastasis on bone scan. The largest lesion in the liver was 102 mm. (B) After 12 months of treatment, his PSA had declined to 11.2 ng/mL, and his index lesion measured 46 mm. (C) Patient 214 had previously experienced progression on LHRH agonists and bicalutamide. Before starting treatment, he had a PSA of 129 ng/mL, mediastinal lymphadenopathy measuring 21 mm, and bone metastasis on bone scan. He also had bilateral pleural effusions indicated by the red arrows. (D) After 12 months of treatment, his PSA was 7.4 ng/mL, and his mediastinal lymphadenopathy measured 11 mm. His bone disease remained stable on bone scan, and the pleural effusions had resolved. (E) Patient 227 had previously experienced progression on LHRH agonists and bicalutamide. Before treatment, he had a PSA of 870 ng/mL and retroperitoneal lymphadenopathy measuring 15 mm. (F) After 9 months of treatment, his retroperitoneal lymphadenopathy measured 6 mm. His PSA had declined to 471 ng/mL but then increased to 1,334 ng/mL, necessitating addition of dexamethasone 0.5 mg daily. This resulted in a secondary decline in PSA to 820 ng/mL, and he continues on treatment after 12 months.

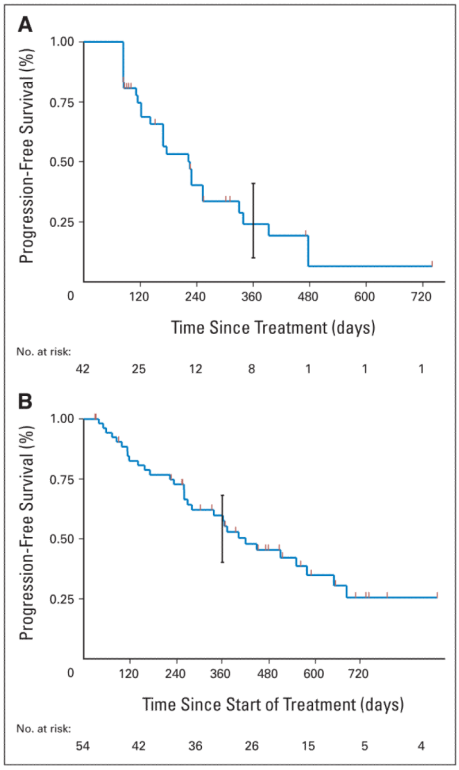

Fig 3.

Time on treatment with abiraterone acetate. (A) Kaplan-Meier (KM) plot showing time to prostate-specific antigen progression (TTPP) on abiraterone acetate alone for 42 patients treated at 1,000 mg. (B) KM plot for TTPP for all patients (N = 54) after progression on addition of dexamethasone (or abiraterone acetate alone if dexamethasone was not added).

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Table 1

Baseline Patient Demographics and Clinical Characteristics of Patients Treated With Abiraterone Acetate 1,000 mg

Patient Demographics and Clinical Characteristics	No. of Patients	%
Age, years		
Median	70	
Range	50-84	
Gleason score (diagnostic biopsy)		
6	8	
7	10	
8	16	
9	4	
10	1	
Unknown	3	
Baseline PSA, ng/mL		
Median	110	
Range	9.7-964	
ECOG performance status		
0	20	
1	22	
Site of baseline metastases		
Increasing PSA only	4	
Lymph nodes only	4	
Visceral lesions only	1	
Lymph nodes + visceral	1	
Bone lesions only	14	
Bone + lymph nodes	12	
Bone + lymph nodes + visceral	6	
LDH		
Raised	13	
Normal	29	
Prior hormone therapy		
LHRH analogues	42	100
Antiandrogens	41	98
Dexamethasone	14	33
Diethylstilboestrol	20	48
Ketoconazole	2	5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; LHRH, luteinizing hormone–releasing hormone.

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Table 2

Association of Pretreatment Serum Investigations (continuous variable) in Patients Who Received Any Amount of Abiraterone Acetate (N = 54) With Probability of a ≥ 50% PSA Decline

Serum Marker	OR	95% CI	*P*
DHEA	4.84	1.47 to 15.97	.01
DHEA-S	3.6	1.14 to 11.38	.029
Androstenedione	4.64	1.5 to 14.35	.008
Estradiol	5.15	1.33 to 19.97	.018
Alkaline phosphatase	0.71	0.27 to 1.86	.492
PSA	0.83	0.46 to 1.48	.519
Lactate dehydrogenase	0.45	0.05 to 3.99	.477

NOTE. OR applies to a unit log change in value. Unacceptably high levels of discordance between the three super-sensitive assays used for testosterone measurement (radioimmunoassay ×1 and liquid chromatography/mass spectrometry/mass spectrometry ×2) led to these results not being included in these analyses.

Abbreviations: PSA, prostate-specific antigen; OR, odds ratio; DHEA, dehydroepiandrostenedione; DHEA-S, dehydroepiandrostenedione-sulfate.

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Table 3

Association of Pretreatment Serum Investigations (continuous variable) in Patients Who Received Any Amount of Abiraterone Acetate (N = 54) With TTPP on Abiraterone Acetate and Dexamethasone

Serum Marker	HR	95% CI	*P*
DHEA	0.57	0.34 to 0.98	.04
DHEA-S	0.71	0.51 to 1.0	.05
Androstenedione	0.5	0.32 to 0.98	.002
Estradiol	0.38	0.2 to 0.71	.003
Alkaline phosphatase	0.95	0.55 to 1.62	.84
PSA	1.32	0.97 to 1.8	.08
Lactate dehydrogenase	1.1	0.33 to 3.63	.87

NOTE. HR applies to a unit log change in value. Unacceptably high levels of discordance between the three super-sensitive assays used for testosterone measurement (radioimmunoassay ×1 and liquid chromatography/mass spectrometry/mass spectrometry ×2) led to these results not being included in these analyses.

Abbreviations: TTPP, time to prostate-specific antigen progression; HR, hazard ratio; DHEA, dehydroepiandrostenedione; DHEA-S, dehydroepiandrostenedione-sulfate; PSA, prostate-specific antigen.