Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy†

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Background: Fatigue is a common, debilitating side-effect of prostate cancer and its treatment. Patient-reported fatigue was evaluated as part of COU-AA-301, a randomized, placebo-controlled, phase III trial of abiraterone acetate and prednisone versus placebo and prednisone in metastatic castration-resistant prostate cancer (mCRPC) patients after docetaxel chemotherapy. This is the first phase III study in advanced prostate cancer to evaluate fatigue outcomes using a validated fatigue-specific instrument.

Patients and methods: The Brief Fatigue Inventory (BFI) questionnaire was used to measure patient-reported fatigue intensity and fatigue interference with activities of daily life. All analyses were conducted using prespecified responder definitions of clinically meaningful changes.

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Results: A total of 797 patients were randomized to abiraterone acetate and prednisone, and 398 were randomized to placebo and prednisone. Compared with prednisone alone, in patients with clinically significant fatigue at baseline, abiraterone acetate and prednisone significantly increased the proportion of patients reporting improvement in fatigue intensity (58.1% versus 40.3%, \( P = 0.0001 \)), improved fatigue interference (55.0% versus 38.0%, \( P = 0.0075 \)), and accelerated improvement in fatigue intensity (median 59 days versus 194 days, \( P = 0.0155 \)).

Conclusions: In patients with mCRPC progressing after docetaxel chemotherapy, abiraterone acetate and prednisone yielded clinically meaningful improvements in patient-reported fatigue compared with prednisone alone.

Key words: advanced prostate cancer, palliation, patient-reported outcome

Introduction

Fatigue is a dominant symptom in prostate cancer [1, 2], resulting from the disease itself, disease-specific treatments, or reactive depression. Manifestations include tiredness and lack of mental energy and/or physical strength [2], which can cause a significant reduction in quality of life (QoL) [3]. It is well understood that androgen deprivation therapy, administered to noncastrated men, is frequently associated with fatigue [4–6]. Fatigue is also one of the most common adverse events reported in trials for metastatic castration-resistant prostate cancer (mCRPC), independent of whether chemotherapy-naïve [7–10] or post-chemotherapy [11–14] patients are enrolled, or whether the treatment is taxane- or nontaxane-based chemotherapy or the biologic agent sipuleucel-T [15–18]. More important is that, to date, other than supportive treatment, no therapeutic option has been shown to have a positive impact on this symptom in advanced disease. Besides fatigue, patients with mCRPC also face other significant morbidities, such as skeletal-related events, pain, and functional impairment [2]. New therapeutic options that improve survival and concurrently reduce the symptomatic manifestations of mCRPC are needed. In fact, many experts believe that improved QoL should be a major goal of all new CRPC therapies [19, 20], and that patient-based QoL assessments should be mandatory for clinical trials in metastatic prostate cancer [21].

In castration-resistant disease, androgen synthesis in the adrenal glands and in the tumor itself, along with overexpression of the androgen receptor, allows for continued AR signaling and contributes to castration-resistant tumor growth [22, 23]. Intratumoral androgen production might contribute to tumor progression despite suppressed serum androgen levels [24]. As a specific inhibitor of CYP17 (17α-hydroxylase/C17, 20-lyase), abiraterone potently inhibits the synthesis of testosterone and other androgens in the adrenal glands and the tumor microenvironment, leading to the suppression of prostate cancer growth and tumor regressions [25]. In COU-AA-301, a large phase III trial in patients with mCRPC progressing after docetaxel, abiraterone acetate, and prednisone chemotherapy significantly lengthened overall survival versus placebo and prednisone (14.8 months versus 10.9 months, \( P < 0.0001 \)) at the time of the preplanned interim analysis [26]. In a final analysis conducted before crossover of placebo patients to active drug, this overall survival benefit increased from 3.9 to 4.6 months [27, 28]. Abiraterone acetate has a much better safety profile than cytotoxic chemotherapy, while early evidence from phase I–II studies suggested that it might produce symptomatic improvement [29–31]. Patient-reported outcomes were therefore included as exploratory end points in this phase III trial.

To determine whether abiraterone acetate would improve the fatigue so frequently experienced by patients with mCRPC, we evaluated patient-reported fatigue data from the final analysis of the COU-AA-301 trial, collected using the Brief Fatigue Inventory (BFI) questionnaire. Despite the prevalence and detrimental impact of fatigue in this setting, ours is the first phase III trial in advanced prostate cancer to systematically assess fatigue outcomes using a validated fatigue-specific instrument.

Methods

Study Design

COU-AA-301 was a phase III, randomized, double-blind, placebo-controlled study conducted in patients with mCRPC who had previously failed docetaxel-based chemotherapy (clinicaltrials.gov identifier: NCT00638690). Patients were randomly assigned (2 : 1 ratio) to abiraterone acetate (1 g daily) and low-dose prednisone/prednisolone (5 mg twice daily) or placebo and prednisone/prednisolone (5 mg twice daily). The primary end point was overall survival. The study design and primary/secondary outcomes have previously been described in detail [26].

Assessments

The BFI was administered at baseline (~14 days before the first dose of study treatment) and on the first day of each treatment cycle until treatment discontinuation. The BFI is a standard, reliable instrument used to rapidly assess fatigue in patients with cancer, and is significantly correlated with other validated fatigue questionnaires [32]. It consists of three questions assessing fatigue severity and six questions assessing the interference of fatigue with the patient’s mood and social/physical functioning (Figure 1).

‘Fatigue intensity’ was defined as the score of the ‘worst level of fatigue (weariness, tiredness) in the last 24 h’ item (i.e. BFI questionnaire item 3) on a 0–10 scale with 0 = ‘no fatigue’ and 10 = ‘as bad as you can imagine’. ‘Fatigue interference’ was defined as the average score of all interference items (i.e. BFI questionnaire items 4A through 4F), which assess interference of fatigue with several functional domains, including general activity, mood, walking ability, work (both outside the home and normal chores), relationships, and enjoyment of life (Figure 1). Each of these six items measures fatigue interference on a 0–10 scale, with 0 = ‘does not interfere’ and 10 = ‘completely interferes’.

Statistical Analysis

Clinically meaningful changes in eligible patients were prespecified before conducting all analyses. A patient was considered to have ‘fatigue intensity improvement’ if their fatigue intensity score decreased by ≥2 points from baseline at two or more consecutive assessments (i.e. 4
weeks apart); conversely, an increase by the same amount at two or more consecutive assessments (i.e. 4 weeks apart) was considered ‘fatigue intensity progression’. Similarly, ‘fatigue interference improvement’/‘fatigue interference progression’ were defined as a decrease/increase of ≥1.25 points from baseline in the average BFI interference scale at two or more consecutive assessments (i.e. 4 weeks apart). Of note, all analyses of improvement were only conducted in patients with clinically significant fatigue at baseline, i.e. scores of ≥5 points in fatigue intensity or fatigue interference, respectively. The analyses of fatigue progression were conducted in the overall intent-to-treat population.

These change thresholds were chosen based on the baseline distributions of fatigue scores: a change equal to or greater than one-half the baseline standard deviation (SD) was considered clinically meaningful, a definition that is well supported and accepted by the existing literature as a difference that is robust and likely significant to patients [33–36]. For fatigue interference scores, the baseline SD of the mean of all interference items was ~2.5, therefore, a change of 1.25 points was defined as clinically meaningful to patients in this particular study. For fatigue intensity scores, the baseline SD was about 2.6 and a change of ≥1.3 points would therefore be considered clinically meaningful. However, unlike fatigue interference (which is an average of several scores), the fatigue intensity score is based on a single item and can thus only be a whole number, not a fraction; a change of ≥2 points was therefore the closest measurable threshold to represent clinically meaningful change, making it a conservative estimate of change in fatigue severity.

Figure 1. Sample Brief Fatigue Inventory questionnaire. (Reprinted with permission of the University of Texas MD Anderson Cancer Center.)
Proportions of patients with improvement or progression in fatigue were compared between treatment groups using the chi-squared test. Time to improvement and time to progression were estimated using the Kaplan–Meier method, and the differences between treatment groups were compared using a log-rank test stratified by Eastern Cooperative Oncology Group performance status, pain score, number of prior chemotherapy regimens, and type of progression. Corresponding hazard ratios were also estimated, using a Cox proportional hazard model stratified by the same parameters.

In analyzing patient-reported outcomes, missing data have the potential to bias the overall results, and sensitivity analyses compensating for missing data are of great benefit. Therefore, two different types of models were developed as post-hoc sensitivity analyses, i.e. (i) repeated measure mixed effects models and (ii) joint mixed effects and log time-to-dropout models. These models were based on previously published methods [37, 38], and their purpose was to estimate mean fatigue scores over time using different approaches to account for missing data. The model estimates therefore minimized potential attrition bias due to missing data/study dropout. Repeated measure mixed effects models estimated fatigue intensity and fatigue interference scores using the following fixed effects: treatment group (i.e. abiraterone acetate or placebo), time (i.e. treatment cycle), and interaction between time and treatment group. Serial correlation was assumed, and a compound symmetry correlation matrix was used to account for the correlations between repeated measures within patients. The fatigue scores generated by these models were used to estimate mean changes in scores from baseline at each treatment cycle, which were then compared between the two treatment groups at each cycle using the t-test.

This type of model assumed that data were missing at random. As this is unlikely to be the case in a metastatic cancer trial, joint mixed effects and log time-to-dropout models, which assumed that data were not missing at random, were also employed. These models compared the fatigue profiles of abiraterone–prednisone versus prednisone-only over treatment cycles as a series of piecewise linear models (because fatigue scores were not linear over time), assuming the slope to change at weeks 16, 28, and 40; these models were truncated at week 56. The area under the curve (AUC) for each treatment arm was then calculated using the trapezoidal rule as follows: Intercept + week × Tx × week + week 16 + Tx × week 16 + week 28 + Tx × week 28 + week 40 + Tx × week 40

Piecewise linear regression, where:

- Week 16 = max(0, week-16)
- Week 28 = max(0, week-28)
- Week 40 = max(0, week-40)

The AUCs for each treatment arm were then compared using the t-test. All models were developed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

results

patient characteristics

A total of 797 patients were randomized to abiraterone acetate and prednisone and 398 to placebo and prednisone. Median treatment durations were 8 and 4 months, respectively [26], and median duration of follow-up for the overall study population was 20.2 months [27, 28]. Baseline fatigue scores were well balanced between treatment arms (Table 1). BFI data were available for the great majority of patients throughout the study; the cumulative amount of missing data ranged from 4.69% at cycle 1 to 7.42% at cycle 28.

fatigue outcomes

Among intent-to-treat patients with clinically significant baseline fatigue, significantly more patients in the abiraterone acetate arm experienced improvement in fatigue intensity (58.1% versus 40.3%) and fatigue interference (55.0% versus 38.0%), based on results from the final dataset (Table 2). The median time to improvement of fatigue intensity was 135 days shorter with abiraterone acetate ($P = 0.0117$), although the difference in time to fatigue interference improvement was not statistically significant (Table 2 and Figure 2A and B). Furthermore, abiraterone–prednisone significantly delayed progression of both fatigue intensity and interference (Table 2 and Figure 3A and B). Abiraterone–prednisone also yielded significantly higher proportions of improvement in fatigue intensity and interference in the overall intent-to-treat population, i.e. including those patients without clinically significant baseline fatigue (supplementary Table S1, available at Annals of Oncology online). A Cochran–Mantel–Haenszel test for general association showed that the association between treatment and fatigue improvement remained significant ($P < 0.0001$ for fatigue intensity; $P = 0.0002$ for fatigue interference) after adjusting for baseline score (i.e. score of either $<5$ or $\geq 5$).

The estimates obtained from both post-hoc sensitivity analyses lent further support to the observation that patients in the abiraterone–prednisone arm experienced superior fatigue outcomes than patients receiving prednisone alone. Notably, the results of the joint mixed effects and log time-to-dropout models yielded significantly ($P < 0.0001$) smaller AUCs for abiraterone–prednisone than for prednisone-only, for both fatigue intensity and interference (Supplementary Figure S1, online).

Table 1. Baseline characteristics of specific relevance to fatigue analyses

<table>
<thead>
<tr>
<th></th>
<th>Abiratone + Prednisone</th>
<th>Placebo + Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue intensity, median score</td>
<td>3.78</td>
<td>3.62</td>
</tr>
<tr>
<td>Patients with clinically significant fatigue intensity, n (%)</td>
<td>384/797 (48.2)</td>
<td>186/398 (46.7)</td>
</tr>
<tr>
<td>Fatigue interference, median score</td>
<td>3.05</td>
<td>2.90</td>
</tr>
<tr>
<td>Patients with clinically significant fatigue interference, n (%)</td>
<td>189/797 (23.7)</td>
<td>92/398 (23.1)</td>
</tr>
<tr>
<td>Patients from English-speaking countries, n (%)</td>
<td>628/797 (78.8)</td>
<td>322/398 (80.9)</td>
</tr>
<tr>
<td>Patients from non-English-speaking countries, n (%)</td>
<td>169/797 (21.2)</td>
<td>76/398 (19.1)</td>
</tr>
</tbody>
</table>

*Defined as baseline score of $\geq 5$ points.

*This baseline factor is of importance given that fatigue is more culturally dependent than other patient-reported outcomes. Non-English-speaking countries in this trial were Austria, Belgium, France, Germany, Hungary, Italy, The Netherlands, and Spain. English-speaking countries were Australia, Canada, Ireland, United Kingdom, and United States.
available at *Annals of Oncology* online). As smaller AUCs are the direct result of lower fatigue scores, these model estimates thus suggest better overall fatigue outcomes for abiraterone–prednisone from the time of treatment initiation to week 56 (when the model was truncated). In addition, the estimates obtained from repeated measures mixed effects models suggested that the mean change in fatigue scores compared with baseline was significantly ($P < 0.05$) better with abiraterone–prednisone at cycles 1–8, 11, and 15 for fatigue intensity and at cycles 2–11, 13, 15, and 16 for fatigue interference (Supplementary Figure S1, available at *Annals of Oncology* online).

### Table 2. Symptomatic changes in terms of number of patients with fatigue improvement, number of patients with fatigue progression, time to fatigue improvement, and time to fatigue progression, compared between both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone + Prednisone</th>
<th>Placebo + Prednisone</th>
<th>$P$</th>
<th>Stratified Cox analysis hazard ratio (95% CI)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue intensity improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement, n/eligible (%)</td>
<td>223/384 (58.1)</td>
<td>75/186 (40.3)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Time to improvement [median], days</td>
<td>59</td>
<td>194</td>
<td>0.0117$^a$</td>
<td>1.392 (1.065–1.818)</td>
</tr>
<tr>
<td>Fatigue interference improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement, n/eligible (%)</td>
<td>104/189 (55.0)</td>
<td>35/92 (38.0)</td>
<td>0.0075</td>
<td></td>
</tr>
<tr>
<td>Time to improvement [median], days</td>
<td>57</td>
<td>113</td>
<td>0.0868$^a$</td>
<td>1.393 (0.936–2.071)</td>
</tr>
<tr>
<td>Fatigue intensity progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression, n/eligible (%)</td>
<td>186/786 (23.7)</td>
<td>100/389 (25.7)</td>
<td>0.4426</td>
<td></td>
</tr>
<tr>
<td>Time to progression [25th percentile], days$^b$</td>
<td>232</td>
<td>139</td>
<td>0.0050$^a$</td>
<td>0.704 (0.550–0.902)</td>
</tr>
<tr>
<td>Fatigue interference progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression, n/eligible (%)</td>
<td>176/782 (22.5)</td>
<td>100/389 (25.7)</td>
<td>0.2242</td>
<td></td>
</tr>
<tr>
<td>Time to progression [25th percentile], days$^b$</td>
<td>281</td>
<td>139</td>
<td>0.0008$^a$</td>
<td>0.655 (0.510–0.841)</td>
</tr>
</tbody>
</table>

$^a$Stratified by Eastern Cooperative Oncology Group (ECOG) performance status score (0–1, 2), pain score (absent, present), number of prior chemotherapy regimens (1, 2), and type of progression (prostate-specific antigen only, radiographic).

$^b$25th percentiles are reported instead of medians because fewer than 50% of patients met progression criteria.

BFI, Brief Fatigue Inventory; CI, confidence interval.

**Figure 2.** Time to symptomatic improvement: (A) fatigue intensity; (B) fatigue interference.
All corresponding results obtained at the time of the interim analysis are presented in the supplementary Table S2 and Figures S3–S5, available at Annals of Oncology online.

**discussion**

This is the first phase III clinical trial in the setting of advanced prostate cancer to specifically evaluate fatigue outcomes, using an established instrument that has been validated for the assessment of cancer-related fatigue [32, 39]. The results demonstrate that abiraterone acetate and prednisone provide substantial and meaningful improvements in self-reported fatigue outcomes in patients with mCRPC after docetaxel chemotherapy compared with prednisone alone. Treatment with abiraterone–prednisone led to significant increases in the proportions of patients exhibiting improvements in fatigue intensity and fatigue interference; the higher proportion with improved fatigue interference is particularly notable, given that this represents a functional measure that until now had never been reported for an oncology agent. Abiraterone–prednisone was also significantly better than prednisone-only in reducing the time until improvement of fatigue intensity was achieved and significantly delayed progression of both fatigue intensity and interference. Estimates from two different sensitivity analyses provided additional evidence that fatigue improvements with abiraterone–prednisone were sustained across treatment cycles and lent further support to the directly observed outcomes. Of note, the use of such sophisticated methods to overcome the challenge of missing data is now specifically recommended in consensus guidelines on fatigue assessment in oncology clinical trials [39]. Few previous studies in patients with cancer have shown such a positive impact on fatigue with a disease-specific intervention (rather than supportive care), and this trial is the first to do so in the setting of mCRPC.

In the same study, we have previously reported that abiraterone–prednisone significantly improve overall survival, time to prostate-specific antigen (PSA) progression, radiographic progression-free survival, and PSA response compared with prednisone-only [26–28]. The abiraterone–prednisone arm also exhibited delayed occurrence of skeletal-related events and marked improvements in other patient-reported outcomes, including significantly better and faster palliation of pain, longer duration of pain palliation, and significant improvements in functional status [40, 41]. Administering abiraterone acetate together with low-dose prednisone appears to optimize the former’s safety profile by managing potential side-effects due to a rise in mineralocorticoids. Prednisone and other corticosteroids are known to have palliative effects in patients with advanced prostate cancer [42–45]; this was reflected in the observation that about 40% of patients in the prednisone-only arm also reported improvements in fatigue. Nevertheless, this magnitude of improvement was substantially less than that observed in the abiraterone–prednisone arm for both fatigue intensity (58%) and fatigue interference (55%). Of note, discontinuation of treatment with abiraterone–prednisone led to significant increases in the proportions of patients exhibiting improvements in fatigue intensity and fatigue interference; the higher proportion with improved fatigue interference is particularly notable, given that this represents a functional measure that until now had never been reported for an oncology agent. Abiraterone–prednisone was also significantly better than prednisone-only in reducing the time until improvement of fatigue intensity was achieved and significantly delayed progression of both fatigue intensity and interference. Estimates from two different sensitivity analyses provided additional evidence that fatigue improvements with abiraterone–prednisone were sustained across treatment cycles and lent further support to the directly observed outcomes. Of note, the use of such sophisticated methods to overcome the challenge of missing data is now specifically recommended in consensus guidelines on fatigue assessment in oncology clinical trials [39]. Few previous studies in patients with cancer have shown such a positive impact on fatigue with a disease-specific intervention (rather than supportive care), and this trial is the first to do so in the setting of mCRPC.

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Figure 3. Time to symptomatic progression: (A) fatigue intensity; (B) fatigue interference.
prior chemotherapy (a known cause of fatigue) likely also contributed to fatigue amelioration in both study arms; unless there is a worsening of underlying disease, patients would be expected to experience less fatigue over time after chemotherapy. The number of previous cytotoxic chemotherapy regimens and the duration from last docetaxel dose to first dose of study treatment was not different between treatment groups [46], implying that the differences in fatigue improvement cannot be ascribed to differences in chemotherapy exposure.

Our results are of practical importance to mCRPC treatment. General clinical guidelines for management of cancer-related fatigue recommend various nonpharmacologic (exercise, psychosocial interventions, nutrition, and sleep) and pharmacologic approaches (stimulants and antidepressants) [47, 48]. However, these are supportive treatments—until now, no prostate cancer-specific therapy had been shown to improve fatigue. Of note, no other phase III trial in the mCRPC setting specifically evaluated patient-reported fatigue. While prednisone was previously reported to improve fatigue in symptomatic CRPC [42], this conclusion was based on results obtained via the EORTC QoL-30 questionnaire; the validity of the respective fatigue subscale in patients with advanced cancer has been questioned, and CRPC trials that include fatigue as a prospective end point should utilize a fatigue-specific instrument [49], such as the BFI or the Fatigue Symptom Inventory [50] or the Functional Assessment of Cancer Therapy Fatigue Scale [51].

Our analyses are strengthened by the fact that the criteria for fatigue improvement and progression were specified before data analysis, and the thresholds for clinically meaningful changes in fatigue levels were defined according to accepted, evidence-based methodology [33-36]. Each threshold represented at least a 0.50 effect size, a substantial change in fatigue levels that can be expected to be clearly perceivable by a patient; due to the nature of the fatigue intensity analysis (i.e. based on a single item that could only be a whole number), a more conservative threshold was chosen, equating to about a 0.75 effect size in that measure. Notably, the results remained robust after adjusting for mortality, dropout, and missing data (cumulative missing data for BFI were <7%). As the data were obtained at the clinic during scheduled outpatient visits, it is conceivable that the most seriously ill patients may have been inadvertently excluded from these analyses; however, the remarkably low amount of missing data suggests this was not the case. Baseline fatigue levels and the proportion of English versus non-English-speaking patients (fatigue is more culturally dependent than other patient-reported outcomes) were well balanced between treatment arms. Finally, our results are consistent with treatment differences in mortality and other patient-reported outcomes seen in this study.

We restricted all analyses of fatigue improvement to patients with what we considered to be clinically significant baseline fatigue (i.e. scores of ≥5), because assessing fatigue improvement in patients experiencing no or only low-grade fatigue at treatment initiation would have been irrelevant. It should be noted, however, that the exact cutoff between mild and moderate severity levels is unclear, with greater linearity at the lower range of fatigue scores [32, 52]; scores of ≥5 have been shown to be in the ‘moderate’ to ‘severe’ range [32]. Our approach did not seem to create bias through restricting the sample, since a post-hoc analysis showed that abiraterone–prednisone also significantly improved fatigue in the overall intent-to-treat population. Furthermore, the association between treatment arm and fatigue improvement remained significant after adjusting for baseline fatigue scores.

For our analysis of fatigue intensity, we focused exclusively on question 3 of the BFI (i.e. ‘... worst level of fatigue during last 24 h’). This is often used as a stand-alone, single-item assessment of fatigue severity, in part because of its conceptual simplicity and because it has the greatest correlation with fatigue interference [32, 52]. Single questions about fatigue intensity have been suggested as a simple and acceptable way to evaluate fatigue in patients with cancer [53].

While we were able to demonstrate a more rapid recovery from fatigue after chemotherapy and a delay of fatigue occurrence with abiraterone–prednisone, we did not attempt to determine the mechanism underlying fatigue improvement. Cancer-related fatigue, as a consequence of both the disease and its treatment, is a complex phenomenon influenced by numerous physiological factors [54]. The benefits of abiraterone acetate to patient-reported fatigue could be the result of amelioration in tumor burden and/or disease progression. However, this hypothesis requires additional study, and future exploratory analyses will assess potential associations between changes in fatigue and overall survival, PSA response/progression, radiological response/progression, and hemoglobin levels. Of note, in patients with cancer, fatigue is independently predicted by physical (drowsiness, dyspnea, pain, lack of appetite) and psychological symptoms (depression, anxiety, and irritability) [55-59]. It is therefore perhaps not surprising that an agent shown to improve pain [40] and physical and emotional well-being [41] also improves fatigue. This association will also be explored further in future post-hoc analyses. Aligning the implications of the current findings with other therapeutic options in the mCRPC setting is challenging, due to the paucity of data examining patient-reported outcomes, including fatigue. It is thus hoped that all future studies in mCRPC will include well-designed fatigue end points; in this context, studies comparing abiraterone acetate with chemotherapy would be of particular interest.

In conclusion, abiraterone acetate and prednisone was associated with delayed fatigue progression and improvements in patient-reported fatigue outcomes compared with prednisone alone in patients with mCRPC after docetaxel chemotherapy. Abiraterone–prednisone was also associated with more rapid fatigue improvement. The effect size of these benefits is very likely perceivable by and meaningful to patients. This clinically meaningful relief of a debilitating symptom of advanced prostate cancer further supports abiraterone acetate as a valuable option for the treatment of mCRPC after docetaxel chemotherapy, in particular when considering the previously reported overall survival and progression-free survival benefit, as well as the multidimensional improvements across various other QoL domains.
original articles

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disclosure

CNS has served as a consultant to and received speaker honoraria from Amgen, Astellas, Dendreon, Johnson & Johnson, Millenium, Novartis, and Sanofi-Aventis and research funding from Cougar Biotechnology (now Janssen Biotech). AM is a full-time employee of Janssen R&D and holds stock options in Johnson & Johnson. SN has served as a consultant to Abraxis, Amgen, AstraZeneca, Glaxo-Smith Kline, Novartis, Ortho Biotech/Janssen Biotech, Pfizer, and Sanofi-Aventis, and has received speaker honoraria from Novartis and Ortho Biotech (now Janssen Biotech). PM has served as a consultant to Janssen R&D. KF has served on advisory boards for or received lecture fees from Amgen, Astellas-Medivation, AstraZeneca, Bayer, BMS, Celgene, Cougar Biotechnology/Janssen Biotech, Dendreon, Exelixis, Kecoyt, Millenium-Takeda, Novartis, and Sanofi-Aventis. YH and MR are employees of Janssen Global Services and hold stock options in Johnson & Johnson. DDG is a full-time employee of Truven Health Analytics who served as consultants to Janssen Global Services in connection with these analyses, and owns stock in Johnson & Johnson. TK is a full-time employee of Janssen R&D and holds stock options in Johnson & Johnson. CMH was an employee of Cougar Biotechnology (now Janssen Biotech) at the time this study was conducted and completed and holds stock options in Johnson & Johnson. CC has served as a consultant to Amgen, Exelixis, Genentech, and Janssen R&D. JSSB has served as a consultant to Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, Glaxo-Smith Kline, Janssen R&D, Medivation, Merck, Novartis, Ortho Biotech (now Janssen Biotech), Pfizer, Roche, Sanofi-Aventis, Supergen, and Takeda, has received grant support from AstraZeneca, has received speaker fees from Johnson & Johnson, has received travel support from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, GSK, Medivation, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Supergen, and Takeda, and is an employee of The Institute of Cancer Research and is supported by Cancer Research UK, both of which have a commercial interest in the development of abiraterone acetate. HIS has served as a consultant to Aragon, AstraZeneca, Bristol-Myers Squibb, Enzon, Cougar Biotechnology/Janssen R&D, Janssen Global Services, Medivation, Millennium, and Sanofi-Aventis, and has previously owned stock in Johnson & Johnson (sold).

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