CLINICAL INVESTIGATION

Challenges in overcoming hormonal resistance in prostate cancer

The treatment landscape for prostate cancer has changed remarkably in the last few years, with several US FDA-approved drugs and a promising pipeline of new agents. The current paradigm of treatment for advanced prostate tumors, which are androgen dependent, is hormone ablation therapy. This can be achieved chemically through LHRH agonists or antagonists, or surgically through orchiectomy. Most tumors respond favorably to this treatment, but eventually the tumor develops a more aggressive castration resistant phenotype. This review will help the reader gain a better understanding of the current paradigm for treatment, efforts to overcome resistance, and the strategies for future development of targeted agents.

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Prostate cancer is the most common non-cutaneous cancer in men in the USA, with an estimated 238,590 men diagnosed and 29,720 men dying of their disease in 2013 [1]. This disease depends upon androgens to proliferate and to activate the androgen receptor (AR). While hormonal suppression has shown efficacy in this disease, the responses are not durable and it is increasingly critical to understand why.

The use of androgen-deprivation therapy (ADT) for prostate cancer has been the mainstay of treatment since its conception over 70 years ago. In 1939 Gutman and Gutman showed that in Rhesus monkeys prepubertal 'acid' and 'alkaline' phosphatase were negligible, and that after testosterone injection the acid phosphatase activity increased [2]. Two years later Huggins and Hodges found that by eliminating androgens through castration or neutralization of their activity by estrogen injection, one could treat disseminated prostate carcinoma [3]. In fact, they found healing pathological fractures following orchiectomy in one of their patients as well as improvement in symptoms [4].

The use of diethylstilbestrol (DES), which inhibits LHRH from the hypothalamus, had unfortunate cardiovascular side effects at moderate-to-high doses [5]. LHRH agonists were much better tolerated and the initial concurrent use of anti-androgen blocked the potential for a tumor flare [6]. Approximately 85% of prostate cancers will have an initial favorable response to hormone therapy [7]. Over time, molecular and cellular changes that allow prostate cancer cells to grow despite low serum testosterone will result in castration-resistant prostate cancer (CRPC), which is universally lethal in metastatic patients. Of the five recently approved agents in CRPC, two focus on ways to suppress either androgen production or AR binding.

Current therapeutic landscape
Hormonal agents are often combined with other therapeutics, both in clinical trials and in practice. Initial treatment for localized or locally advanced

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disease is often radical prostatectomy or radiation therapy sometimes combined with ADT (Figure 1) [8–12]. Biochemical recurrence is often the first sign of recurrent disease. Approximately 30–40% of men who undergo treatment with curative intent will have a PSA recurrence [13,14]. Following a radical prostatectomy, this is defined as a PSA of >0.2 ng/ml and following radiotherapy, biochemical recurrence is generally the nadir + 2 ng/ml [15,16].

ADT in the case of relapse following radical prostatectomy (RP) or radiotherapy can often be delayed until the onset of metastases. However, many men will commence ADT simply for a rising PSA, despite the lack of meaningful evidence. Clinical parameters such as PSA doubling time, pathological Gleason score, and time from surgery to biochemical recurrence can help risk stratify patients for prostate cancer-specific mortality following biochemical recurrence after RP [13]. Identifying patients with a higher risk of prostate-cancer specific mortality allows for enrollment in early aggressive treatment trials.

Patients without metastatic disease whose PSA rises on ADT have nonmetastatic castration resistant prostate cancer. A third of these patients will develop metastases within 2 years [14]. The two main risk factors for metastases are a high PSA and a rapidly rising PSA [17]. Many will respond to second-line endocrine therapy options such as the addition of an antiandrogen, antiandrogen withdrawal, estrogen, ketoconazole or steroids. It should be noted that there is no data showing overall survival (OS) benefit, cancer-specific survival, or progression-free survival from these secondary endocrine therapies.

For patients who have metastatic disease at diagnosis and are hormone naive, the standard treatment options are immediate castration using a LHRH agonist, LHRH antagonist, or bilateral orchiectomy. An anti-androgen should be used for the first 3–4 weeks if an LHRH agonist is chosen to prevent a testosterone flare. Given the US Preventive Services Task Force recommendations against prostate cancer screening by PSA, it is possible that the number of patients who present with metastatic disease will increase in the next decade [18].

◼ Therapeutic cancer vaccines

The goal of therapeutic cancer vaccines is to generate a targeted immune response leading to immune-mediated antitumor activity. Sipuleucel-T, an autologous active cellular immunotherapy, was US FDA approved in 2010 for patients with asymptomatic or minimally symptomatic mCRPC based on a 4.1 month improvement in median overall survival, 25.8 months versus 21.7 months [11]. While this particular drug has not been prospectively combined with other therapies traditionally, the combination of androgen ablation and vaccination has been studied in animal models. In general, these studies have shown that castration reverses tumor-specific T-cell tolerance, suggesting the possibility of an additive or synergistic effect in patients [19,20]. Preliminary data from a randomized Phase II trial presented at ASCO evaluating the optimal sequencing of sipuleucel-T and ADT suggests that in men with biochemically recurrent prostate cancer, sipuleucel-T results in a similar prime-boost pattern of immune activation and antigen-specific cellular and humoral responses independent of the sequencing with ADT [21].

A therapeutic cancer vaccine, PROSTVAC-V/F, which was developed at the National Cancer Institute (NCI), is currently in Phase III testing alone or in combination with GM-CSF in patients with minimal to no symptoms with mCRPC. This vaccine was also studied at the NCI in patients with nonmetastatic CRPC, with patients randomized to receive either the vaccine or nilutamide
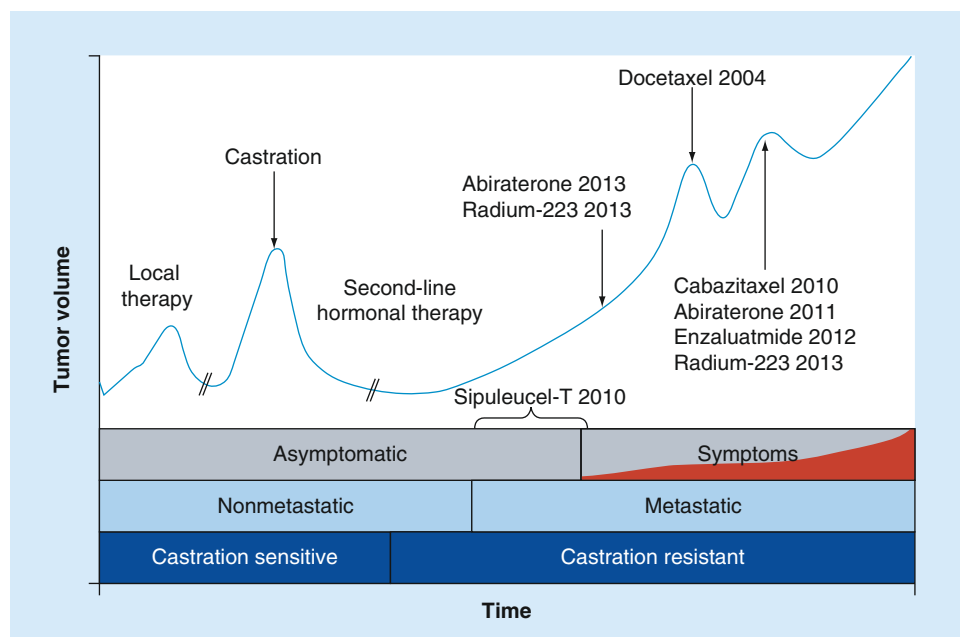

Figure 1. The current landscape of US FDA approved therapies for prostate cancer, moving from a castration-sensitive to -resistant state.

first. Patients in either arm who had a rising PSA without radiographic evidence of metastasis could then cross over to receive the combined therapies. The median survival exhibited a trend towards improved overall survival in patients randomized to receive the vaccine first, suggesting patients who receive vaccine before second line hormonal therapy may potentially result in improved overall survival [22].

Therapeutic cancer vaccines as monotherapy have demonstrated clear benefit in selected patients, possibly by the ability to initiate a dynamic process of host immune responses that can be exploited in further therapies [23]. The combination approach of vaccine with novel antiandrogens such as enzalutamide could lead to even greater successes. PROSTVAC- F/TRICOM is currently undergoing testing in combination with enzalutamide versus enzalutamide alone for patients with non-metastatic castration sensitive prostate cancer, as well as in the minimally symptomatic mCRPC population.

■ Chemotherapy

Docetaxel and cabizataxel are the only chemotherapeutic options that have been shown to improve survival in mCRPC. Mitoxantrone in combination with prednisone was approved for improving quality of life but not survival. The TAX 327 study compared three arms: docetaxel weekly, docetaxel every three weeks, or mitoxantrone alone. The median overall survival was higher for the group that received docetaxel every 3 weeks than for the mitoxantrone group, but not for the group that received weekly docetaxel. This 18.9-month median survival versus 16.5 months in the mitoxantrone arm alone led to the approval of this microtubule-stabilizing agent [24]. Cabizataxel, a novel tubulin-binding taxane drug, has antitumor activity in docetaxel-resistant cancers. When compared with mitoxantrone post-docetaxel, patients who were treated on the cabizataxel arm had a median overall survival of 15.1 months as opposed to 12.7 months in the mitoxantrone arm [12].

Earlier trials with docetaxel in combination with second-generation antihormonal agents such as ketoconazole have shown promising results, but the dose of ketoconazole required was quite high [25,26]. Newer antiandrogen therapies such as enzalutamide could be both efficacious and better tolerated. In fact, preliminary results from a Phase I study evaluating docetaxel in combination with enzalutamide found that enzalutamide did not affect tolerability of docetaxel or have a clinically meaningful impact on docetaxel pharmacokinetics [27]. It will be interesting to see if the newer hormonal agents when combined with chemotherapeutic agents will lead to a meaningful clinical benefit.

■ Bone-targeting therapy

The most recent FDA approved agent is Radium-223, an α-emitter that selectively targets bone metastases with α-particles. Given that more than 90% of patients with mCRPC have radiological evidence of bone metastases, and current bone-targeting agents such as bisphosphonates or denosumab do not improve survival, there was clearly an unmet clinical need. Patients with advanced disease frequently have significant pain, disability and quality of life issues due to these metastases. Radium-223 is a bone-seeking calcium mimetic that binds to newly formed bone stroma particularly within the microenvironment of osteoblastic or sclerotic metastases. It is relatively well tolerated and was found to have an improved overall survival at 14.9 months versus 11.3 months in the placebo arm.

It is important to note that patients with visceral metastases, occurring in up to 25% of CRPC patients, were excluded [12]. All patients also received best standard of care, which included local external beam radiation therapy, glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine. In clinical practice, this will likely be combined with another standard option with minimal toxicity, such as enzalutamide or abiraterone. Currently, a Phase I–II trial of Radium-223 in combination with docetaxel is underway [8].

Recent FDA approvals
■ Abiraterone acetate

Abiraterone acetate, a pregnenolone analog, is a small molecule that irreversibly inhibits CYP17, a rate-limiting enzyme in androgen biosynthesis, to block residual androgen synthesis in the adrenal gland and tumor cells. Although the testes are the primary source of testosterone, it can also be produced from the peripheral conversion of adrenal sex hormone precursors dehydroepiandrosterone (DHEA) and androstenedione (AD) in the prostate and other tissues [28]. CYP17 plays a key role in testosterone biosynthesis, functioning in the conversion of pregnenolone to 17-α-hydroxypregnenolone (via a 17-α-hydroxylase), and in the subsequent conversion of this moiety to DHEA via a 17, 20-lyase [29].

Abiraterone has been FDA approved for use pre- and post-chemotherapy based on two large Phase III trials. COU-AA-301 found that treatment with abiraterone in patients post-chemotherapy resulted in a statistically significant overall survival improvement from 10.9 months to 14.8 months [10]. The Phase III mCRPC trial in pre-chemotherapy patients, COU-AA-302, was stopped early after an interim analysis found that there was an improved radiographic progression-free survival and a strong

trend towards OS in the abiraterone arm, resulting in unblinding of the study and allowing crossover to the abiraterone arm [30].

■ Enzalutamide

The recent FDA approved agent focused on AR signaling, enzalutamide, is a second-generation antiandrogen. This drug binds to the AR with higher affinity than standard androgen receptor antagonists (ARA) and prevents ligand-dependent activation and receptor translocation to the nucleus without agnostic activity [31,32]. It prevents the downstream effects including nuclear translocation, DNA binding and signaling to coactivators [33]. Enzalutamide is currently FDA approved for the treatment of mCRPC patients who have progressed on chemotherapy based on an overall survival of 18.4 months as compared with 13.6 months for placebo [9]. The trial for chemotherapy-naive patients is complete, with expected results in the next few months.

Unfortunately, like all other treatment for CRPC, the success of enzalutamide is not durable. Compounded by this is the fact that when using these agents sequentially, the benefit is not as great. Through BC Cancer Agency, Cross Center Institute and Duke Cancer Registries, men with mCRPC who had progressed on enzalutamide and then received abiraterone were retrospectively identified. Median progression-free survival was only 15.4 weeks in patients treated with abiraterone post-enzalutamide. Of the 21 patients evaluable for response, only three patients (14%) had a 30% PSA decline [34]. In comparison, the COU-AA-301 study, which evaluated men on abiraterone who were also treated with prior docetaxel, showed a 22.4-week progression-free survival and a 38% PSA response rate. PSA response rate was in fact slightly more strigent, defined as ≥50% PSA decline [10].

AR & mechanisms of resistance

The AR is a member of the supergene family of ligand responsive transcriptional regulators, involved in the regulation of prostate growth, muscle and bone mass, and spermatogenesis in males. Androgens such as testosterone and 5 α-dihydrotestosterone mediate their actions via binding to intracellular receptor proteins that belong to a family of ligand-responsive transcription factors, including receptors for different classes of steroid hormones, multiple receptor species of thyroid hormones and retinoic acids, and the receptor for vitamin D [35]. In the absence of ligand, steroid receptors are maintained in an inactive state, complexed to heat shock proteins and/or corepressors. After ligand binding occurs, there is resultant dissociation of the receptor from the inactive complex and subsequent

translocation to the nucleus where it binds as either a homo- or heterodimer to specific elements in the promoter and/or enhancer regions of the responsive genes to up- or down-regulate their transcription [36].

Several groups have reported cloning and sequencing the androgen receptor cDNAs. AR mRNA is 10 kilobases in length and encodes a 110,000-dalton protein that contains 919 amino acid residues [35,37]. The AR structure consists of a variable amino-terminal activation function domain (NTD), a highly conserved DNA-binding domain (DBD), a hinge region including the nuclear localization signal (H), a C-terminal ligand-binding domain (LBD) consisting of a 12 helical structure that surrounds a ligand binding pocket (LBP), a second activation function domain (AF-2) located at the carboxy terminal end of the LBD, and a secondary binding function domain (BF-3) located on the surface of the AR controlling the allosteric modulation of the AF-2 (Figure 2) [38,39]. It becomes increasingly important to understand the structure of the AR as well as possible mutations in order to understand possible targets for treatments. The postulated mechanisms to explain resistance to hormonal therapies are separated into three main categories [40]. They often apply not only to resistance of standard anti-androgen therapies, but also to the newer therapies such as enzalutamide and abiraterone.

■ DNA-based alterations

The complex process of androgens interacting with the receptor ultimately resulting in transcriptional activation involves an integrated sequence of molecular events. A single mutation in an essential part of the ligand binding domain of the AR could lead to a decrease in steroid binding specificity and reverses the effects of commonly used antiandrogens [41,42]. AR amplification or mutation occurs in 20–30% of CRPCs [43,44]. As early as the mid-1990s, it was found that a number of mutations in the hormone-binding domain could alter the specificity of the AR [44]. By studying structure-activity relationships for nonsteroidal AR ligands through crystallography and site-directed mutagenesis, the mechanism by which nonsteroidal ligands interact with the wild-type AR was demonstrated [45]. Mutations in the hormone-binding site of the AR (including T877A and W741L/C) will convert first-generation antiandrogens such as hydroxyflutamide and bicalutamide from antagonists to agonists [45,46].

■ Active AR signaling

The majority of patients do not have *AR* mutations or amplification, but do retain active androgen receptor signaling (Figure 3) [40]. Mitogen-activated protein kinase signaling regulates AR function in part by

activating the AR in the absence of ligand or sensitizing the AR to reduced levels of ligand [47,48]. This may be mediated by oncogenes such as ERBB2 or HRAS. The AR is regulated either directly or indirectly by phosphorylation, and studies have been done investigating the stimulatory effects of growth factors on AR-mediated transcription.

In the late 1990s studies of differential gene expression between androgen-dependent and androgen-independent sublines demonstrated a consistent increase in HER-2/neu protein levels in association with progression to androgen-independence in the LAPC-4 line. Through forced expression of HER-2/neu in androgen-dependent prostate cancer, researchers were able to confer androgen-independent growth *in vitro* and accelerate progression to androgen-independence in animal models. This demonstrated cross-talk between the HER-2/neu and AR pathways, and a possible insight as to the mechanism of androgen-independent prostate cancer. This forced overexpression of HER-2/neu in androgen dependent prostate cancer cells allowed for ligand-independent growth, with HER-2/neu activating the AR pathway in the absence of ligand [47].

Thus, recruitment of non-steroid receptor signal transduction pathways can activate AR in the setting of androgen deprivation. AR can potentially become activated in a ligand-independent manner by IGF-1, EGF and KGF, similar to estrogen and progesterone receptor activation. DU145 cells, a prostate cancer cell line that expresses neither AR or PSA, were cotransfected with an expression vector encoding the AR and chloramphenicol acetyltransferase reporter constructs driven by either a synthetic androgen response element or by the PSA promoter [47]. IGF-1, EGF and KGF were able to stimulate reporter gene expression. Similar studies showed that a PKA activator could activate the AR in the absence of androgen. Several studies in fact show that kinase cascades regulate AR function in part by activating the AR in the absence of ligand or sensitizing the AR to reduced levels of ligand [48].
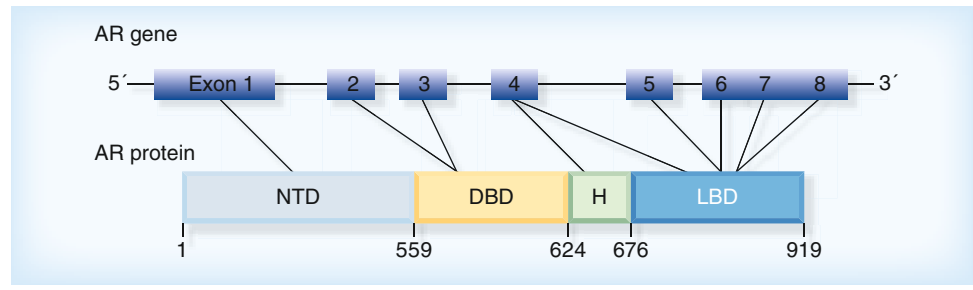

Figure 2. The structure of the androgen receptor, containing eight exons and 919 amino acids. Exon 1 encodes the NTD. Exons 2–3 encode the DBD. The 5´ region of exon 4 forms the H region, which contains the nuclear localization signal. The 3´ region of exon 4 and exons 5–8 encode the LBD.
AR: Androgen receptor; DBD: DNA-binding domain; H: Hinge; LBD: Ligand-binding domain; NTD: Amino-terminal domain.

■ **Alternative signaling pathways**
The third category of hormone resistance mechanisms, the AR bypass hypothesis, suggests that the growth and survival promoting functions of the AR can be bypassed by alternative signaling pathways, and that the AR is no longer relevant to disease progression [40,49]. For example, the apoptosis-suppressing oncoprotein, Bcl-2, has been shown to be uniformly expressed in a number of hormone refractory prostate adenocarcinomas, whereas normal human prostatic secretory cells do not express the Bcl-2 protein [50]. A study to determine the degree to which overexpression of Bcl-2 can protect human prostate cells from apoptotic stimuli *in vitro* and *in vivo* was conducted. LNCaP/Bcl-2 cells were highly resistant to a variety
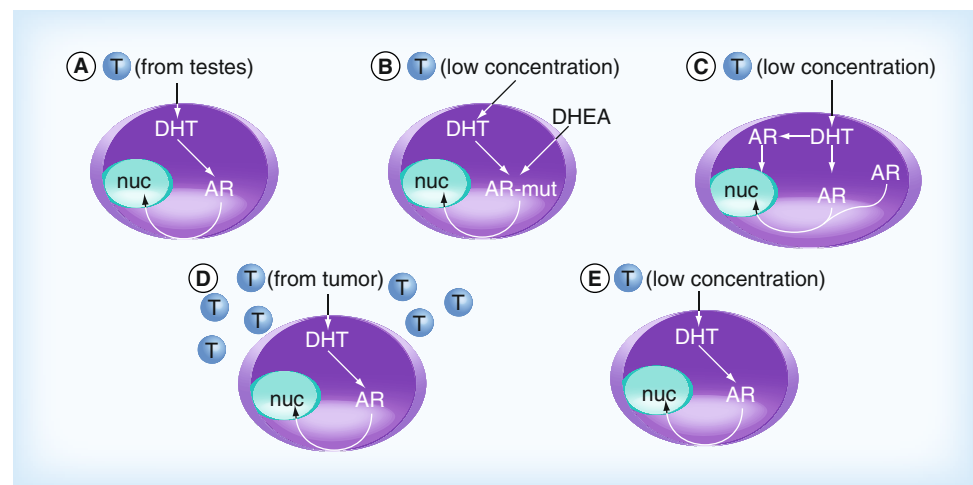

Figure 3: Testosterone-related mechanisms for maintaining androgen receptor signaling during androgen-deprivation therapy. (A) Normal mechanistm, **(B)** AR-mutation confers androgen promiscuity, **(C)** AR overexpression confers hypersensitivity during ADT, **(D)** increased intratumoral AR production and **(E)** testosterone scavanging mechanisms (e.g., through OATP1B3). ADT: Androgen-deprivation therapy; AR: Androgen receptor; DHEA: Dehydroepiandrosterone; DHT: Dihydrotestosterone; mut: Mutated; nuc: Nucleus; T: Testosterone.

of apoptotic stimuli *in vitro*, and the overexpression of Bcl-2 by prostate cells altered their tumorigenic potential such that in a nude mouse assay, subcutaneous injections of LNCaP/Bcl-2 cells resulted in earlier and larger tumor formation as compared with control-transfected LNCaP cells. In fact, when these variant cell lines were injected into castrated male nude mice, only the LNCaP/Bcl-2 transformed cells gave rise to tumors [50].

This bypass hypothesis is consistent with the fact that advanced hormone-independent prostate cancer is characterized by a significant loss of AR expression in 20–30% of tumors. One proposed mechanism of this transcriptional block is methylation of CpG sites in the AR promoter that may reversibly inactivate transcription of the AR [51]. Using detailed methylation analysis, methylation of several consensus sequences in the AR promoter is tightly linked to the loss of AR expression in mCRPC cell lines. No such methylation was demonstrated in normal or primary prostate cancers that express the AR. Thus it is possible that the AR promoter contains specific CpG methylation hot spots that are markers for gene silencing [52].

■ **Enzalutamide resistance**
While enzalutamide, a second-generation antiandrogen targeting the LBD, has superior selectivity as compared with conventional antiandrogens, the efficacy remains time limited. Given that one mechanism of resistance is the mutation of the AR in previous antiandrogens, *Sawyers* prospectively identified AR mutations that may confer resistance to enzalutamide. A report-based mutagenesis screen identified a novel mutation, F876L, which converted enzalutamide into an AR agonist. This is very similar to the mutation that converts flutamide and nilutamide into agonists, AR T877A. Molecular dynamics stimulations performed on the antiandrogen–AR complexes suggested a mechanism by which the F876L substitution caused agonistic rather than antagonistic activity through the repositioning of the coactivator recruiting helix 12 [53]. Currently, a series of chemical modifications to enzalutamide are being performed to convert the agent back to the antagonist form. This agent, DR103, is able to inhibit growth of cells that are enzalutamide resistant [54].

AR splice variants are detected in both normal and malignant human prostate tissue, with highest levels in late-stage disease [55]. AR gene rearrangement promotes the synthesis of constitutively active truncated AR splice variants (AR-V) that lack the AR-ligand binding domain. Cells with AR gene rearrangements expressing both full-length and AR-Vs are androgen independent and enzalutamide resistant [56]. However, through selective knock-down of AR-V expression androgen-independent growth can be inhibited and response to antiandrogens is restored. ARv567es is one such variant that lacks portions of the ligand-binding domain, increasing expression of full-length AR and enhancing transcriptional activity of AR in human prostate cancer cell lines [57].

Another potential mechanism that could in-part drive growth in enzalutamide resistant cellular and xenograft models is upregulation of the glucocorticoid receptor. The data suggests that glucocorticoid associated pathways can activate some AR-drivers of cellular proliferation. *Logothetis* studied 22 patients with mCRPC who had bone marrow biopsies prior to starting enzalutamide as well as 8 weeks after treatment. Worst outcomes were seen in three of 22 patients who had glucocorticoid receptor expression in tumor cells from the marrow. In fact, patients who had upregulated glucocorticoid receptors after 8 weeks of enzalutamide, also had a relatively shorter response to enzalutamide [54].

Abiraterone resistance & novel therapeutics
Mechanisms of resistance to abiraterone are similar to enzalutamide and other antiandrogen therapies, including the induction of steroidogenesis and AR splice variants [58]. The majority of patients who progress on abiraterone have a rise in their PSA, suggesting resumption of the transcription of hormone-regulated genes. In fact, up to 20% of serum androgens in the noncastrate male are nongonadal in origin, and serum androstenedione and DHEA levels in castrate men are similar to noncastrate men and could activate the AR and other steroid receptors [59].

One study evaluating androgen signaling in bone marrow-infiltrating prostate cancer found that 25% of patients (14 of 56 patients) had a primary resistance to abiraterone, as evidenced by low AR nuclear staining on immunohistochemistry and CYP17 lyase less than 10% [60]. They also found low doses of androgen concentration at progression, suggesting that perhaps it is not due to the autocrine production of androgens. The progression on abiraterone despite testosterone depletion leads to the possible conclusion that the mechanisms of resistance are ligand independent [60,61].

While CYP17A1 inhibition with single-agent abiraterone is not associated with adrenal insufficiency due to a compensatory increase in ACTH levels leading to corticosterone levels to maintain the glucocorticoid requirements, corticosterone precursors do lead to mineralocorticoid excess. In order to prevent the side effects of mineralocorticoid excess such as hypokalemia, fluid retention and hypertension, prednisone is coadministered. However, studies have shown that the AR can become activated by very low levels of androgens, steroid metabolites and drugs that bind the AR, such

as the glucocorticoids that are coadministered with abiraterone [10].

TAK-700 (orteronel), inhibits 17,20 lyase activity 5.4-times more potently than the 17-α-hydroxylase activity, but still required concomitant steroids. Unfortunately, the Phase III trial was unblinded after the prespecified interim analysis indicated that the study would not likely meet the primary end point of improved overall survival [101]. A newer agent, VT-464, is also a potent inhibitor of CYP17 lyase, with greater potency for the lyase reaction than the hydrolase reaction, and does not deplete cortisol or cause accumulation of steroids upstream of the hydrolase step [62]. This drug may prove to have superior efficacy and tolerability given the lack of concomitant steroids required.

Conclusion & future perspective

The androgen pathway has been a target of therapy for several decades, with current agents targeting the AR improving survival. One consideration is to move ADT or AR targeted therapy to the adjuvant setting in the hope to improve survival. The ultimate role of enzalutamide in the treatment of prostate cancer may be in earlier stage disease. While we have seen a clear benefit since the introduction of ADT, it isn't without side effects. Patients experience troubling hot flashes, sexual impotence, decreased bone mineral density, fatigue and decreased insulin sensitivity among other things. In patients with a known history of CHF or MI, ADT is associated with a higher mortality in men receiving brachytherapy in all populations, even high risk patients [63].

Bicalutamide monotherapy has been shown to preserve BMD, muscle strength and health-related quality of life in osteoporotic men with non-metastatic locally advanced prostate cancer [64]. It is an alternative to medical castration for men at high risk of fracture; however, less efficacious than ADT [65,66]. Therefore, the potentially equal if not more efficacious alternative, enzalutamide, could change the current paradigm of treatment.

In fact, enzalutamide monotherapy could potentially be used in the adjuvant setting for high-risk prostate cancer. A Phase II study presented at the ASCO 2013 meeting set out to achieve that, and found that in men who would otherwise get ADT, when using enzalutamide monotherapy there was a 99.6% median decrease in PSA at 25 weeks. It was also associated with less metabolic effects than ADT, less of an effect on serum cholesterol and triglycerides, and a higher rate of PSA response. However, the study is still ongoing and the question as to the durability of the response is currently unanswered [67].

Even if enzalutamide is not used in the adjuvant setting, it will likely be used before abiraterone and docetaxel due to its minimal side effects. Unlike abiraterone, enzalutamide does not require daily prednisone. Enzalutamide therapy will thus avoid the potential long-term side effect of prednisone in earlier stage disease, an important consideration for future treatment strategies in this population. In addition, if the glucocorticoid receptor were in fact involved in enzalutamide resistance or in androgen resistance, avoidance of glucocorticoid treatment would be beneficial.

It would be ideal to develop an efficacious drug that blocks intracellular androgens while preserving circulating androgens. The challenge is that when developing treatments to be used in the adjuvant setting, a benefit in overall survival can take up to 10 years. It becomes increasingly important to find a surrogate end point, which the Intermediate Clinical Endpoint of Prostate Cancer Effort is trying to determine when looking at the efficacy of localized prostate cancer therapy [68].

Perhaps then a novel mechanism of action without added toxicity is necessary. The selective androgen receptor downregulation Drug, AZD 3514, was a hopeful and unique mechanism of action inhibited both androgen-dependent and -independent AR signaling. It modulates AR signaling through inhibition of ligand driven nuclear translocation of AR and a downregulation of receptor levels [69]. Unfortunately, the problematic side effects of nausea, vomiting and thrombocytopenia have caused the company to terminate the drug. Although the drug was technically found to be safe, the poor tolerability along with insufficient exposure to downregulate the AR was what led to its ultimate demise [70].

There have been significant advances in our understanding of the molecular and cellular mechanisms that confer resistance in patients with prostate cancer. This is an extremely prolific era in the field, with five recent FDA approved agents and the promise of more targeted therapies to come. With the targeted therapies being used earlier in the disease process, there is a greater potential for cure with fewer side effects. It becomes increasingly important to identify an intermediate clinical end point to expedite development of treatments and provide potentially curative and life-altering therapies to patients.

Executive summary

- Prostate cancer is the most common non-cutaneous cancer in men in the USA, and depends upon androgens to proliferate and to activate the androgen receptor (AR). While hormonal suppression has shown efficacy in this disease, the responses are not durable.
- 30–40% of men who undergo treatment with curative intent will have a PSA recurrence. A third of these patients with non-metastatic castration resistant prostate cancer will develop metastases within 2 years, with high PSA and high PSA velocity being the major risk factors.
- Hormonal therapies usually include a LHRH agonist, antagonist or bilateral orchiectomy, with the use of antiandrogens the first 3–4 weeks of LHRH agonist therapy to prevent testosterone flare.
- Abiraterone acetate and enzalutamide are hormonal therapies developed in the last decade, having shown improvement in survival for men with castration-resistant prostate cancer.
- Sipuleucel-T, an autologous active cellular immunotherapy, is the first US FDA-approved vaccine for the treatment of solid tumors, showing a survival benefit. PROSTVAC-V/F, a therapeutic cancer vaccine developed at the National Cancer Institute, is currently undergoing an international Phase III clinical trial and smaller studies in combination with the antiandrogen enzalutamide.
- Older studies combining docetaxel with the second-generation antihormonal therapy ketoconazole showed promising results. Current testing is underway using docetaxel in combination with enzalutamide.
- There are many potential mechanisms of resistance to newer androgen therapies including DNA-based alterations such as mutations or amplifications, active AR signaling despite castrate levels through pathways that activate the AR in the absence of ligand or sensitizing the AR to reduced levels of ligand, and through alternative signaling pathways.
- It becomes critical to understand these mechanisms of resistance in an effort to overcome it, such as the mutation F876L, which converts enzalutamide into an AR agonist. It can then become possible to develop additional agents to overcome these mechanisms of resistance.
- Newer agents have been developed similar to abiraterone acetate with greater inhibition of the 17,20 lyase activity versus the 17-α-hydroxylase activity, such as TAK700 and VT-464.
- There have been significant advances in our understanding of the molecular and cellular mechanisms that confer resistance in patients with prostate cancer, with an increased need to identify an intermediate clinical end point so that these potentially curative and life-altering therapies may be offered sooner.

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