Molecular Pathways: Inhibiting Steroid Biosynthesis in Prostate Cancer

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Abstract

A significant proportion of castration-resistant prostate cancers (CRPC) remains driven by ligand activation of the androgen receptor. Although the testes are the primary source of testosterone, testosterone can also be produced from peripheral conversion of adrenal sex hormone precursors DHEA and androstenedione in the prostate and other tissues. CYP17A1 catalyzes two essential reactions in the production of DHEA and androstenedione: the hydroxylation (hydroxylase activity) and the subsequent cleavage of the C17-20 side chain (lyase activity). Potent and selective inhibition of CYP17A1 by abiraterone depletes residual nongonadal androgens and is an effective treatment for CRPC. Elucidation of the mechanisms that underlie resistance to abiraterone will inform the development of novel therapeutic strategies post-abiraterone. Preclinical evidence that androgen biosynthesis in prostate cancer cells does not necessarily follow a single dominant pathway, and residual androgens or alternative ligands (including administered glucocorticoids) can reactivate androgen receptor signaling, supports cotargeting of more than one enzyme involved in steroidogenesis and combining a CYP17A1 inhibitor with an antiandrogen. Furthermore, given the drawbacks of 17α-hydroxylase inhibition, there is considerable interest in developing new CYP17A1 inhibitors that more specifically inhibit lyase activity and are therefore less likely to require glucocorticoid coadministration. Clin Cancer Res; 19(13): 1–7. © 2013 AACR.

Background

For the past 70 years, gonadal androgen depletion by medical or surgical castration has been the standard of care for men with metastatic prostate cancer (1). Despite significant initial responses, patients invariably relapse, and several studies suggest intratumoral androgens (most commonly testosterone) in castration-resistant prostate cancer (CRPC) tumors are restored to equivalent levels found in noncastrate prostates (2–4). Intratumoral testosterone and/or dihydrotestosterone (DHT) in castrate men could be generated from conversion of circulating adrenal androgens (4, 5) or could be synthesized de novo from cholesterol (6). The latter has been suggested in a number of preclinical models but remains unproven in patients. High doses of ketoconazole, which inhibits many cytochrome P450 enzymes, have been used for over a decade to inhibit androgen biosynthesis and induce tumor responses in CRPC. The high doses of ketoconazole required to inhibit cytochrome P450c17 (17α-hydroxylase/17,20-lyase, CYP17A1), however, are associated with significant toxicity in up to 30% of patients. Moreover, CYP17A1 inhibition with ketoconazole is incomplete, and a rise in adrenal androgens has been reported at disease progression (7). The development of abiraterone as a specific and irreversible inhibitor of CYP17A1 offered a less toxic and more effective option. Abiraterone acetate is now approved in combination with prednisone for the treatment of CRPC, based on demonstration of an improvement in survival when administered with prednisone to docetaxel-treated patients and progression-free survival in chemotherapy-naïve patients (8, 9). Abiraterone acetate and prednisone also significantly delay pain progression and skeletal-related events and improve quality of life and pain control (10). These data have unequivocally confirmed that directly targeting androgen biosynthesis is a valid therapeutic option for prostate cancer. This review discusses the challenges of inhibiting CYP17A1 and other enzymes involved in steroid synthesis and reviews strategies that are being evaluated to further improve results achieved to date with abiraterone.

Androgen biosynthesis pathways

Steroidogenesis entails processes by which cholesterol is converted to biologically active steroid hormones. Steroidogenesis begins with the irreversible cleavage of a 6-carbon group from cholesterol, producing pregnenolone by
cytochrome P450scc (side-chain cleavage enzyme, CYP11A1). A small repertoire of cytochrome P450 and non-P450 enzymes then convert pregnenolone to other 21-carbon steroids (including progестins, glucocorticoids, and mineralocorticoids), 19-carbon steroids (androgens), and 18-carbon steroids (estrogens; ref. 11). The transformations catalyzed by the P450s, 3α-reductases, and 3β-hydroxysteroid dehydrogenase-$\Delta^{3}/\Delta^{4}$-isomerase (3βHSD) are all irreversible reactions, giving rise to the general pathways of steroidogenesis (Fig. 1). In contrast, the 3α, 11β, and 17βHSD reactions at the terminal stages of the pathways are reversible pseudoequilibria, with each isoenzyme strongly favoring either steroid oxidation or reduction in intact cells. In human beings, each steroidogenic P450 derives from one gene yielding one isoform, whereas all other enzymes exist as two or more isozymes, each with a unique cognate gene expressed in a tissue-specific fashion. Consequently, steroidogenesis generally follows a canonical pathway up to a point, but the final steps vary among tissues and cells, particularly in cancer cells, where genetic changes are frequent and ectopic expression of various enzymes exists. CYP17A1 is the key enzyme for the synthesis of 19-carbon sex steroid precursors from 21-carbon pregnenolone directly to progesterone and pregnenolone. The latter activity requires the presence of adequate amounts of cytochrome b5 (12). Exploiting the requirement of the 17,20-lyase, but not 17α-hydroxylase reaction for cytochrome b5, could allow development of therapeutics that specifically inhibit the former reaction. As cytochrome b5 is involved in a multitude of other essential processes, this approach will be challenging but could be possible because the critical residues of b5 for stimulating 17,20-lyase activity are E48 and E49, and these are not required for enhancing the activities of CYP2E1 or CYP2C19 (13, 14). In addition to its two primary activities, human CYP17A1 also 16α-hydroxylates progesterone during 25% of turnovers and cleaves pregnenolone and allo-pregnanolone directly to their $\Delta^{18}$, 19-carbon homologs in the presence of b5.

Although small amounts of androstenedione, testosterone, and other 19-carbon steroid metabolites can be directly produced by the adrenal glands, most $\Delta^{3}$-androgens in the castrated male are produced in peripheral tissues, where 3βHSD converts DHEA to androstenedione and $\Delta^{3}$-androstenediol to testosterone, respectively (Fig. 1). In the tumors, 17βHSD3 efficiently converts androstenedione to testosterone and DHEA to $\Delta^{3}$-androstenediol, respectively, but in the adrenal and peripheral tissues, the much slower type 5-(17βHSD5) enzyme catalyzes these conversions, and

Figure 1. Androgen biosynthesis pathway. The basic pathways are demarcated with respect to CYP17A1 and SRD5A activities. The 17-deoxy, 21-carbon steroids upstream of CYP17A1 are shown at left in the pink box, including 11-deoxycorticosterone. The 17-hydroxy, 21-carbon steroids are in the center in the peach box, and 19-carbon steroids are at the right in the green box, generated via 17-hydroxylase and 17,20-lyase reactions of CYP17A1, respectively. The 5α-reduced steroids are highlighted with darker background at bottom right. Reversible interconversions catalyzed by HSDs are shown with double arrows at terminal steps. CYP17A1, cytochrome P450scc17.
17βHSD1 also reduces DHEA to Δ<sup>5</sup>-androstenediol. Testosterone is then irreversibly 5α-reduced to the higher affinity ligand DHT by steroid 5α-reductase (SRD5A) iso-enzymes (this is referred to as the canonical or “conventional” pathway for DHT synthesis). DHT is inactivated in part by 3-keto-reduction to 5α-androstan-3α,17β-diol through a single step, catalyzed by the AKR1C isoenzymes 1 to 4 (reductive 3αHSDs; mainly AKR1C2) and to 3α-androsterone through two steps (Fig. 1). DHT, 5α-androstan-3α,17β-diol, and 3α-androsterone can all be inactivated by the enzymes UDP glucuronosyltransferase 2, B15 (UGT2B15), or UGT2B17 (15). The sulfotransferase 2A1 (SULT2A1) rapidly sulfonates the majority of DHEA synthesized in the adrenal gland, and most of the adrenal androgenic product therefore circulates as dehydroepiandrosterone sulfate (DHEA-S).

The interconversion of the 5α-reduced androgens occurs through reversible HSD reactions with the possibility of “back conversion” of inactive terminal products to DHT. 5α-reduction of upstream steroids, as opposed to 5α-reduction of testosterone, leads to DHT synthesis that bypasses testosterone through at least two pathways. In the 5α-androstanedione pathway, androstenedione is converted by SRD5A1 to 5α-androstanedione, which is then converted into DHT by 17βHSD(s; ref. 16; Fig. 1). The alternative or “backdoor” pathway to DHT synthesis occurs when progesterone and 17OHP accumulate and SRD5A enzymes are present. In this pathway, 17OHP is 5α- and 3α-reduced before the 17,20-lyase reaction of CYP17A1, yielding the 5α-reduced androgen androsterone (Fig. 1). If 17βHSD activity is also present, 3α-androsterone is converted to 5α-androstan-3α,17β-diol via oxidative 3α-HSD activity, possibly catalyzed by 17βHSD6 (17). This pathway yields DHT without DHEA, androstenedione, and testosterone as intermediates and occurs naturally in tammar wallaby pouch young testes, in the neonatal testes of several rodent species, and in certain types of congenital adrenal hyperplasia (18, 19).

Clinical–Translational Advances

**Metabolic consequences of therapeutic inhibition of CYP17A1**

Abiraterone was rationally designed in the early 1990s using pregnenolone as a backbone to bind the active site of CYP17A1 and inhibit its activity (20). This inhibition occurs secondary to formation of an essentially irreversible coordination complex between the heme iron, which is required in the CYP17A1 active site for enzymatic activity, and the azole nitrogen atom of abiraterone, plus hydrogen-bonding interactions between the abiraterone 3β-OH and conserved polar residues in CYP17A1 (21, 22). The structural similarities between the latter interactions and ligands binding to steroid receptors could explain abiraterone’s (and that of other CYP17A1 inhibitors) weak (relatively) antagonism of the androgen receptor (AR; ref. 23). The specificity of abiraterone for inhibition of 17,20-lyase versus 17α-hydroxylase is low (1.4-fold, IC<sub>50</sub> = 2.9 nmol/L, compared with 4 nmol/L; ref. 21), and treatment with abiraterone acetate therefore blocks both activities. When used as a single agent, abiraterone acetate suppresses cortisol and causes a rise in adrenocorticotropic hormone (ACTH) with a consequent increase in 11-deoxycorticosterone (DOC) and corticosterone, mimicking the effects observed in families with congenital inactivating CYP17A1 mutations (24). When administered to noncastrate men, abiraterone acetate (a maximum of 750 mg was evaluated) suppresses testosterone, but a subsequent luteinizing hormone surge overcomes inhibition of gonadal testosterone synthesis (25). Significantly higher doses than the currently approved 1,000 mg would be required to suppress androgens if abiraterone acetate were administered to noncastrate men, probably without any obvious sparing of the side effects associated with pharmacologic castration with gonadotropin-releasing hormone agonists (GnRHα). Importantly, when abiraterone is administered with GnRHα, significant suppression of circulating DHEA, DHEA-S, androstenedione, testosterone, and estradiol is achieved with no obvious rise at disease progression (26–28). Evaluation of the latter has, however, been limited by the sensitivity of assays used.

CYP17A1 inhibition with single-agent abiraterone acetate is not associated with adrenocortical insufficiency, because a compensatory increase in ACTH leads to very high levels (30–40-fold rise) of the weak glucocorticoid corticosterone that maintains the glucocorticoid requirements of patients. However, raised levels of corticosterone precursors that have mineralocorticoid properties, particularly DOC, lead to a syndrome of mineralocorticoid excess characterized by hypokalemia, hypertension, and fluid retention (26, 29, 30). To effectively prevent or treat ACTH-induced side effects of mineralocorticoid excess, two different strategies could be adopted: (i) the administration of exogenous glucocorticoids to prevent a compensatory ACTH rise, and (ii) the administration of mineralocorticoid receptor antagonists (MRA) that inhibit the peripheral effects of raised mineralocorticoids.

Prednisone (prednisolone in the United Kingdom), 5 mg twice a day, was used in the regulatory phase III studies of abiraterone, primarily because most patients with CRPC are already receiving this glucocorticoid during taxane treatment. Prednisone is a glucocorticoid prodrug that is converted by 11βHSD1 in the liver into the active form, prednisolone. Prednisolone is 4 times a more potent glucocorticoid than cortisol, and 5 to 7.5 mg daily is used to manage adrenal insufficiency (31). However, in the COU-301 and COU-302 phase III studies, up to 40% of patients treated with prednisone and placebo suffered side effects associated with mineralocorticoid excess (8, 9), suggesting prednisone (or prednisolone) or their metabolites could activate the mineralocorticoid receptor. Moreover, as anticipated, side effects of mineralocorticoid excess were significantly more common in the abiraterone–prednisone arm in both studies. The half-life of prednisone is 3 hours, and the biologic effect of 5 mg lasts up to 12 hours (32) although this can be variable due to prednisone’s interconversion with prednisolone. Once-daily prednisone dosing is being...
used in several clinical studies in early prostate cancer and breast cancer (for e.g., NCT01751451, NCT01381874, NCT00268476) but there is a hypothetical increased risk of more mineralocorticoid excess due to a compensatory nocturnal rise in ACTH. Modified-release formulations or higher doses could be considered for once-daily dosing if these studies report significant mineralocorticoid excess. Overall, hypokalemia is usually corrected with oral potassium supplementation, and less than 2% of patients treated with prednisone, 5 mg twice a day, and abiraterone require MRA or intervention to control these side effects (8). Dexamethasone is a potent glucocorticoid, and a dose of 0.5 mg daily is usually used. In retrospective studies, dexamethasone was reported to have a significant response rate (equivalent or potentially superior) to prednisone as monotherapy for CRPC (33). Dexamethasone has no mineralocorticoid activity and a long duration of action: This could make it the preferred combination glucocorticoid. Orthostatic hypotension has been rarely reported (~2/100 patients) after addition of dexamethasone to patients on single-agent abiraterone, presumably due to dexamethasone’s absence of mineralocorticoid properties coupled with a rapid decline in raised mineralocorticoids (28, 29). Hydrocortisone (cortisol) could be administered at a daily dose of 10 to 12 mg/m$^2$/d in divided doses (corresponding to a total daily dose of 15–25 mg). However, due to its short duration of action even 3-times-a-day dosing is unlikely to completely suppress ACTH without overdosing.

Overall, it is challenging to suppress ACTH while not administering supraphysiologic glucocorticoid doses and avoiding coughing symptoms from long-term treatment. Moreover, it is possible that long-term use of exogenous glucocorticoids is detrimental (see final section). The alternative option is to use abiraterone acetate alone and treat patients who develop mineralocorticoid excess with a MRA. However, spironolactone, the first-generation, cheapest, and most readily available (competitive) MRA binds to the AR as a mixed agonist/antagonist and could lead to disease progression (34, 35). Eplerenone, a second-generation MRA was developed as a more selective MRA that does not bind wild-type AR but can activate AR mutations previously detected in prostate cancer (23). Also, significantly raised levels of steroids upstream of CYP17A1 in patients on single-agent abiraterone acetate could activate mutant AR, and very high levels of 17α-hydroxylase substrates could overcome CYP17A1 inhibition by abiraterone. In fact, when dexamethasone was added to single-agent abiraterone in patients with a rising prostate-specific antigen (PSA) level, a secondary PSA decline of more than 50% was reported in 25% of patients regardless of prior treatment with the same dose and regimen of dexamethasone, suggesting that high levels of upstream steroids were causing resistance (29). Amiloride and triamterene, which are potassium-sparing diuretics and inhibitors of the epithelial sodium channel in the distal nephron, are useful agents for controlling the hypokalemia and hypertension of mineralocorticoid excess states and might be effective treatments for these complications of abiraterone therapy without activating AR.

**Novel CYP17A1 inhibitors in clinical development**

Given the drawbacks of 17α-hydroxylase inhibition, there is considerable interest in developing new CYP17A1 inhibitors that more specifically inhibit 17,20-lyase and are therefore less likely to require glucocorticoid coadministration. Orteronel (TAK-700; Millennium Pharmaceuticals) inhibits 17,20-lyase activity 5.4 times more potently than 17α-hydroxylase activity (36). This relative specificity might, however, require a compromise between higher doses that achieve maximum profound inhibition of 17,20-lyase with the risk of a decrease in cortisol and consequent raised ACTH and mineralocorticoid excess versus lower doses that do not suppress cortisol. Orteronel is currently undergoing evaluation in phase III studies in chemotherapy-naive and chemotherapy-treated CRPC (NCT01193244; NCT01193257). Both studies use a dose of 400 mg twice daily and combine orteronel with prednisone. Lower doses of orteronel (e.g., 300 mg twice a day) that may not require concomitant exogenous glucocorticoids are also being evaluated. Another CYP17A1 inhibitor, galeterone (VN/124-1, TOK-001; Tokai Pharmaceuticals), is a combined inhibitor of CYP17A1, AR, and SRD5A (37) that has recently completed phase I testing (38). VT-464 (Viamet Inc.) has a 60-fold greater specificity for C17,20-lyase than 17α-hydroxylase. Treatment of monkeys with VT-464 did not cause a rise in steroids upstream of CYP17A1 in contrast to treatment with abiraterone (39). This agent is now in early clinical trials.

**Reactivation of AR signaling in patients progressing on abiraterone—will combination therapy prove more effective?**

The mechanisms that underlie resistance to abiraterone are unknown, and their elucidation will inform on the development of novel therapeutic strategies post-abiraterone and biomarkers for selecting patients for treatment. The majority of patients progressing on abiraterone have a rise in PSA, suggesting reactivation of AR or other steroid signaling pathways that could increase PSA transcription (40). Several studies have shown that the AR can become promiscuously activated by very low levels of androgens (that could persist in patients treated with abiraterone acetate), other steroid metabolites, and drugs that bind the AR (41–44). The latter could include abiraterone or coadministered glucocorticoids. AR mutations previously described in prostate cancer can be activated by cortisol and other glucocorticoids at levels significantly lower than are reported in breast cancer (for e.g., NCT01751451, NCT01381874, NCT00268476) but there is a hypothetical increased risk of more mineralocorticoid excess due to a compensatory nocturnal rise in ACTH. Modified-release formulations or higher doses could be considered for once-daily dosing if these studies report significant mineralocorticoid excess. Overall, hypokalemia is usually corrected with oral potassium supplementation, and less than 2% of patients treated with prednisone, 5 mg twice a day, and abiraterone require MRA or intervention to control these side effects (8). Dexamethasone is a potent glucocorticoid, and a dose of 0.5 mg daily is usually used. In retrospective studies, dexamethasone was reported to have a significant response rate (equivalent or potentially superior) to prednisone as monotherapy for CRPC (33). Dexamethasone has no mineralocorticoid activity and a long duration of action: This could make it the preferred combination glucocorticoid. Orthostatic hypotension has been rarely reported (~2/100 patients) after addition of dexamethasone to patients on single-agent abiraterone, presumably due to dexamethasone’s absence of mineralocorticoid properties coupled with a rapid decline in raised mineralocorticoids (28, 29). Hydrocortisone (cortisol) could be administered at a daily dose of 10 to 12 mg/m$^2$/d in divided doses (corresponding to a total daily dose of 15–25 mg). However, due to its short duration of action even 3-times-a-day dosing is unlikely to completely suppress ACTH without overdosing.

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Gene expression studies have identified alterations in the expression of multiple steroidogenic enzymes in CRPC tissue, including increased levels of SRD5A1, 3βHSD, 17β-HSD5 (also called AKR1C3), and a new isoform of SRD5A (SRD5A3) and reduced expression of SRD5A2 (4, 48–50). Moreover, CYP17A1 and other steroidogenic enzymes have been shown to become upregulated as a consequence of abiraterone treatment in preclinical models (51, 52). Although increased expression of steroidogenic enzymes does not necessarily equate with increased androgen production, these observations raise the possibility that resistance to abiraterone may be due in part to mechanisms that maintain androgen synthesis. Translational studies to date have failed to identify a rise in circulating androgens on treatment (27, 53), but measurement of intracellular androgens has been limited by the availability of CRPC tissue and the technical and analytic challenges of controlling for losses during extraction and processing, and definitively separating, detecting, and identifying particular steroids among highly related compounds. It is hypothesized that androgen biosynthesis in prostate cancer cells does not necessarily follow a single dominant pathway, particularly under therapy pressure (17). This model would support cotargeting of more than one enzyme involved in steroidogenesis. Nonetheless, both the conventional and alternative pathways of androgen biosynthesis are dependent on CYP17A1 17,20-lyase for production of androgens, and to date a CYP17A1-independent mechanism for androgen biosynthesis has not been identified. The role of non-CYP17A1 steroidogenesis inhibitors may therefore be limited to combinations with CYP17A1 inhibitors when 17,20-lyase blockade is incomplete, potentially reversing resistance or allowing the use of doses that do not concurrently suppress 17α-hydroxylase activity.

Significant pathway diversity and redundancy pose a challenge to targeting steroidogenesis downstream of CYP17A1. SRD5A1 is highly expressed in prostate cancer and mediates the 5α-androstenedione pathway synthesis of DHT that appears to be preferentially activated in prostate cancer cell lines and freshly collected CRPC patient tissue (16, 54–56). Although most studies to date suggest that testosterone concentrations are higher than DHT in CRPC, this could be explained by inefficient testosterone 5α-reduction by SRD5A1, leading to its accumulation. (4, 16, 57). Furthermore, studies of intratumoral androgens disproportionately sample the interstitial space and cellular cytoplasm, and DHT concentrations are enriched in the cellular nucleus, which is where most of the AR protein resides in the presence of an agonist (58). Combinations of a 5α-reductase inhibitor with 17,20-lyase inhibition would prevent 5α-reduction of 17OHP and could prevent the accumulation of “backdoor pathway” steroids upstream of CYP17A1 (27). A phase II study is evaluating the addition of dutasteride to abiraterone acetate in metastatic CRPC and studying levels of testosterone and DHT at baseline and at progression (NCT01393730). Dutasteride is preferred to finasteride, as the latter is relatively specific for the type 2 enzyme, whereas dutasteride inhibits all three isoforms (17). 17β-HSDs play an important role by catalyzing the reduction of 19-carbon-17-ketosteroids to their corresponding 17β-hydroxy forms, as well as the reverse reaction (oxidation). To date, 14 different 17β-HSD genes and cognate isoenzymes have been identified; consequently, specific inhibition of one isoform could be bypassed if other 17β-HSDs are also expressed. For example, inhibition of 17β-HSD3 would not prevent DHT synthesis due to SRD5A-mediated conversion of androstenedione to 5α-androstandione, followed by 17β-HSD5-mediated conversion to DHT (Fig. 1). Similarly, inhibition of 17βHSD5 could be bypassed by the 5α-androstenedione pathway. Inhibition of 3βHSD could effectively block the conventional pathway at the less active metabolite DHEA, but 3βHSD inhibitors developed to date show unfavorable properties such as AR agonism (59). Interestingly, abiraterone also inhibits 3βHSD1 and 3βHSD2 in vitro (albeit less potently than CYP17A1) and could therefore prevent conversion to active androgens of any DHEA that leaks through abiraterone’s block of 17,20-lyase (60). Steroid sulfatase hydrolyzes steroid sulfates, such as estrone sulfate and DHEA-S, to their unconjugated, biologically active forms, estrone and DHEA. The first trial with a first-generation single-agent steroid sulfatase inhibitor (SXT64, 667 COUMATE) in postmenopausal women with locally advanced or metastatic breast cancer confirmed inhibition of sulfatase that was associated with reductions in serum Δ5-androstenediol, androstenedione, and testosterone (61). Second- and third-generation steroid sulfatase inhibitors have now been developed (62). Inhibiting sulfatase activity in combination with abiraterone in men with prostate cancer could reduce the production of AR-activating androgens from DHEA-S, which would be particularly relevant in select patients for whom DHEA-S rises on abiraterone treatment.

Increasing drug exposure of abiraterone could reverse resistance through more potent CYP17A1 (and 3βHSD) inhibition and increasing AR antagonism. This strategy could potentially be achieved by exploiting increased absorption of abiraterone in the presence of a high-fat meal. To date, antitumor activity data are not available from randomized trials of different abiraterone doses. The hypothesis that reactivation of AR signaling by residual low levels of androgens, reactivation of steroid biosynthesis, or alternative ligands (including administered glucocorticoids) supports the combination of an antiandrogen with a CYP17A1 inhibitor. Moreover, this combination would prevent a rise in androgens that could occur on treatment with an antiandrogen: As testosterone and DHT have a higher affinity for the AR than enzalutamide and other antiandrogens developed to date, out-competing the antiandrogen by natural ligand could reverse AR inhibition. A phase I/II safety evaluation of enzalutamide (MDV3100; Medivation) in combination with abiraterone acetate and prednisone in CRPC with bone metastases is currently ongoing (NCT01650194). Finally, inhibition of steroid biosynthesis merits evaluation in early-stage prostate cancer when greater efficacy and increased cure rates could be achieved. The STAMPEDE study (NCT00268476) is
currently comparing abiraterone with androgen deprivation therapy (ADT) to ADT alone in high-risk M0 or newly diagnosed patients with M1.

Disclosure of Potential Conflicts of Interest

N. Sharifi has a commercial research grant from Janssen and is a consultant/advisory board member of Medivation and Janssen. R.J. Auchus is consultant/advisory board member of Janssen Pharmaceuticals, Viamet Pharmaceuticals, Tokai Pharmaceuticals, and BioMarin Pharmaceuticals. G. Attard has commercial research grants from AstaZeneca and Genentech; has received honoraria speakers' fees and travel support from Janssen, Sanofi-Aventis, Ipsen, Takeda, and Roche/Ventana; has ownership interest (including patents) in Abiraterone; and is a consultant/advisory board member of Janssen, Astellas, Veridex, Novartis, and Millennium. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Attard

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