Abiraterone acetate and prednisone in chemotherapy-naïve prostate cancer patients: rationale, evidence and clinical utility

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Abstract: Abiraterone acetate 1000 mg/day, combined with prednisone 5 mg PO twice daily, is indicated for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Abiraterone acetate is the oral prodrug of abiraterone, a specific CYP17 inhibitor that blocks androgen biosynthesis within the adrenal glands, testes and tumor microenvironment. In a phase III trial of men with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC, treatment with oral abiraterone acetate plus prednisone led to a statistically significant improvement in the co-primary endpoints of overall survival and radiographic progression-free survival when compared with placebo plus prednisone. In long-term follow-up of phase III trials, the incidence of corticosteroid-associated adverse events was 25.5% in the abiraterone acetate plus prednisone arm compared with 23.3% in the placebo plus prednisone arm. The need for regular patient monitoring and appropriate management of symptoms during long-term use of prednisone must be placed in context with the improvement in survival seen with abiraterone plus prednisone. Within the multidisciplinary environment that is emerging to meet quality and cost imperatives, abiraterone acetate plus prednisone is suitable for use in the chemotherapy-naïve population with minimal symptoms as well as in patients who have been treated with docetaxel and may have symptomatic disease. Ongoing trials are evaluating the role of abiraterone acetate plus prednisone in patients with nonmetastatic CRPC and metastatic hormone-sensitive prostate cancer, while further trials in the mCRPC setting are evaluating its use in combination regimens.

Keywords: abiraterone acetate, chemotherapy-naïve, prednisone, prostate cancer

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Introduction

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among men worldwide.[1] In the majority of men with newly diagnosed prostate cancer, the disease is discovered in the local or regional stages.[2] After a decline in the incidence of metastatic disease that started in the 1990s, recent data suggest that the incidence of localized disease has decreased dramatically, with a corresponding shift toward advanced-stage tumors such that regional and metastatic tumors currently account for approximately 50% and 20%

of cases at diagnosis, respectively.[3,4] There is now evidence in the United States that the incidence of metastatic prostate cancer is increasing – one study reported a 72% higher incidence of cases in 2013 compared with 2004, with the greatest increase among men aged 55–69 years.[5] Prostate cancer deaths predominantly result from progression to metastatic castration-resistant prostate cancer (mCRPC).[6] More than one-third of nonmetastatic CRPC (nmCRPC) cases progress to mCRPC each year, with an annual mortality rate in newly diagnosed local or locally advanced disease of just 5%, compared with 16% of nmCRPC

cases and 56% of mCRPC cases.[7] These findings indicate that effective therapies applied early in the disease course may help to reduce the incidence of morbidity and mortality in mCRPC.

Androgen deprivation therapy (ADT), which reduces serum concentrations of androgens and their subsequent interaction *via* the androgen receptor (AR), provides initial response in >90% of patients with androgen-sensitive prostate cancer.[8] However, detectable serum concentrations of androgens (testosterone) remain in a majority of patients with CRPC, and almost all patients will eventually develop disease progression if they do not succumb to another comorbidity.[9] In CRPC, continued androgen synthesis following ADT occurs in the testes, adrenals and the tumor itself, with consequent ongoing activation of AR signaling.[10,11] It has been postulated that, among men with hormone-sensitive disease, those with a testosterone level that falls below 20 ng/dl during ADT have a longer time to castration resistance and survival compared with those who fail to achieve this level of castration.[12] Subsequently, the further lowering of suppressed androgen levels using novel agents was proposed to provide benefit for patients with castration-resistant disease. The understanding that adaptive mechanisms in the tumor microenvironment can drive prostate cancer progression despite castrate levels of androgens led to the development of novel agents aimed at further decreasing androgen production or blocking AR function for administration in the chemotherapy-naïve setting.[13,14] As a result, several guideline-supported treatment options are now available for the use of these novel hormonal agents within the chemotherapy-naïve setting. These agents include enzalutamide and abiraterone acetate plus prednisone, which target the androgen axis with different mechanisms of action, with differing effects on the testosterone/androstenedione axis and resulting testosterone levels.[15–19]

More than 50% of patients with mCRPC never receive secondary treatment with docetaxel chemotherapy, which is known to offer a survival benefit.[20,21] Potential reasons for this include differences in management style between medical oncologists and urologists,[20] comorbidities and patient ineligibility,[21] and patient refusal presumably due to concerns around toxicity, perceived effectiveness of treatment and issues surrounding communication and the patient–physician relationship.[22] Chemotherapy-naïve patients constitute a broad population along the prostate cancer disease continuum, ranging from those with low-volume disease and low prostate-specific antigen (PSA) to those with more rapidly progressive disease who may benefit from, but nevertheless refuse, chemotherapy.[23] The prognosis for these symptomatic patients is worse than that for patients with asymptomatic disease. Evidence from the COU-AA-302 trial suggests a benefit associated with the use of abiraterone acetate plus prednisone early in the clinical course of mCRPC.[24] The future for optimizing mCRPC therapy should be predicated upon a knowledgeable understanding of all approved therapies, as well as the relevant evolving fields of biomarker assessment and advanced imaging in order to maximize patient outcomes and health-care economic burden.

This review will evaluate the rationale, evidence and clinical utility for use of abiraterone acetate plus prednisone in the chemotherapy-naïve patient population, including those with metastatic hormone-sensitive prostate cancer (mHSPC) and mCRPC.

Use of abiraterone acetate and prednisone in the chemotherapy-naïve prostate cancer setting

Abiraterone acetate is the oral prodrug of abiraterone, a specific CYP17 inhibitor that blocks extragonadal, testicular and tumor androgen biosynthesis.[25] Abiraterone acetate is approved by the US Food and Drug Administration (FDA) for use with prednisone for the treatment of patients with mCRPC.[26] The pivotal COU-AA-302 trial randomized 1088 chemotherapy-naïve patients with mCRPC to receive oral abiraterone acetate 1000 mg daily plus prednisone 5 mg twice daily or placebo plus prednisone.[23,24,27] For the final analysis (median follow-up 49.2 months), the median overall survival (OS) was 34.7 months with abiraterone acetate plus prednisone compared with 30.3 months with placebo plus prednisone (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70–0.93; $p = 0.0033$). Abiraterone acetate plus prednisone also showed superiority over placebo plus prednisone with respect to time to opiate use for cancer-related pain (HR, 0.72; 95% CI, 0.61–0.85; $p < 0.0001$).[24] At the second interim analysis (median follow-up 22.2 months), the co-primary endpoint of median radiographic

Table 1. Abiraterone acetate plus prednisone *versus* placebo plus prednisone.

	Abiraterone acetate plus prednisone	Placebo plus prednisone	Between-group comparison	References
Co-primary endpoints				
Median rPFS	16.5 months	8.2 months	HR, 0.52 (95% CI, 0.45–0.61; *p* < 0.0001)	27
Median OS	35.3 months	30.1 months	HR, 0.79 (95% CI, 0.66–0.95; *p* = 0.0151)	
Secondary endpoints				
Time to opiate use for cancer pain	NR	23.7 months	HR, 0.71 (95% CI, 0.59–0.85; *p* = 0.0002)	27
Time to chemotherapy	26.5 months	16.8 months	HR, 0.61 (95% CI, 0.51–0.72; *p* < 0.0001)	
Time to ECOG deterioration	12.3 months	10.9 months	HR, 0.83 (95% CI, 0.72–0.94; *p* = 0.005)	
Time to PSA progression	11.1 months	5.6 months	HR, 0.50 (95% CI, 0.43–0.58; *p* < 0.0001)	
Final OS analysis				
Median OS	34.7 months	30.3 months	HR, 0.81 (95% CI, 0.70–0.93; *p* = 0.0033)	24
Patient-reported outcomes				
Median TTP of mean pain intensity	26.7 months	18.4 months	HR, 0.82 (95% CI, 0.67–1.00; *p* = 0.0490)	28
Median TTP of worst pain intensity	26.7 months	19.4 months	HR, 0.85 (95% CI, 0.69–1.04; *p* = 0.109)	
Median TTP of pain interference	10.3 months	7.4 months	HR, 0.79 (95% CI, 0.67–0.93; *p* = 0.005)	
Median time to functional status deterioration (FACT-P PCS score)	11.1 months	5.8 months	HR, 0.70 (95% CI, 0.60–0.83; *p* < 0.0001)	
Primary outcomes in elderly (≥75 years) *versus* younger (<75 years) patients				
Median rPFS (elderly)	14.9 months	8.3 months	HR, 0.63 (95% CI, 0.48–0.83; *p* = 0.0009)	30
Median rPFS (younger)	16.6 months	8.3 months	HR, 0.49 (95% CI, 0.40–0.59; *p* < 0.0001)	
Median OS (elderly)	28.6 months	25.6 months	HR, 0.71 (95% CI, 0.53–0.96; *p* = 0.0268)	
Median OS (younger)	35.3 months	30.9 months	HR, 0.81 (95% CI, 0.63–1.03; *p* = 0.0841)	
Primary outcomes in patients with BTT *versus* no BTT				
Median rPFS (with BTT)	16.6 months	10.4 months	HR, 0.63 (95% CI, 0.48–0.84; *p* = 0.001)	29
Median rPFS (without BTT)	16.3 months	8.2 months	HR, 0.48 (95% CI, 0.40–0.58; *p* < 0.0001)	
Median OS (with BTT)	NE	30.9 months	HR, 0.71 (95% CI, 0.50–1.00; *p* = 0.050)	
Median OS (without BTT)	31.6 months	30.1 months	HR, 0.84 (95% CI, 0.67–1.05; *p* = 0.13)	

AE, adverse event; BTT, bone-targeted therapy; CA, corticosteroid-associated; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; PCS, prostate-cancer-specific subscale; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; TTP, time to progression.

progression-free survival (rPFS) was 16.5 months with abiraterone acetate plus prednisone compared with 8.3 months with placebo plus prednisone (HR, 0.53; 95% CI, 0.45–0.62; *p* < 0.001). Abiraterone acetate plus prednisone also showed superiority over placebo plus prednisone with respect to time to initiation of cytotoxic chemotherapy, time to opiate use for cancer pain, time to deterioration in Eastern Cooperative Oncology Group (ECOG) performance status and time to PSA progression (Table 1).[23,27]

Safety findings of COU-AA-302 showed that adverse events (AEs) of any grade that occurred more frequently for abiraterone acetate plus prednisone *versus* placebo plus prednisone included arthralgia in 29% *versus* 24% of patients, respectively, peripheral edema in 26% *versus* 21%, hot flush in 23% *versus* 18%, diarrhea in 23% *versus* 18% and hypertension in 22% *versus* 14%, respectively. AEs were predominantly of grades 1 or 2. AEs that appeared more frequently for abiraterone acetate plus prednisone *versus* placebo plus

prednisone included grade 1–4 fatigue in 40% *versus* 35% of patients, grade 1–4 fluid retention in 29% *versus* 24%, grade 1–4 hypertension in 22% *versus* 14%, grade 1–4 (grade 3–4) cardiac disorders in 20% (7%) *versus* 17% (4%), grade 1–4 hypokalemia in 17% *versus* 13%, grade 1–4 (grade 3–4) alanine aminotransferase increased in 12% (6%) *versus* 5% (1%) and grade 1–4 (grade 3–4) aspartate aminotransferase increased in 11% (3%) *versus* 5% (1%).[27] Over longer-term follow-up, there were no notable changes in the safety profile of abiraterone acetate plus prednisone in COU-AA-302.[24]

Other notable benefits were observed for abiraterone acetate plus prednisone *versus* placebo plus prednisone in the COU-AA-302 trial (Table 1). Consistent with prolonging OS compared with placebo plus prednisone, abiraterone acetate plus prednisone also delayed the time to pain progression, interference of pain in daily activities and deterioration in health-related quality of life.[28] Moreover, the survival and safety findings of subgroup analyses were consistent with the results seen in the overall population in COU-AA-302. Abiraterone acetate plus prednisone *versus* placebo plus prednisone yielded significant improvements in OS in patients aged 75 years and older and in those with and without concomitant bone-targeted therapy.[29,30] The clinical benefit of abiraterone acetate plus prednisone *versus* placebo plus prednisone in elderly patients was similar to that in younger patients, confirming that abiraterone acetate plus prednisone represents a treatment option for elderly patients who might not tolerate other therapies with greater toxicity.[30] Mineralocorticoid excess associated with abiraterone acetate plus prednisone was similar among the age subgroups. The incidence of fluid retention/edema, hypokalemia, hypertension, hepatotoxicity and cardiac disorders was higher with abiraterone acetate plus prednisone than with placebo plus prednisone in elderly (grades 1–4, 73.6% *versus* 59.1%; grades 3–4, 24.2% *versus* 17%) and younger (grades 1–4, 65.8% *versus* 47.9%; grades 3–4, 17.8% *versus* 9.3%) patients. Elderly patients in both treatment arms had a higher incidence of fluid retention and cardiac disorders than younger patients, as well as a higher rate of dose reductions; however, rates of treatment interruptions due to AEs were similarly low in both age groups.[30]

Post-hoc analyses of COU-AA-302 and also the COU-AA-301 trial, which enrolled men with mCRPC who had previously failed docetaxel, provided robust evidence of long-term safety of abiraterone acetate plus prednisone.[31] Although the COU-AA-301 trial included patients in the post-chemotherapy setting, the study provides long-term data for abiraterone acetate plus prednisone that are relevant for its application in the early disease setting, where patients are expected to have a longer duration of exposure to the drug. A *post-hoc* analysis of 2267 patients in COU-AA-301 and COU-AA-302 found that long-term exposure to low-dose prednisone in combination with abiraterone acetate is not associated with a higher incidence of corticosteroid-associated AEs than placebo plus prednisone.[31] Patients enrolled in these trials received prednisone 5 mg twice daily for a median of 8.3 months (range, 0.1–34.9 months), representing >2000 patient-years of prednisone exposure. The discontinuation rate for abiraterone acetate and prednisone in the two trials was low, with side-effects readily manageable and reversible, despite the advanced disease status of the COU-AA-301 population. The overall incidence of corticosteroid-associated AEs was 25.5% in the abiraterone acetate plus prednisone arm compared with 23.3% in those assigned to placebo plus prednisone. The most common corticosteroid-associated events of any grade were hyperglycemia (7.8% *versus* 6.9%, respectively) and weight increase (3.9% *versus* 4.8%). The overall incidence of grade ⩾3 corticosteroid-associated AEs in either treatment arm was 4.5% (5.1% in the abiraterone acetate arm plus prednisone arm *versus* 3.7% in the placebo plus prednisone arm); hyperglycemia (2.0%), cataract (0.4%), diabetes mellitus (0.4%) and gastrointestinal hemorrhage (0.3%) were the most common. Even weight gain, which is a common concern for patients taking corticosteroids, was not impacted by the addition of abiraterone acetate to prednisone. Considered together, these clinical trial findings suggest that treatment with abiraterone acetate plus prednisone is effective and well tolerated during long-term administration.

Although the COU-AA-302 trial did not address the role of abiraterone acetate plus prednisone in patients with symptomatic, chemotherapy-naïve CRPC, relevant data are beginning to emerge supporting the use of this regimen in such patients, particularly in combination with radiotherapy or radium-223.[32,33] Data from an early access program suggest that radium-223 can be safely combined with abiraterone plus prednisone

in patients with asymptomatic and symptomatic mCRPC.[32] Interim results of a phase II study of radium-223 administered concurrently with abiraterone acetate plus prednisone in patients with symptomatic CRPC showed encouraging findings with respect to bone pain, quality of life and stability in ECOG scores.[33] The findings of real-world studies further support the use of abiraterone acetate plus prednisone in symptomatic patient populations, who achieve similar survival despite higher ECOG performance status scores and shorter duration of therapy.[34,35]

Other therapies and regimens in the chemotherapy-naïve prostate cancer setting

In the chemotherapy-naïve M1 CRPC setting, current guidelines such as those of the National Comprehensive Cancer Network and the American Urological Association support a role for abiraterone acetate plus prednisone, enzalutamide and sipuleucel-T for patients with asymptomatic or minimally symptomatic disease.[13] Although both abiraterone acetate and enzalutamide target the androgen axis, the former does so by inhibiting androgen biosynthesis within the adrenal glands, testes and tumor microenvironment. Enzalutamide, in contrast, targets the AR, including its intracellular signaling functions. Enzalutamide was evaluated in the PREVAIL trial, in which 1717 patients with mCRPC received oral enzalutamide 160 mg daily or placebo as prechemotherapy.[36] rPFS data were evaluated after 12 months and showed superiority for enzalutamide *versus* placebo (median, not reached *versus* 3.9 months; $p < 0.001$), with an 81% risk reduction. After a median follow-up of 26 months, OS also favored enzalutamide *versus* placebo (median, not reached *versus* 31.0 months; $p < 0.001$), with a 29% reduction in risk of death. Notably, a survival advantage was observed for enzalutamide *versus* placebo in patients with visceral disease. Further benefit for enzalutamide was shown with respect to secondary endpoints of time to initiation of cytotoxic chemotherapy, time to first skeletal-related events, complete or partial soft-tissue response, time to PSA progression and ≥50% rate of decline of PSA. AEs of any grade that occurred more frequently for enzalutamide *versus* placebo included fatigue in 36% *versus* 26%, back pain in 27% *versus* 22%, constipation in 22% *versus* 17%, arthralgia in 20% *versus* 16%, hot flush in 18% *versus* 8%, hypertension in 13% *versus* 4%, asthenia in 13% *versus* 8% and falls in 12% *versus* 5%. Specific AEs, including cardiac

AEs, acute renal failure and elevated liver enzymes, occurred with similar frequency in the enzalutamide and placebo arms.[36]

Primary resistance or lack of initial response with respect to measures of clinical benefit affects approximately 20–40% of patients treated with enzalutamide or abiraterone acetate plus prednisone, and virtually all patients with an initial response will eventually acquire secondary resistance over time.[37] A number of mechanisms for continued AR activation in a low-androgen environment have been proposed.[10,11,38,39] Among these is the generation of variant forms of AR through somatic mutation or aberrant RNA splicing, resulting in receptors that lack the C-terminal domain. Instead of losing function, these variants encode protein isoforms that activate the AR pathway in the absence of androgens and can render resistance to treatment.[40] In addition, androgen synthesis may continue via the 3-beta-hydroxysteroid dehydrogenase pathway, which is able to convert dehydroepiandrosterone and delta$_5$-androstenediol to androstenedione and testosterone, respectively.[41] In the case of enzalutamide and abiraterone acetate, whose activities are dependent on the C-terminal domain of the AR, resistance is likely to be mediated by AR splice variants and associated aberrations in AR signaling.[40] Overexpression of the glucocorticoid receptor and upregulation of enzymes involved in steroid biosynthesis may also be involved.[40,42] Interestingly, reports of an association between AR splice variant 7 (AR-V7) expression localizing on circulating tumor cells (CTCs) and resistance to enzalutamide and abiraterone acetate plus prednisone indicate the potential for treatment-specific biomarkers in mCRPC.[43] This finding needs to be tempered with the understanding that most men with mCRPC do not have detectable CTCs, and enhanced survival among those men who do express AR-V7-positive CTCs is associated with taxane therapy rather than AR-directed therapy.[44]

Sipuleucel-T is an autologous active cellular immunotherapy that is prepared by isolating antigen-presenting cells from the peripheral blood of individual patients; these are subsequently cultured *ex vivo* with a prostatic acid phosphatase/granulocyte-macrophage colony-stimulating factor recombinant fusion protein before being administered to the patient.[45] In a randomized phase II trial, sipuleucel-T was evaluated in patients with mCRPC both as concurrent and sequential therapy with abiraterone acetate plus prednisone.[46] Abiraterone acetate plus

prednisone was administered 1 day after the first sipuleucel-T infusion in the concurrent arm and 10 weeks after the first sipuleucel-T infusion in the sequential arm. In both arms, the peripheral immune responses and other parameters of the sipuleucel-T product profile were consistent with previous trials of sipuleucel-T, indicating that the combination of these agents is feasible. A similarly designed study using enzalutamide also found no difference in immune function when enzalutamide was administered concomitantly *versus* sequentially with sipuleucel-T.[47]

Another therapy approved by the US FDA for use in mCRPC in the prechemotherapy setting is radium-223, an alpha-emitting radiopharmaceutical agent that preferentially accumulates in bone metastases.[48] Compared with placebo, six injections of radium-223 at 4-weekly intervals between injections resulted in a significant improvement in OS (14.0 *versus* 11.2 months; HR, 0.70; 95% CI, 0.55–0.88; $p = 0.002$), with significant benefits also for secondary endpoints of time to first symptomatic skeletal event, time to increase in total alkaline phosphatase level and time to increase in PSA level. As previously mentioned, there are preliminary data supporting the efficacy and safety of concurrent therapy with radium-223 and abiraterone acetate plus prednisone in patients with mCRPC.[32,33]

In the setting of mHSPC, recent data support the early introduction of docetaxel concurrent with ADT, particularly in patients with high-volume disease characterized by visceral metastases, or multiple bone lesions.[49–52] In particular, the significant improvement in median OS for patients receiving ADT plus docetaxel compared with ADT alone (4.7–13.6 months longer) suggests that chemohormonal combination therapy given early in the disease course may offer improved outcomes compared with the more traditional sequenced monotherapy approach.[45] Given that many patients are eligible for multiple treatments, the preferred strategy is to tailor the treatment plan to the individual patient by determining which treatment is more appropriate as the initial therapy.[45]

Multidisciplinary care of patients in the chemotherapy-naïve mCRPC setting with a focus on treatment with abiraterone acetate plus prednisone

Multidisciplinary care, such as that provided at specialized prostate cancer clinics, offers a unique management approach whereby newly diagnosed patients may simultaneously meet with urologic, radiation and medical oncologists.[53] This model of care is intended to provide the patient an opportunity to learn about all management options, providing for shared decision-making. When offered to men with low-risk disease, multidisciplinary care significantly increases the rate of active surveillance while increasing the likelihood that they receive a balanced perspective on various treatment benefits and risks, and reducing physician bias over preferred treatment modality.[53,54] In one study, attendance of men with prostate cancer at a multidisciplinary clinic resulted in almost 30% having a change in their risk category or stage.[54] The long-term experience of one multidisciplinary genitourinary cancer clinic found benefits in terms of survival rate in patients with high-risk, locally advanced disease, and high levels of patient satisfaction.[55]

In the context of abiraterone acetate plus prednisone therapy, a multidisciplinary approach to patient care is useful for ensuring that the patient receives the treatment at a time when he is most likely to derive maximum benefit. Abiraterone acetate plus prednisone represents an alternative to chemotherapy after hormone treatment failure, and one that may be especially attractive to urologists, in that it is an oral medication that can be easily managed in the office setting.[56] The ease of administration of abiraterone acetate plus prednisone provides a viable alternative to docetaxel and ensures continuity of care between the patient and his urologist. Having access to a multidisciplinary team ensures that the patient has simultaneous access to support from urologists and medical oncologists such that all available treatments are considered in the overall treatment plan and are administered at an appropriate juncture in the treatment sequence, and that referral to clinical trials is considered when appropriate.

Safe use of prednisone in mCRPC
At the indicated co-administered dose of 10 mg with abiraterone acetate, prednisone has minimal mineralocorticoid activity.[57] Given the long-term administration of prednisone in combination with abiraterone acetate, there is the potential for high levels of total corticosteroid exposure, placing patients at risk of corticosteroid-related AEs.[58] Corticosteroid use is associated with edema, hypertension, weight gain, hyperglycemia and

steroid-induced diabetes, cataracts, glaucoma, osteoporosis, loss of muscle mass, insomnia and immunosuppression. The development of these events is dependent on pre-existing medical conditions, disease state, corticosteroid dose and duration of therapy, with daily and cumulative prednisone doses associated with many of these events typically higher than those used for the treatment of mCRPC.[58]

The consequences of certain mineralocorticoid-associated AEs, such as hyperglycemia and diabetes, must be placed in context of the life expectancy of the patient.[57] If the decision is made to start a patient on abiraterone acetate plus prednisone, the patient should be monitored regularly for corticosteroid-associated AEs.[57] Monitoring should include all known side-effects of corticosteroid use, including thrush and hyperglycemia, the presence of which may necessitate dose adjustment and proper tapering if corticosteroid use needs to be discontinued.[58] In the aforementioned study of long-term exposure to low-dose prednisone administered with abiraterone acetate in 2267 patients with mCRPC from COU-AA-301 and COU-AA-302, when assessed by duration of exposure (i.e. 3-month intervals up to ⩾30 months), no discernable trend was detected for corticosteroid-associated AEs, including incidence of overall hyperglycemia.[31] The Zytiga® (Janssen Biotech Inc., Horsham, PA, USA) product label recommends caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, and in patients with cardiovascular disease.[26] Monitoring for signs and symptoms of adrenocortical insufficiency is recommended if prednisone is stopped or withdrawn, if the prednisone dose is reduced or if the patient experiences unusual stress.

Liver function should be monitored, including measurement of serum transaminases (alanine aminotransferase and aspartate aminotransferase) and bilirubin levels prior to initiating treatment with abiraterone acetate and prednisone, every 2 weeks for the first 3 months of treatment and monthly thereafter. Modification, interruption or discontinuation of abiraterone acetate dosing should occur as recommended.[26] Abiraterone should be used with caution in patients with a history of cardiovascular disease with monitoring for hypertension, hypokalemia and fluid retention at least once per month, with control of hypertension and hypokalemia before and during treatment

with abiraterone acetate and prednisone.[26] Recent studies have implemented prednisone at lower than the indicated 5 mg twice daily dose co-administered with abiraterone acetate. In the neoadjuvant setting, prednisone 5 mg daily was well tolerated, with rates of occurrence of mineralocorticoid-associated AEs not different from those reported in prior phase III studies.[59,60] Several studies are also being conducted at the 5 mg daily dose, including the phase II IMAAGEN (Impact of Abiraterone Acetate in Prostate Specific Antigen) trial[61] and the phase III LATITUDE trial,[62] and the abiraterone arms of the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial, which are described in more detail later in this article. These further investigations will help determine whether abiraterone acetate plus a lower prednisone dose can be safely and efficaciously co-administered. An ongoing study is evaluating different steroid regimens (i.e. 5 mg prednisone twice daily, 5 mg prednisone once daily, 2.5 mg prednisone twice daily, and 0.5 mg dexamethasone once daily) for side-effects related to mineralocorticoid excess prevention in prostate cancer prior to chemotherapy (NCT01867710). In a retrospective study of 30 CRPC patients who underwent a steroid switch from prednisolone to dexamethasone while on abiraterone acetate, durable PSA responses occurred in up to 40% of patients.[63] The biological mechanism responsible for the observed delay of resistance, as well as induction of radiological response in selected patients, requires prospective clinical trials.

Treatment considerations with abiraterone acetate

Food considerations. There have been several clinical studies of abiraterone acetate in both healthy subjects and mCRPC patients with various food conditions that allow for the evaluation of food effect on abiraterone pharmacokinetics.[9,23,64–67] On the basis of these data, it is recommended that abiraterone acetate be taken in accordance with product labeling[26] and pivotal phase III trials,[23,65] namely in a fasted or modified fasted state.

Drug interactions. Concomitant CYP3A4 inducers with abiraterone acetate and prednisone should be avoided, but if they must be used, abiraterone dosing frequency should be increased. Co-administration of CYP2D6 substrates with a

narrow therapeutic index should be avoided. If required, the clinician should exercise caution and consider a dose reduction of the CYP2D6 substrate.[26]

Clinical implications of PSA change in making treatment decisions for the individual patient.

Although the lack of a formal standard definition of PSA flare presents difficulty in interpreting clinical trial data and informing real-world clinical practice, patients should be made aware of the potential for delayed PSA decline and/or PSA flare during the first 3 months. Time to PSA decline is not an indicator of clinical benefit and should not be used to guide treatment choice or continuation of treatment, especially within the first 3 months. However, a recent retrospective study conducted at one center suggests that early PSA decline may be associated with survival. Of 274 mCRPC patients treated with abiraterone acetate plus prednisone before or after docetaxel, patients who failed to achieve a 30% decline in PSA at 4 weeks relative to baseline had significantly inferior OS.[68] Future prospective multicenter studies are required for confirmation.

Reports of rhabdomyolysis in patients treated with abiraterone acetate. Clinicians should be aware of two case studies of rhabdomyolysis in patients treated with abiraterone acetate reported in the literature. In one case study, rhabdomyolysis was associated with the use of abiraterone acetate plus prednisone and the patient showed gradually decreased creatine kinase upon drug discontinuation.[69] In the other case study, rhabdomyolysis-induced acute kidney injury was observed with exposure to denosumab and abiraterone acetate plus prednisone, so it is unclear whether this could be attributed to abiraterone acetate.[70] This patient also responded with normalization of creatine kinase upon discontinuation of treatment with both drugs.

Sequencing of abiraterone and other therapies in the chemotherapy-naïve prostate cancer setting

Currently, there are no head-to-head data to establish the relative effectiveness and tolerability of individual therapies and to guide treatment sequencing.[45] Since abiraterone acetate plus prednisone and enzalutamide have different mechanisms of action, combination therapy and

sequencing of these therapies will need to be the focus of future studies.[72]

Cross-resistance among these AR-targeted agents is emerging, and may also have a bearing on treatment decisions.[45] Retrospective studies have attempted to address the issue of treatment sequencing, although the majority of published reports are from small, retrospective cohorts from mostly single centers.[45,71] A phase II open-label study recently evaluated the effects of concurrent or sequential treatment with abiraterone acetate plus prednisone on sipuleucel-T in patients with mCRPC.[46] The study found that immunologic effects of sipuleucel-T were similarly observed with either concurrent or sequential administration of abiraterone acetate plus prednisone.

Current data support the sequential use of abiraterone acetate plus prednisone in relation to both pre- and post-docetaxel settings, as well as post-enzalutamide treatment.[72] When docetaxel was administered following treatment with abiraterone acetate plus prednisone, 26% of patients had a PSA decline of ⩾50% and the median OS was 12.5 months.[73] This level of activity was lower than anticipated and no responses to docetaxel were observed in patients who were refractory to abiraterone acetate plus prednisone, although implications of possible cross-resistance need to be explored. In the post-docetaxel setting, abiraterone acetate plus prednisone treatment was associated with poor prognosis in men with high lactate dehydrogenase levels, an ECOG performance score of 2, liver metastases, low albumin, high alkaline phosphatase and time from start of initial ADT to start of treatment of ⩽36 months.[72,74] Among patients who progress following treatment with enzalutamide, the activity of abiraterone acetate plus prednisone is limited.[75,76] In patients previously treated with both docetaxel and enzalutamide who were then given abiraterone acetate and prednisone, just 8% achieved a ⩾50% decline in PSA levels, with a median progression-free survival of 2.7 months.[75] Similarly, among patients who progressed following treatment with enzalutamide only, no radiographic responses were observed and median OS was <1 year.[76] In the phase IV PLATO trial, the primary endpoint of improvement in progression-free survival was not met in chemotherapy-naïve mCRPC patients who progressed on enzalutamide and were then subsequently treated with enzalutamide and abiraterone acetate plus prednisone compared with abiraterone acetate plus prednisone alone.[77]

Key ongoing trials of abiraterone acetate plus prednisone and other regimens in the chemotherapy-naïve prostate cancer setting

Abiraterone acetate plus prednisone is currently indicated for use in the mCRPC setting, both pre- and post-chemotherapy, but there are a number of ongoing studies to evaluate the role of abiraterone acetate and prednisone as treatment for chemotherapy-naïve patients in both the nonmetastatic and metastatic settings (Table 2). Currently, there is no approved therapy for nmCRPC. The IMAAGEN study is a phase II, multicenter, open-label trial that enrolled 131 patients with nmCRPC with a rising PSA level despite castrate levels of testosterone.[61] Patients are being treated with abiraterone acetate 1000 mg plus prednisone 5 mg daily. The primary endpoint is the proportion of patients with a ≥50% reduction in PSA during cycles 1–6 of treatment, with key secondary endpoints of time to PSA progression, time to radiographic evidence of disease progression, proportion of patients with ≥50% reduction in PSA after three treatment cycles absolute PSA reduction, and PSA and testosterone levels over time. Three further studies are investigating other agents for use in the nmCRPC setting. ARAMIS is a randomized, double-blind placebo-controlled trial comparing the novel second-generation oral AR inhibitor ODM-201 with placebo in high-risk patients with nmCRPC (NCT02200614). Patients are being assigned 2:1 to ODM-201 at a dose of 600 mg twice daily or placebo. The primary endpoint is metastasis-free survival. SPARTAN (Selective Prostate AR Targeting with ARN) is a multicenter, double-blind, placebo-controlled phase III trial of apalutamide 240 mg daily compared with placebo, both with ADT, in men with high-risk nmCRPC.[78] Apalutamide is an advanced AR antagonist that targets the ligand-binding domain of AR with high affinity, prevents AR nuclear translocation, DNA binding and transcription of AR gene targets, and achieves potent antitumor activity.[79] The primary endpoint is metastasis-free survival. A further trial in the nmCRPC setting is PROSPER, a randomized, double-blind, placebo-controlled international phase III trial investigating enzalutamide 160 mg/day compared with placebo.[80] The primary endpoint is metastasis-free survival.

The combination of enzalutamide and abiraterone acetate plus prednisone is currently being investigated in the STAMPEDE trial (NCT00268476). STAMPEDE is a multistage, multiarm trial currently being conducted in patients with locally advanced or metastatic HSPC. The trial has included abiraterone acetate and prednisone 5 mg as one of five comparators given early in the course of disease in combination with hormone treatment. In addition to abiraterone acetate plus prednisone, the comparator therapies are zoledronic acid, docetaxel, celecoxib, prostate radiotherapy, and enzalutamide. The abiraterone acetate plus prednisone arm is now complete; an abiraterone acetate plus prednisone and enzalutamide arm is in progress. Results have not yet been published.

LATITUDE (NCT01715285) and PEACE1 (NCT01957436) are phase III trials evaluating the role of abiraterone acetate plus prednisone in patients with mHSPC. In LATITUDE, patients are randomized to ADT plus abiraterone acetate and prednisone 5 mg once daily or ADT alone. The co-primary endpoints are OS and rPFS. PEACE1 is a randomized, open-label study in which patients are assigned to one of four treatment arms: ADT (active comparator), ADT plus abiraterone acetate and prednisone 5 mg twice daily, ADT plus radiotherapy, or ADT plus abiraterone acetate and prednisone 5 mg twice daily plus radiotherapy. The primary endpoints are OS and progression-free survival. Other ongoing phase III trials in mHSPC include ENZAMET (NCT02446405), TITAN (NCT02489318) and SWOG S1216, which are evaluating enzalutamide, apalutamide and orteronel, respectively.

In the mCRPC setting, a randomized, open-label phase III trial is currently comparing enzalutamide alone with enzalutamide, abiraterone acetate and prednisone (NCT01949337). The primary endpoint is OS. Also in this setting, ERA 223, a randomized, double-blind, placebo-controlled phase III trial, is evaluating radium-223 and abiraterone acetate plus prednisone compared with abiraterone acetate plus prednisone alone in patients who are asymptomatic or mildly symptomatic with bone-predominant metastatic disease (NCT02043678). The primary endpoint is symptomatic skeletal event-free survival, and OS is a secondary endpoint. PEACE III is an ongoing open-label, phase III trial evaluating upfront enzalutamide plus radium-223 compared with enzalutamide alone in patients with asymptomatic or mildly symptomatic mCRPC (NCT02194842).

There is increasing interest in the use of novel imaging modalities in men with nmCRPC to improve the early detection of metastases that might not otherwise be detected using

Table 2. Ongoing trials of abiraterone acetate/prednisone and other regimens in prostate cancer.

	LATITUDE	PEACE1	STAMPEDE	ENZAMET	TITAN	SWOG S1216	IMAAGEN	ARAMIS	SPARTAN	PROSPER	ALLIANCE[a]	ERA 223
Setting	mHSPC	mHSPC	LA or mHSPC	mHSPC	mHSPC	mHSPC	nmCRPC	nmCRPC	nmCRPC	nmCRPC	mCRPC	mCRPC
Phase	III	III	III	III	III	III	II	III	III	III	III	III
Interventions	ADT + ABI 1000 mg/day + PRED 5 mg daily versus ADT	ADT ± PRT ± ABI 1000 mg/day + PRED 5 mg BID	ADT and up to two of: ZOL, DOC, CEL, ABI 1000 mg/day + PRED 5 mg, PRT, ENZ	ADT + ENZ 160 mg/day versus ADT + antiandrogen	ADT ± APA 240 mg/day	ADT + orteronel 300 mg BID versus ADT + BIC	ABI 1000 mg + PRED 5 mg daily	ODM 600 mg BID + ADT versus PBO + ADT	APA 240 mg/day + ADT versus PBO + ADT	ENZ 160 mg/day versus PBO	ENZ 160 mg/day QD versus ENZ + ABI 1000 mg QD + PRED 5 mg BID	Radium-223 + ABI 1000 mg/day + PRED 5 mg BID versus PBO + ABI 1000 mg/day + PRED 5 mg BID
Study design	r, db, phase III	r, ol, phase III	r, ol, phase II and III	r, ol, phase III	r, db, phase III	r, ol, phase III	ol, sa, mc, phase II	r, db, pc, mc, phase III	r, db, pc, mc, phase III	r, db, pc, mc, phase III	r, ol, phase III	r, db, pc, phase III
Primary endpoints	OS, rPFS	OS, PFS	OS	OS	rPFS, OS	OS	≥50% reduction in PSA	MFS	MFS	MFS	OS	Symptomatic skeletal event-free survival
NCT number	NCT01715285	NCT01957436	NCT00268476	NCT02446405	NCT02489318	NCT01809691	NCT01314118	NCT02200614	NCT01946204	NCT02003924	NCT01949337	NCT02043678

[a]Sponsored by Alliance for Clinical Trials in Oncology.
ABI, abiraterone acetate; ADT, androgen deprivation therapy; APA, apalutamide; BIC, bicalutamide; BID, twice daily; CEL, celecoxib; db, double-blind; DOC, docetaxel; ENZ, enzalutamide; LA, locally advanced; mc, multicenter; MFS, metastasis-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ODM, ODM-201; ol, open-label; OS, overall survival; PBO, placebo; pc, placebo-controlled; PFS, progression-free survival; PRED, low-dose prednisone; PRT, prostate radiotherapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; QD, once daily; r, randomized; sa, single arm; ZOL, zoledronic acid.

conventional imaging, computed tomography or technetium bone scintigraphy. This will no doubt have a role in ongoing and/or future clinical trials of abiraterone acetate plus prednisone. Among these modalities, whole-body magnetic resonance imaging may be a suitable replacement for both computed tomography and bone scintigraphy, with or without targeted X-rays.[81] Another, serial 18F-choline positron emission tomography, has been evaluated in mCRPC patients receiving enzalutamide, with baseline maximum standardized uptake value found to be an independent prognostic factor.[82]

Conclusion

The chemotherapy-naïve population constitutes a broad range of patients along the prostate cancer disease continuum, ranging from those with low-risk, low-volume disease to those with advanced, symptomatic disease. Abiraterone acetate in combination with prednisone has proven benefit in men with mCRPC; however, benefit in other disease states is still undergoing study.

While prostate cancer care is best delivered in a multidisciplinary setting, this is not always possible. The toxicities of both abiraterone acetate and low-dose prednisone can be managed by the urologist as well as the medical oncologist with the appropriate knowledge. This review should provide information specific to the population of patients commonly shared by both urologists and medical oncologists and, less commonly, by radiation oncologists. Abiraterone acetate plus prednisone may, however, have a role in earlier-stage disease when used in combination with radiation therapy. At that point, it will be necessary for radiation oncologists to also have greater familiarity with the toxicities of both abiraterone acetate and low-dose prednisone. Currently, low-dose prednisone (5 mg twice daily) is specified in combination with abiraterone acetate. The use of abiraterone acetate with low-dose prednisone decreases steroid build-up upstream of CYP17 and prevents mineralocorticoid excess. When there is evidence of mineralocorticoid excess despite prednisone, switching to prednisolone should be considered. The phase III trials have demonstrated that low-dose prednisone is generally well tolerated, although it can exacerbate some underlying conditions such as diabetes or hypertension.

The results of ongoing trials in the chemotherapy-naïve setting will identify other prostate cancer patient populations that will benefit from abiraterone acetate and prednisone therapy. In the meantime, efforts to better refine treatment pathways for clinicians administering abiraterone acetate with prednisone are in process.

Conflict of interest statement
E. David Crawford is a consultant/adviser to Bayer, MDx, Genomic Health, Janssen Pharmaceuticals, Dendreon and Ferring, and has received grant support from NIH and the University of Colorado Cancer Center. His spouse is an employee at Dendreon.

Neal D. Shore is a consultant/adviser to Amgen, Astellas, Bayer, BNI, Dendreon, Ferring, Janssen Pharmaceuticals, Medivation, Sanofi, Takeda and Tolmar.

Daniel P. Petrylak is a consultant/adviser to Bayer, Bellicum, Dendreon, Sanofi, Johnson & Johnson, Exelixis, Ferring, Millennium, Medivation, Pfizer, Roche Laboratories, and Tyme Pharmaceuticals, has received research funding from, Oncogenix, Progenics, Johnson & Johnson, Merck, Millennium, Dendreon, Sanofi, Agenysis, Eli Lilly, and Roche Laboratories and has ownership interest/investment in Bellicum and Tyme.

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References
1. Siegel R, Ma J, Zou Z, *et al.* Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9–29.

2. DeSantis CE, Lin CC, Mariotto AB, *et al.* Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014; 64: 252–271.

3. Guy D, Ghanem G, Loblaw A, *et al.* Diagnosis, referral, and primary treatment decisions in newly diagnosed prostate cancer patients in a multidisciplinary diagnostic assessment program. *Can Urol Assoc J* 2016; 10: 120–125.

4. Reese AC, Wessel SR, Fisher SG, *et al.* Evidence of prostate cancer "reverse stage migration" toward more advanced disease at diagnosis: data from the Pennsylvania Cancer Registry. *Urol Oncol* 2016; 34: 335. e21–e28.

5. Weiner AB, Matulewicz RS, Eggener SE, *et al.* Increasing incidence of metastatic prostate cancer in the United States (2004–2013). *Prostate Cancer Prostatic Dis* 2016; 19: 395–397.

6. Siddiqui E, Mumtaz FH and Gelister J. Understanding prostate cancer. *J R Soc Promot Health* 2004; 124: 219–221.

7. Scher HI, Solo K, Valant J, *et al.* Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. *PLoS One* 2015; 10: e0139440.

8. Oudard S. Progress in emerging therapies for advanced prostate cancer. *Cancer Treat Rev* 2013; 39: 275–289.

9. Attard G, Reid AH, Yap TA, *et al.* Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol* 2008; 26: 4563–4571.

10. Mostaghel EA, Page ST, Lin DW, *et al.* Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. *Cancer Res* 2007; 67: 5033–5041.

11. Mostaghel EA and Nelson PS. Intracrine androgen metabolism in prostate cancer progression: mechanisms of castration resistance and therapeutic implications. *Best Pract Res Clin Endocrinol Metab* 2008; 22: 243–258.

12. Suzman DL and Antonarakis ES. Does degree of androgen suppression matter in hormone-sensitive prostate cancer? *J Clin Oncol* 2015; 33: 1098–1100.

13. Cookson MS, Roth BJ, Dahm P, *et al.* Castration-resistant prostate cancer: AUA guideline. *J Urol* 2013; 190: 429–438.

14. Montgomery RB, Mostaghel EA, Vessella R, *et al.* Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008; 68: 4447–4454.

15. Attard G, Cooper CS and de Bono JS. Steroid hormone receptors in prostate cancer: a hard habit to break? *Cancer Cell* 2009; 16: 458–462.

16. Cookson MS, Lowrance WT, Murad MH, *et al.* Castration-resistant prostate cancer: AUA guideline amendment. *J Urol* 2015; 193: 491–499.

17. Golshayan AR and Antonarakis ES. Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer. *Core Evid* 2013; 8: 27–35.

18. Mostaghel EA, Marck BT, Plymate SR, *et al.* Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. *Clin Cancer Res* 2011; 17: 5913–5925.

19. Mottet N, Bellmunt J, Briers E, *et al. Guidelines on Prostate Cancer.* European Association of Urology, http://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf (2015, accessed 19 July 2016).

20. Engel-Nitz NM, Alemayehu B, Parry D, *et al.* Differences in treatment patterns among patients with castration-resistant prostate cancer treated by oncologists versus urologists in a US managed care population. *Cancer Manag Res* 2011; 3: 233–245.

21. Harris V, Lloyd K, Forsey S, *et al.* A population-based study of prostate cancer chemotherapy. *Clin Oncol (R Coll Radiol)* 2011; 23: 706–708.

22. Frenkel M. Refusing treatment. *Oncologist* 2013; 18: 634–636.

23. Ryan CJ, Smith MR, de Bono JS, *et al.* Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–148.

24. Ryan CJ, Smith MR, Fizazi K, *et al.* Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015; 16: 152–160.

25. Molina A and Belldegrun A. Novel therapeutic strategies for castration resistant prostate cancer: inhibition of persistent androgen production and androgen receptor mediated signaling. *J Urol* 2011; 185: 787–794.

26. Janssen Biotech Inc. Zytiga [abiraterone acetate] (package insert). Horsham, PA: Janssen Biotech Inc, 2016.

27. Rathkopf DE, Smith MR, de Bono JS, *et al.* Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol* 2014; 66: 815–825.

28. Basch E, Autio K, Ryan CJ, *et al.* Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1193–1199.

29. Saad F, Shore N, van PH, *et al.* Impact of bone-targeted therapies in chemotherapy-naive metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: post hoc analysis of study COU-AA-302. *Eur Urol* 2015; 68: 570–577.

30. Smith MR, Rathkopf DE, Mulders PF, *et al.* Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naive patients with metastatic castration resistant prostate cancer. *J Urol* 2015; 194: 1277–1284.

31. Fizazi K, Chi KN, de Bono JS, *et al.* Low incidence of corticosteroid-associated adverse events on long-term exposure to low-dose prednisone given with abiraterone acetate to patients with metastatic castration-resistant prostate cancer. *Eur Urol* 2016; 70: 438–444.

32. Saad F, Carles J, Gillessen S, *et al.* Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol* 2016; 17: 1306–1316.

33. Shore ND. Open-label phase II study evaluating the efficacy of concurrent administration of radium Ra 223 dichloride (Ra-223) and abiraterone acetate (AA) in men with castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases. *J Clin Oncol* 2016; 34(Suppl. 2): abstract 177.

34. Svensson J, Andersson E, Persson U, *et al.* Value of treatment in clinical trials versus the real world: the case of abiraterone acetate (Zytiga) for postchemotherapy metastatic castration-resistant prostate cancer patients in Sweden. *Scand J Urol* 2016; 50: 286–291.

35. Van PC, Rottey S, Van HF, *et al.* Abiraterone acetate post-docetaxel for metastatic castration-resistant prostate cancer in the Belgian compassionate use program. *Urol Oncol* 2016; 34: 254.

36. Beer TM, Armstrong AJ, Rathkopf DE, *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–433.

37. Boudadi K and Antonarakis ES. Resistance to novel antiandrogen therapies in metastatic castration-resistant prostate cancer. *Clin Med Insights Oncol* 2016; 10: 1–9.

38. Antonarakis ES, Lu C, Wang H, *et al.* AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* 2014; 371: 1028–1038.

39. Green SM, Mostaghel EA and Nelson PS. Androgen action and metabolism in prostate cancer. *Mol Cell Endocrinol* 2012; 360: 3–13.

40. Nelson PS. Targeting the androgen receptor in prostate cancer–a resilient foe. *N Engl J Med* 2014; 371: 1067–1069.

41. Evaul K, Li R, Papari-Zareei M, *et al.* 3beta-hydroxysteroid dehydrogenase is a possible pharmacological target in the treatment of castration-resistant prostate cancer. *Endocrinology* 2010; 151: 3514–3520.

42. Maughan BL and Antonarakis ES. Enzalutamide in chemo-naive castration-resistant prostate cancer: effective for most but not for all. *Asian J Androl* 2014; 16: 807–808.

43. Nguyen HG, Welty CJ and Cooperberg MR. Diagnostic associations of gene expression signatures in prostate cancer tissue. *Curr Opin Urol* 2015; 25: 65–70.

44. Scher HI, Lu D, Schreiber NA, *et al.* Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. *JAMA Oncol* 2016; 2: 1441–1449.

45. Crawford ED, Higano CS, Shore ND, *et al.* Treating patients with metastatic castration resistant prostate cancer: a comprehensive review of available therapies. *J Urol* 2015; 194: 1537–1547.

46. Small EJ, Lance RS, Gardner TA, *et al.* A randomized phase II trial of sipuleucel-T with concurrent versus sequential abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2015; 21: 3862–3869.

47. Quinn DI, Drake CG, Dreicer R, *et al.* Immune response from STRIDE, a randomized, phase 2, open label study of sipuleucel-T (sip-T) with concurrent vs sequential enzalutamide (enz) administration in metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2015; 33(Suppl): abstract 5040.

48. Parker C, Nilsson S, Heinrich D, *et al.* Alpha emitter radium-223 and survival in metastatic

prostate cancer. *N Engl J Med* 2013; 369: 213–223.

49. Gravis G, Fizazi K, Joly F, *et al*. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; 14: 149–158.

50. James ND, Sydes MR, Clarke NW, *et al*. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016; 387: 1163–1177.

51. Sweeney CJ, Chen YH, Carducci M, *et al*. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; 373: 737–746.

52. Vale CL, Burdett S, Rydzewska LH, *et al*. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol* 2016; 17: 243–256.

53. Aizer AA, Paly JJ, Zietman AL, *et al*. Multidisciplinary care and pursuit of active surveillance in low-risk prostate cancer. *J Clin Oncol* 2012; 30: 3071–3076.

54. Sundi D, Cohen JE, Cole AP, *et al*. Establishment of a new prostate cancer multidisciplinary clinic: Format and initial experience. *Prostate* 2015; 75: 191–199.

55. Gomella LG, Lin J, Hoffman-Censits J, *et al*. Enhancing prostate cancer care through the multidisciplinary clinic approach: a 15-year experience. *J Oncol Pract* 2010; 6: e5–e10.

56. Sartor AO and Fitzpatrick JM. Urologists and oncologists: adapting to a new treatment paradigm in castration-resistant prostate cancer (CRPC). *BJU Int* 2012; 110: 328–335.

57. Auchus RJ, Yu MK, Nguyen S, *et al*. Use of prednisone with abiraterone acetate in metastatic castration-resistant prostate cancer. *Oncologist* 2014; 19: 1231–1240.

58. Dorff TB and Crawford ED. Management and challenges of corticosteroid therapy in men with metastatic castrate-resistant prostate cancer. *Ann Oncol* 2013; 24: 31–38.

59. Efstathiou E, Li W, Gormley M, *et al*. Biological heterogeneity in localized high-risk prostate cancer (LHRPC) from a study of neoadjuvant abiraterone acetate plus leuprolide acetate (LHRHa) versus LHRHa. *J Clin Oncol* 2015; 33(Suppl): abstract 5005.

60. Taplin ME, Montgomery B, Logothetis CJ, *et al*. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. *J Clin Oncol* 2014; 32: 3705–3715.

61. Ryan CJ, Crawford ED, Shore ND, *et al*. IMAAGEN trial safety and efficacy update: effect of abiraterone acetate and low dose prednisone on PSA and radiographic disease progression in patients with non-metastatic castration-resistant prostate cancer. *J Clin Oncol* 2016; 34(Suppl): abstract 5061.

62. Fizazi K, Larsen JS, Matheny S, *et al*. Randomized double-blind, comparative study of abiraterone acetate (AA) plus low-dose prednisone (P) plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed, high-risk, metastatic hormone-naive prostate cancer (mHNPC). *J Clin Oncol* 2013; 31(Suppl): abstract TPS5097.

63. Lorente D, Omlin A, Ferraldeschi R, *et al*. Tumour responses following a steroid switch from prednisone to dexamethasone in castration-resistant prostate cancer patients progressing on abiraterone. *Br J Cancer* 2014; 111: 2248–2253.

64. Chi KN, Spratlin J, Kollmannsberger C, *et al*. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol* 2015; 55: 1406–1414.

65. de Bono JS, Logothetis CJ, Molina A, *et al*. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005.

66. Inoue K, Shishido A, Vaccaro N, *et al*. Pharmacokinetics of abiraterone in healthy Japanese men: dose-proportionality and effect of food timing. *Cancer Chemother Pharmacol* 2015; 75: 49–58.

67. Ryan CJ, Smith MR, Fong L, *et al*. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol* 2010; 28: 1481–1488.

68. Rescigno P, Lorente D, Bianchini D, *et al*. Prostate-specific antigen decline after 4 weeks of treatment with abiraterone acetate and overall survival in patients with metastatic castration-resistant prostate cancer. *Eur Urol* 2016; 70: 724–731.

69. Moore DC and Moore A. Abiraterone-induced rhabdomyolysis: a case report. *J Oncol Pharm Pract* 2017; 23: 148–151.

70. Neyra JA, Rocha NA, Bhargava R, *et al.* Rhabdomyolysis-induced acute kidney injury in a cancer patient exposed to denosumab and abiraterone: a case report. *BMC Nephrol* 2015; 16: 118.

71. Zobniw CM, Causebrook A and Fong MK. Clinical use of abiraterone in the treatment of metastatic castration-resistant prostate cancer. *Res Rep Urol* 2014; 6: 97–105.

72. Mukherji D, Omlin A, Pezaro C, *et al.* Metastatic castration-resistant prostate cancer (CRPC): preclinical and clinical evidence for the sequential use of novel therapeutics. *Cancer Metastasis Rev* 2014; 33: 555–566.

73. Mezynski J, Pezaro C, Bianchini D, *et al.* Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol* 2012; 23: 2943–2947.

74. Chi KN, Kheoh T, Ryan CJ, *et al.* A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. *Ann Oncol* 2016; 27: 454–460.

75. Loriot Y, Bianchini D, Ileana E, *et al.* Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013; 24: 1807–1812.

76. Noonan KL, North S, Bitting RL, *et al.* Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013; 24: 1802–1807.

77. Pfizer News & Media. Pfizer and Astellas announce top-line results from phase 4 PLATO trial of XTANDI® (enzalutamide) capsules in patients with metastatic castration-resistant prostate cancer. *Pfizer website*, http://press.pfizer.com/press-release/pfizer-and-astellas-announce-top-line-results-phase-4-plato-trial-xtandi-enzalutamide- (2016, accessed 21 December 2016).

78. Smith MR, Liu G, Shreeve SM, *et al.* A randomized double-blind, comparative study of ARN-509 plus androgen deprivation therapy (ADT) versus ADT alone in nonmetastatic castration-resistant prostate cancer (M0-CRPC): the SPARTAN trial. *J Clin Oncol* 2014; 32(Suppl. 5): abstract TPS5100.

79. Rathkopf DE, Morris MJ, Fox JJ, *et al.* Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. *J Clin Oncol* 2013; 31: 3525–3530.

80. Hussain M, Fizazi K, Saad F, *et al.* PROSPER: a phase 3 study of enzalutamide in nonmetastatic (M0) castration-resistant prostate cancer (CRPC) patients. *J Clin Oncol* 2014; 32(Suppl. 5): abstract TPS5094.

81. Linton KD and Catto JW. Whole-body magnetic resonance imaging and prostate cancer metastases: a new gold standard of detection, but does it help us and at what cost? *Eur Urol* 2012; 62: 76–77.

82. Maines F, Caffo O, Donner D, *et al.* Serial 18F-choline-PET imaging in patients receiving enzalutamide for metastatic castration-resistant prostate cancer: response assessment and imaging biomarkers. *Future Oncol* 2016; 12: 333–342.

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