Targeting Continued Androgen Receptor Signaling in Prostate Cancer

Christophe Massard and Karim Fizazi

Abstract
Prostate cancer is the most common cancer and the second leading cause of death from cancer in males in most Western countries. Prostate cancer has an exquisite sensitivity to androgen deprivation therapy and is the most endocrine-sensitive solid neoplasm, although advanced disease eventually progresses to castration-resistant prostate cancer (CRPC). Recent evidence has shown that cancer progression at the CRPC stage is often mediated by androgen receptor signaling, so that subsequent androgen receptor targeting may further contribute to disease control and, eventually, survival improvement. Abiraterone acetate, an androgen biosynthesis inhibitor, was tested in patients with CRPC pretreated with docetaxel in a phase III trial with demonstration of an overall survival benefit, confirming that CRPC remains hormone driven, even in advanced stages of the disease. Several novel agents also targeting androgen receptor signaling are currently being evaluated, including MDV3100 and orteronel (TAK-700). With the availability of newer endocrine treatments and also nonendocrine treatments (e.g., chemotherapy, immunotherapy, and bone-targeting agents), data supporting a more rational use of therapeutic agents are urgently required in patients with CRPC. It is likely that molecular characterization of prostate cancer will lead to the identification of different subsets of prostate cancer disease with a different natural history, sensitivity, and resistance to treatment; efforts to develop, validate, and implement predictive biomarkers in clinical trials and eventually in routine care should now be strongly supported.

Introduction
Prostate cancer is the most common malignancy in Western countries and the second leading cause of cancer-related deaths in males (1–3). Although advanced disease is initially sensitive to androgen deprivation therapy (ADT), most deaths occur following progression toward castration-resistant prostate cancer (CRPC), which is currently incurable, and metastatic dissemination and resistance to ADT (4, 5). Further, the development of novel therapies has been limited because of poor understanding of the molecular mechanisms of resistance to ADT (6). Until recently, only docetaxel-based chemotherapy had been shown to modestly improve survival, marking the first real advance after the identification of therapeutic castration by Charles Huggins in 1941 (Fig. 1; refs. 7–10).

An increased understanding of the biology of advanced prostate cancer (11) has led to the development of drugs targeting angiogenesis (bevacizumab and VEGF-Trap); agents targeting molecules involved in the onset of bone metastases, such as endothelin-1 receptor A (zibotentan); RANK ligand (denosumab; ref. 12); bone-targeting radiopharmaceutical agents (13); immunotherapy (14); and also a new generation of hormonal manipulations. During the last decade, the androgen receptor (AR) axis has also been shown to remain active in both early and late metastatic prostate cancer (15), which justifies the development of drugs that directly or indirectly target this receptor, such as abiraterone (16) and MDV3100 (Fig. 1; ref. 17). This review describes the rationale for AR pathway inhibition and the main drugs under development.

Androgen Receptor Signaling in Prostate Cancer
The AR belongs to the steroid hormone receptor family of ligand-activated nuclear transcription factors. It contains 4 functional regions: an amino terminal regulatory domain (AF-1 site), a DNA-binding domain, a hinge region containing a nuclear localization signal, and a carboxy-terminal ligand-binding domain (AF-2 site). In the absence of ligand binding, AR is bound to HSPs in the cytoplasm; androgen binding leads to dissociation from HSPs, dimerization, phosphorylation, translocation to the nucleus, DNA binding, coactivator recruitment, and the activation of transcription of androgen-regulated genes (Fig. 2).
Classical Strategies Targeting the Androgen Receptor

Because androgens and AR signaling pathways are regarded as the main oncogenic drivers in prostate carcinogenesis, they represent a logical target for prostate cancer treatment. The clinical activity of ADT (via castration) was first reported more than 70 years ago by Huggins and Hodges (18) and remains the mainstay of systemic therapy, whether by orchiectomy, luteinizing hormone-releasing hormone agonists, by blockade of the AR (e.g., flutamide, bicalutamide), or by combinations. Progression while on ADT defines CRPC. Several large phase III studies reported in 2010 showed a significant overall survival benefit with abiraterone, cabazitaxel, and sipuleucel T now being approved. Further novel hormonal manipulations are in development for CRPC patients in both the post-docetaxel (“Post-doc”) setting and predocetaxel (“Pre-doc”) settings, in combination with ADT.

Nonetheless, despite continuous ADT, the disease eventually progresses, usually after a delay of several years (5). Several mechanisms of resistance to ADT are known, including AR amplification, AR hyper-activation without any androgen binding, AR mutation in the AF-2 site, AR activation by steroids or other ligands, and AR activation by tyrosine kinases or other molecules. More recently, several studies have also shown that intracrine androgen synthesis can activate the AR pathway and maintain cancer survival (19). Moreover, recent reports indicated that CRPC cells can also express AR splicing variants without AF-2 sites (20, 21), which could represent a novel mechanism of antiandrogen resistance to castration.

Traditional and empiric use of second-line hormonal therapy in patients with CRPC has been supported by the demonstration of sustained AR expression and intact AR signaling, even as the disease evolves from androgen sensitive to castration resistant (Table 1; ref. 4). Consequently, the use of hormonal therapy can remain effective. One option following disease progression on antiandrogens is to test the “antiandrogen withdrawal syndrome,” which may result in a biological response in 15 to 20% of cases because of these drugs behaving as agonists of the AR, likely as a consequence of AR mutations. The use of therapeutic estrogens can also be considered at this juncture, although thromboembolic toxicity is a significant concern with these agents (22). Finally, targeting the adrenal secretion of
testosterone has previously been achieved by using glucocorticoids or ketoconazole (23). Prednisone showed a similar biological response rate compared with an antiandrogen (flutamide), but increased benefits in terms of pain control and quality of life (24). Ketoconazole, an antifungal agent, which acts through the inhibition of cytochrome P450, is also associated with a PSA response rate of approximately 20 to 40%, when combined with corticosteroids. Unfortunately, a phase III trial testing antiandrogen withdrawal, with or without ketoconazole, was closed early and, therefore, the contribution of this compound to overall survival when combined with corticosteroids remains unknown (23). Originally conceived as a hormonal therapy, but probably acting through microtubule perturbation, estramustine is a nitrogen mustard-estradiol conjugate that improved overall survival in combination with docetaxel when compared with mitoxantrone [hazard ratio (HR) = 0.77 (95% confidence interval, 0.63–0.93), P = 0.02; ref. 23]. The routine use of estramustine, however, is limited by its toxicity, including a risk of thrombo-embolism.

### Table 1. Prostate cancer biology and androgen receptor–signaling targeted drugs

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NOTE. As discussed above, an incomplete response to ADT and subsequent disease progression might be mediated by continued AR signaling. Different approaches can target continued AR signaling and are being investigated in clinical trials.

Figure 2. AR signaling pathway. Androgens are produced in testes, regulated by the levels of luteinizing hormone–releasing hormone (LHRH) produced by the pituitary gland, under the regulation of GnRH produced by the hypothalamus gland. The androgens are also produced by the adrenal glands and, secondarily, in peripheral tissues including the prostate. In tumor cells, testosterone is converted to dihydrotestosterone (DHT), which is the more potent androgen metabolite. DHT, but also other androgens and steroids, bind to the AR, a nuclear hormone receptor, which is able to bind to androgen response elements (ARE), present in the regulatory regions of different genes involved in the growth, survival, and differentiation of prostate cells and prostate cancer cells. The development of hormonal manipulations in prostate cancer is based on the endocrine regulation of androgens: surgical or chemical castration; inhibition of steroidogenic enzymes; and AR inhibition.

Targeting the Androgen Receptor Axis with New Molecules in Castration-Resistant Prostate Cancer

### Inhibition of steroidogenic pathways

Several enzymes, such as CYP17, can be targeted to inhibit adrenal and intracrine steroid synthesis (Fig. 3).

#### Abiraterone acetate

Abiraterone acetate (CB 7630) is an irreversible inhibitor of cytochrome P450–17 (CYP17), with 17α-hydroxylase
and C17,20-lyase inhibitory properties (25). Because CYP17 is a key enzyme in the production of androgens and estrogens in the adrenal glands and tumor tissue (26–28), abiraterone inhibits both adrenal androgen and intratumoral androgen synthesis. However, because of the upstream inhibition of 17α-hydroxylase, the levels of serum cortisol decrease, which can result in positive feedback on adrenocorticotropic hormone (ACTH) and a risk of hypokalemia and hypertension, which can be circumvented by the concomitant administration of dexamethasone or prednisone.

Figure 3. Adrenal and steroidogenic synthesis pathway. Although castration removes gonadal testosterone in prostate cancer, androgens originate from other sources, including the adrenal gland and the prostate cancer cells themselves (de novo autocrine synthesis or transformation of “weak” androgens previously synthesized by the adrenals). In CRPC patients, adrenal gland and prostate cancer metastases are able to synthesize androgens de novo, with different key enzymes (CYP17A1, HSD3B2, HSD3B1, AKR1C3, and HSD167B3, etc.) involved in the sequential biosynthesis of testosterone and dihydrotestosterone (DHT) from cholesterol precursors.

A phase I study (COU-AA-001) evaluated the safety of continuous daily administration of abiraterone (250–2,000 mg) without steroid adjunction in chemotherapy-naïve men (16). No dose-limiting toxicity was observed; the most frequent side effects were related to mineralocorticoid excess, including hypertension, hypokalemia, and lower-limb edema. Antitumor activity was reported at all dose levels; in total, 66% of the patients exhibited a PSA decrease ≥30%, and 38% had a partial response by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. A second phase I study (COU-AA-002; ref. 29) evaluated the safety and tolerability of abiraterone acetate 1,000 mg/d alone (n = 10), or combined with prednisone (n = 37). Declines in PSA, ≥30%, ≥50%, and ≥90%, were observed in 32 (69%), 24 (51%), and 7 (15%) patients, respectively. Among 35 patients evaluable by RECIST, 6 (17%) had a partial response (32). The drug was well tolerated in the postdocetaxel setting with similar toxicities to predocetaxel patients.

An international, multicenter, randomized, phase III, double-blind, placebo-controlled trial was done in 1,195 patients with metastatic CRPC, who had failed docetaxel-based chemotherapy, to compare the efficacy and safety of abiraterone acetate plus prednisone (AP) with those of placebo plus prednisone (PP; ref. 33). The results of the intermediate analysis were recently released, and the median overall survival in the AP group was 450 days versus 332 days in the PP group (P < 0.0001; HR = 0.65). Time to PSA progression, radiographic progression-free survival, and PSA response rate were also significantly improved in the AP arm. Mineralocorticoid-related adverse events were more common in the AP arm: fluid retention was 30.5% versus 22.3%, and hypokalemia was 17.1% versus 8.4%; however, grade 3 to 4 hypokalemia (3.8% versus 0.8%) and grade 3 to 4 hypertension (1.3% versus 0.3%) were infrequent. This trial showed, for the first time, that targeting the AR pathway can prolong overall survival in patients with metastatic CRPC, who have progressed after docetaxel-based chemotherapy; confirming the concept of targeting continued AR signaling. This study formed the
basis of U.S. Food and Drug Administration (FDA) approval of the agent as this article went to press. Another placebo-controlled randomized phase III study in the predocetaxel setting is now closed to accrual, after more than 1,000 patients have been randomized 1:1 for abiraterone acetate plus prednisolone versus prednisolone plus placebo. The results of this second trial are awaited.

Other Drugs

TAK-700 (Orteronel)

TAK-700 is a selective, but less potent, nonsteroidal inhibitor of 17,20-lyase. The selectivity for 17,20-lyase may improve the safety profile as compared with agents that inhibit both steps in the testosterone synthesis process and may, therefore, affect cortisol precursor synthesis. Preclinical studies indicate that TAK-700 has minimal effects on CYP drug-metabolizing enzymes. A recent open-label phase I and II trial was done in CRPC patients (34). In the phase I trial, TAK-700 was given at 5 dose levels [100, 200, 300, 400, and 600 mg twice daily (BID)], and was associated with a favorable safety profile, the most common side effects including gastrointestinal toxicities and grade 3 fatigue. Preliminary pharmacokinetic results indicated dose-proportional Cmax and area under the curve increases with single and multiple doses over the 100 to 600 mg BID dosage. Pharmacodynamic studies showed androgen synthesis suppression, with reductions in testosterone and DHEA-S (35). In a phase II study, patients were treated at 3 dose levels (300 mg BID, 400 mg BID, or 600 mg BID, with prednisone 5 mg BID also administered at the latter two dose levels). Preliminary results on the first 57 patients enrolled confirmed a manageable toxicity profile, showing antitumor activity with a PSA decrease in 74% of patients receiving TAK-700 for more than 3 cycles (34). The TAK-700 dose selected for the phase III studies in mCRPC was 400 mg twice daily, with concomitant prednisone 5 mg twice daily. Two large phase III randomized clinical trials are ongoing in both the post- and the predocetaxel settings. Moreover, a phase I and II trial is ongoing to evaluate the safety and efficacy of the combination with docetaxel (http://clinicaltrials.gov/ct2/results?term=NCT01084655).

Other agents in development

HE3235 (17a-ethyl-5a-androstane-3a, 17b-diol) is a synthetic androstenediol analog with shown antitumor activity in preclinical CRPC models. HE3235 decreased AR expression in LNCaP cells in vitro, in CRPC LuCaP 35V xenografts, and blocked intratumoral androgen synthesis in the LuCaP 35V tumors. HE3235 did not inhibit CYP17, but inhibited the conversion of cholest-4-en-3-one to pregnenolone. A clinical phase I and II trial in CRPC men is ongoing, and preliminary results have been presented at the American Society of Clinical Oncology (ASCO) Genitourinary 2010 meeting with a promising antitumor activity ref. 36; http://clinicaltrials.gov/ct2/results?term=NCT00716794).

Androgen Receptor Antagonists

MDV3100

MDV3100 is a novel AR antagonist that binds to the AR more avidly than bicalutamide. Unlike bicalutamide, MDV3100 also inhibits AR function by blocking nuclear translocation and DNA binding and has no agonist activity (37).

In a large multicenter, open-label, dose-escalation phase I and II study done in 140 CRPC patients, treated at doses ranging from 30 to 600 mg/d, the authors reported antitumor activity including PSA declines of >50% or more in 78 patients (56%), response in soft tissue in 13 out of 59 patients (22%), and bone disease stabilization in 61 out of 109 patients (56%: ref. 38; http://clinicaltrials.gov/ct2/results?term=NCT00510718). Circulating tumor cell (CTC) counts were done prospectively: 92% of patients with favorable pretreatment counts (i.e., <5 cells/7.5 mL of blood) maintained favorable post-treatment counts, whereas 49% of patients converted from unfavorable pretreatment (i.e., >5 cells/7.5 mL of blood) to favorable post-treatment counts. At the 600-mg/d doses, 2 of 3 subjects had dose-limiting toxicities (seizure and rash, respectively). Fatigue was the most frequently reported adverse event, with grade 3 fatigue occurring in 9%, 15%, and 20% of patients treated at the 240, 360, and 480 mg/d dose groups, respectively. The dose of 240 mg/d was defined as the maximum tolerated dose.

A large, phase III, randomized, double-blind, placebo-controlled study was done to determine the benefit in overall survival of MDV3100 as compared with placebo in patients with progressive CRPC, previously treated with docetaxel-based chemotherapy. More than 1,100 patients were enrolled and randomized 2:1 (MDV3100 versus placebo); the accrual was completed in 2010, and the results are awaited. Another phase III study done in chemotherapy-naive patients has recently commenced accrual. This study will enroll patients with progressive metastatic cancer that has progressed despite ADT, but has not been previously treated with cytotoxic chemotherapy (http://clinicaltrials.gov/ct2/results?term=NCT01212991).

Other Drugs

Other potent antagonists of human AR with affinity to AR superior to that of bicalutamide are in development in phase I and II trials in CRPC patients. For example, ARN-509 is an AR antagonist that inhibits nuclear translocation and DNA binding of the receptor, thereby modulating expression of genes that drive prostate cancer growth. This drug is currently under investigation in a phase I and II study (http://clinicaltrials.gov/ct2/results?term=NCT01171898). BMS-641988, another AR antagonist, showed increased potency relative to bicalutamide in both in vitro and in vivo prostate cancer models, in particular, the resistant model to bicalutamide (39). However, its development was stopped after a first phase I study showed neurologic toxicity and poor efficacy ref. 40; http://clinicaltrials.gov/ct2/results?term=NCT00326586). A new compound
(EPI-001) targets the AF-1 region and inhibits transactivation of the amino-terminal domain of the AR, without interacting with the ligand-binding domain. This agent has the potential to be effective against the constitutively active AR splice variant lacking the ligand binding domain, which has been reported as a putative cause of castration resistance (41). Finally, many other drugs targeting the AR pathway are currently in early clinical development, including CYP17 inhibitors (TOK-001), AR antagonists (ODM-201), drugs aiming to annihilate AR production (SARA or ZD 3514), 17βHSD5 inhibitor (ASP9521), and steroid sulphatase inhibitors (irosustat).

**Perspectives: From Androgen Receptor Inhibition to Personalized Medicine**

Several issues have significantly limited the development of new active treatments (including atrasentan, satraplatin, DN 101, oblimersen, and GVAX) in metastatic prostate cancer, leading to a series of negative randomized trials (11). First of all, response to treatment is notoriously difficult to assess: metastatic prostate cancer does not usually generate radiologically measurable lesions, and measuring changes in existing lesions on bone scans is highly unreliable. Secondly, European and American agencies have sought a proven benefit in overall survival for drug approval, and there is a lack of reliable surrogates for long-term outcome and clinical benefit. Thirdly, the correlation between PSA changes and long-term outcome is controversial, and PSA progression does not qualify as a surrogate for overall survival (5). In the absence of any other potential outcome measures, these issues have led to the development of a consensus guideline for the restricted use of PSA as an endpoint in clinical trials (17). Finally, and probably most importantly, metastatic prostate cancer is currently still treated as a “single disease,” in contrast to other common cancers, although there is evidence of considerable heterogeneity in outcome and sensitivity to anti-prostate cancer therapies. In contrast, the other 3 most frequent cancers in Western countries have all been subclassified on the basis of molecular features [e.g., estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and BRCA-1 in breast cancer; epidermal growth factor receptor (EGFR) in non–small cell lung cancer; and K-ras in colorectal cancer], leading to successful drug development in specific subgroups (42).

As discussed by Attard and de Bono, increased knowledge in prostate cancer biology has led to the identification of a number of molecular alterations, some of which are promising potential targets (43). Prostate cancer shows great molecular heterogeneity, in which several pathways are simultaneously active, leading to tumorigenesis. Several molecular alterations have recently been discovered that affect cell proliferation and homeostasis, such as alterations in angiogenesis, signal transduction, apoptosis, immortality, and invasion. The discovery of recurrent gene fusions in prostate cancers has important clinical and biological implications (44). The fusion of TMPRSS2 and ETS genes was reported by Tomlins and colleagues (45) as the first recurrent genomic alteration in prostate cancer and has now been confirmed by multiple independent groups. The genes involved are the androgen-regulated gene TMPRSS2 and the ETS transcription factor family members, ERG, ETV1, or ETV4. TMPRSS2-ERG fusions are the most predominant molecular subtype, because they have been identified in approximately 40 to 80% of prostate cancers. The detection of the translocation of TMPRSS2 to the ERG gene in prostate cancer tissue could be used as a biomarker in clinical drug development. Moreover, various molecular abnormalities in the AR pathway lead to resistance to castration. AR gene amplification has been reported in 25 to 30% of patients with CRPC, but is present at very low rates (1–2%) in those with primary prostate cancer, indicating that AR amplification is involved in the development of CRPC. AR gene amplification is associated with increased mRNA expression and augmented levels of AR protein. Point mutations in the AR can result in altered ligand specificity, such that mutated ARs can be activated by nonandrogenic ligands such as antiandrogens (46). Another pathway with a prominent role in prostate cancer is the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway, with upregulated signaling found in 30 to 50% of prostate cancers, often through loss of PTEN. Molecular changes in the PI3K/Akt/mTOR signaling pathway have been shown to differentiate benign from malignant prostatic epithelium and are associated with a higher tumor stage, grade, and risk of biochemical recurrence (47).

Ultimately, molecular characterization of prostate cancer will lead to the identification of different molecular alterations (such as TMPRSS2-ERG, loss of PTEN, and activation of AR signaling pathways), and probably subsets of prostate cancer disease with a different natural history, sensitivity, and resistance to treatment. In the future, clinical trials in the adjuvant and metastatic settings will likely need to consider the stratification of patients by molecular subtype.

The detection of CTCs in cancer patients could be useful in determining and monitoring systemic therapies (48, 49). Recent interesting results have been obtained with the CellSearch system, a semiautomated fluorescent-based microscopy system reviewed in this Focus by Danila and colleagues (50). This technology allows robust and reproducible detection of a few CTCs (as few as 1 CTC in 7.5 mL of blood). Several studies in breast cancer, colon cancer, and prostate cancer have suggested that CTCs may even be superior to radiologic evaluation in predicting response to treatment and survival (51–53). Currently the CellSearch system is the only one to have obtained FDA approval for the detection of CTCs in the metastatic setting. However, several studies have shown limitations of this technology, and others are in development (54, 55). An alternative method for CTC analysis uses filters with pores that retain large tumor cells, but not smaller blood cells (ISET). CellSearch technology and other technologies may allow the molecular characterization of CTCs using immunofluorescence for protein expression and FISH for DNA amplification. These techniques have been used to...
sequence the AR and to detect TMPRSS2/ETS gene translocations in CTCs (56, 57). Investigating CTCs for biomarker studies seems very attractive, in order to guide treatment decision-making with the aim of achieving better personalized treatment. Otherwise, the molecular characterization of CTCs remains challenging in daily clinical practice, and only few research groups are able to do a molecular characterization of CTCs. So far, only a few studies have compared the molecular characterization of CTCs and tumor tissue in the same patients. The challenge of the coming years will also be to collect tumor tissue from metastases in CRPC patients to define molecular targets.

In conclusion, recent evidence has shown that progression in prostate cancer is often mediated by AR signaling, so that subsequent AR targeting after initial testosterone suppression therapy may further contribute to disease control and, eventually, survival improvement. Abiraterone acetate, an androgen biosynthesis inhibitor, was tested in patients with CRPC pretreated with docetaxel in a phase III trial, which has shown an overall survival benefit that has led to this drug’s recent FDA approval.

These data confirm that CRPC remains hormone driven, even in advanced stages of the disease. Several novel agents targeting continued AR signaling are currently being evaluated, including MDV3100, orteronel (TAK-700), and other agents in earlier phases of development. Studies are ongoing to identify potential predictors of response or resistance to AR-signaling targeting agents. In the future, tumor samples (initial prostate cancer, biopsy of a metastatic lesion, molecular characterization of CTCs) should allow the identification of various molecular alterations predictive for sensitivity to subsequent hormone manipulations (abiraterone or MDV3100), to taxane-based chemotherapy (docetaxel or cabazitaxel), and nonendocrine, nonchemotherapy agents, including immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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