Androgen Receptor Targeted Treatments of Prostate Cancer: 35 Years of Progress with Antiandrogens

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Purpose: Antiandrogens inhibit the androgen receptor and have an important role in the treatment of prostate cancer. This review provides a historical perspective on the development and clinical benefit of antiandrogens in the treatment of prostate cancer.

Materials and Methods: We searched PubMed® for clinical trials with the search terms antiandrogens and prostate cancer combined with drug names for antiandrogens. This article represents a collaboration of clinical investigators who have made critical scientific contributions leading to the approval of antiandrogens for treating patients with prostate cancer.

Results: Antiandrogens differ in chemical structure and exert varying efficacy and safety profiles. The unfavorable therapeutic index of steroidal antiandrogens led to replacement by safer nonsteroidal agents. Flutamide, nilutamide and bicalutamide, which were designed to target the androgen receptor, were developed primarily for use in combination with castration to provide combined androgen blockade. Modest clinical benefits were observed with the combination of first generation antiandrogens and castration vs castration alone. With increased knowledge of androgen receptor structure and its biological functions a new generation of antiandrogens without agonist activity was designed to provide more potent inhibition of the androgen receptor. Randomized clinical trials in patients with metastatic, castration resistant prostate cancer showed significant survival benefits, which led to the approval of enzalutamide in August 2012. Apalutamide was recently approved while darolutamide is not yet approved in the United States. These next generation antiandrogens are being actively tested in earlier disease states such as nonmetastatic prostate cancer.
Evolving knowledge of resistance mechanisms to androgen receptor targeted treatments will stimulate research and drug discovery for additional compounds. Further testing in nonmetastatic castration resistant prostate cancer as well as castration sensitive disease states will hopefully augment our ability to treat a broader spectrum of patients with prostate cancer.

**Conclusions**: Antiandrogens have already provided important benefits for prostate cancer treatment. Greater knowledge about the structural and functional biology of the androgen receptor in prostate cancer will facilitate further discovery and development of improved antiandrogens with enhanced clinical activity in patients with advanced metastatic disease. Testing these new agents earlier in the course of prostate cancer may further improve the survival and quality of life of patients with current local and/or systemic treatment modalities.

**Key Words**: prostatic neoplasms; androgen antagonists; neoplasm metastasis; receptors, androgen; castration

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**CHANGING ANTIANDROGEN THERAPY STRATEGIES IN PROSTATE CANCER TREATMENT**

HUGGINS and Hodges found that lowering circulating androgen levels by surgical castration or estrogen therapy could palliate symptoms of advanced PC. This finding established the seminal concept that PC is androgen sensitive.\(^1\) Especially in its early stages PC relies on androgens for proliferation\(^2\) and partial ADT by medical or surgical castration alone initially controls the disease, sometimes for many years. However, eventually most PC becomes resistant to ADT and this PC is called CRPC. In the early 1980s after castration significant levels of androgens were shown to exist in PC cells despite a 95% or greater decrease in serum testosterone.\(^3,4\)

CRPC,\(^5\) formerly referred to as hormone refractory or androgen independent disease, is defined as 2 to 3 rising serum PSA concentrations from nadir and/or evidence of radiographic disease progression despite castrate levels of serum testosterone. Responses to secondary hormonal manipulation with agents such as ketoconazole or diethylstilbestrol suggested that the disease was still sensitive to endocrine manipulations. Accordingly the term hormone refractory was replaced by the more biologically accurate term castration resistant. Better understanding of the biology of the AR and resistance mechanisms led to the recognition that androgen signaling remains a significant driver of progression even in the presence of castrate levels of testosterone in the blood.

The AR was first discovered and characterized at 3 laboratories in the late 1960s.\(^6,7,8\) In response to increasing understanding of the importance of the AR in driving PC antiandrogens were developed which would compete with endogenous androgens for the ligand-binding domain of the AR. In this review we describe the clinical development path of the antiandrogens from the beginning phases of the first United States FDA drug approvals to current experience with the newer generation of compounds studied in various clinical disease states (fig. 1).\(^1,3,4,10-17\)

**MATERIALS AND METHODS**

We searched PubMed\(^9\) for clinical trials of antiandrogens in the treatment of PC. Search terms included prostate cancer and antiandrogen combined with the drug name (diethylstilbestrol, cyproterone, megestrol, medroxyprogesterone, flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide [ARN-509] and darolutamide [ODM-201]). The CYP17 inhibitors abiraterone acetate and ketoconazole were not considered as the focus of the current review was antiandrogens. No time restriction was placed on the searches since the aim was to identify pivotal clinical trials offering a historical perspective on the development of antiandrogen therapy. Randomized controlled trials, observational trials and retrospective analyses were considered for study inclusion if in the opinion of the authors they represented a seminal contribution to understanding the role of antiandrogen therapy in the treatment of patients with PC or they indicated a new avenue of research.

**Understanding Current Androgen Receptor Targeted Therapy**

Androgens are critical for the development and regulation of normal prostatic morphology and functions. Androgen signaling is initiated when circulating or locally made androgens bind to ARs in normal or cancerous prostatic cells.\(^3,18,19\) AR is a steroid hormone receptor with ligand binding and DNA binding domains as well as multiple phosphorylation sites.\(^20\) Upon ligand binding the receptor dimerizes, becomes phosphorylated and is translocated from the cytoplasm to the nucleus. There it mediates transcription and activation of various pathways, including those responsible for cellular proliferation and differentiation, and the prevention of cell death (antiapoptotic pathways).\(^20\)

The balance between the rate of cell proliferation and the programmed cell death of prostatic epithelial cells is lost as abnormal AR signaling drives neoplastic cell proliferation and cell survival promotion.\(^20\) Mutations can generate gene fusions to bring together the promoter
sequence of AR responsive genes and the activity of various transcription factors which activate proliferative and cell survival pathways. Withdrawal of androgens or blockade of the AR results in the abrogation of AR mediated signaling and such mechanisms are thought to explain the antineoplastic effect.

The term antiandrogen is used to describe a class of agents which compete with the binding of circulating or locally derived androgens to the AR (fig. 2). Antiandrogens are globally classified as steroidal or nonsteroidal (Appendix 1 and fig. 3). They differ in chemical structure, pharmacological effects and safety profiles (supplementary Appendix 1, http://jurology.com/). Steroidal antiandrogens can lower testosterone levels and also bind to other hormone receptors. Nonsteroidal antiandrogens used as monotherapy tend to raise testosterone levels in intact individuals and are more specific for the AR. Other steroidal antiandrogens are megestrol acetate and diethylstilbestrol for treating advanced PC. Other steroidal antiandrogens are megestrol acetate and medroxyprogesterone acetate. Steroidal antiandrogens have many off target effects, including loss of libido and impotence due to lowering testosterone levels and they have some androgenic activity. These undesirable side effects led to a search for antiandrogens with more selective activity for the AR.

**Nonsteroidal.** Nonsteroidal antiandrogens were developed in the late 1960s and early 1970s, and targeted only the AR without the progestational effects of CPA. As single agents in noncastrated men nonsteroidal antiandrogens increase testosterone levels with the possibility of increased libido and potency. Nonsteroidal antiandrogens eventually proved to be safer than their steroidal counterparts, which are seldom used now to treat PC in the Western world (supplementary Appendix 2, http://jurology.com/).

**First Generation Nonsteroidal Antiandrogens**

The first generation nonsteroidal antiandrogens flutamide and nilutamide, and the second generation nonsteroidal antiandrogen bicalutamide as discussed are derived from anilide. These compounds have similar potency and can eventually develop agonist rather than antagonist activity due to stimulation of the AR, causing PSA to rise.
Clinically the development of agonist activity is demonstrated when PSA decreases after the antiandrogen is discontinued, which is called the antiandrogen withdrawal phenomenon. Occasionally there is also disease regression on imaging and yet the average duration of the response is in the range of 3 months. Flutamide was first described in 1967 by Neri et al as a bacteriostatic agent. However, subsequent animal studies demonstrated its antiandrogenic activity. Flutamide has a short half-life of 6 to 8 hours, which necessitates thrice daily administration. Originally tested in the prePSA era, flutamide was shown to be safe and was mostly administered with medical or surgical castration. In fact, since medical or surgical castration can easily eliminate testicular androgens, antiandrogens are essentially indicated to neutralize androgens made locally in the prostate, mostly from DHEA (dehydroepiandrosterone) of adrenal origin (fig. 4).

Flutamide

Flutamide was first described in 1967 by Neri et al as a bacteriostatic agent. However, subsequent animal studies demonstrated its antiandrogenic activity. Flutamide has a short half-life of 6 to 8 hours, which necessitates thrice daily administration. Originally tested in the prePSA era, flutamide was shown to be safe and was mostly administered with medical or surgical castration. In fact, since medical or surgical castration can easily eliminate testicular androgens, antiandrogens are essentially indicated to neutralize androgens made locally in the prostate, mostly from DHEA (dehydroepiandrosterone) of adrenal origin (fig. 4).

Figure 2. Antiandrogen mechanism of action with focus on newer generation antiandrogens, including blockade of androgen induced AR activation, prevention of AR nuclear translocation and inhibition of DNA binding and impeded AR mediated transcription as well as potential resistance pathways, including AR point mutations, variants and amplification. Adapted from Nelson, and Siberstein and Tan et al.
post-marketing setting, necessitating the FDA mandate that liver enzymes should be monitored.\textsuperscript{51}

Analysis of all studies performed with flutamide and nilutamide associated with castration compared with castration plus placebo showed that overall survival was increased by an average of 3 to 6 months (fig. 5). It should be noted that in all clinical trials comparing combined androgen blockade with placebo (castration only) the antiandrogen was added at the time of progression in the placebo group while the antiandrogen was stopped in the antiandrogen treated group. Thus, all these studies were of early vs late combination therapy.

**Nilutamide.** Nilutamide has a half-life of approximately 2 days, which allows for once daily dosing after 2 weeks of twice daily dosing. In human trials nilutamide monotherapy demonstrated activity in patients with hormone sensitive metastatic PC.\textsuperscript{28,29} The pivotal trial comparing orchiectomy vs orchiectomy plus nilutamide showed improved median time to death and progression, providing the basis for the 1996 FDA approval in combination with orchiectomy or GnRHa (gonadotropin-releasing hormone agonist).\textsuperscript{52}

The most common AEs seen with nilutamide were gastrointestinal toxicity in 65\% of cases, nausea in 27\%, delayed adaptation to darkness in 27\% to 33\% and alcohol intolerance in 6\% to 19\%.\textsuperscript{28,29} Interstitial pneumonitis was experienced by 1\% of patients\textsuperscript{53} and elevated liver enzymes were noted in 8\%.\textsuperscript{52} Other toxicities associated with nilutamide include hot flashes, breast pain and gynecomastia, which are also associated with low serum androgen levels.\textsuperscript{28,52,54,55} Nilutamide, the first nonsteroidal antiandrogen used in combination with castration, showed encouraging results, which led to the demonstration of the importance of androgens made locally in the prostate independently of the testes.\textsuperscript{3,4}

**Second Generation Nonsteroidal Antiandrogen Bicalutamide**

Bicalutamide was synthesized in the 1980s and approved to treat PC in the United States in 1995. Like flutamide and nilutamide, bicalutamide selectively inhibits the AR. The efficacy of bicalutamide is in the same range as that of flutamide and nilutamide. Bicalutamide has a longer half-life of 7 days compared with first generation antiandrogens, which enables once daily dosing. Due to increased testosterone and, therefore, increased estrogen levels when used as monotherapy, bicalutamide 50 mg per day as a single agent is associated with breast pain in 76\% of patients, gynecomastia in 60\%, hot flashes in 25\%, decreased libido and impotence in 25\% to 28\% and suboptimal PSA responses.\textsuperscript{56}
Due to the latter finding subsequent trials of high dose (150 mg) single agent bicalutamide were performed and compared with the standard of care alone (medical or surgical castration) in men with locally advanced or metastatic PC.\textsuperscript{30,31,67} No significant difference in survival could be found in men with locally advanced PC, although the criteria for equivalence were not met.\textsuperscript{30} In addition, the higher dose of single agent bicalutamide resulted in significant gynecomastia and breast pain. Like the first generation antiandrogens, bicalutamide was associated with liver and gastrointestinal toxicity.

Bicalutamide 150 mg was also studied as an adjuvant to standard therapy (watchful waiting, radiotherapy and radical prostatectomy) in 3 large, industry sponsored global trials called the EPC (Early Prostate Cancer) trial program.\textsuperscript{32,58} Combined analysis of these trials revealed that bicalutamide was associated with improved survival in men with early nonmetastatic PC who were receiving primary radiation.\textsuperscript{58} In men with localized PC (T1-2, M0) assigned to watchful waiting the addition of bicalutamide resulted in poorer survival,\textsuperscript{58} which may have been attributable to cardiovascular events.\textsuperscript{59} Based on the EPC trials the indication for bicalutamide 150 mg monotherapy as a treatment option for localized PC was withdrawn in a number of countries. In a large trial of adjuvant bicalutamide with salvage postoperative radiation therapy higher rates of long-term overall survival were observed compared with those of radiation therapy alone.\textsuperscript{60}

The classically available antiandrogens flutamide, bicalutamide and nilutamide exert pure AR antagonistic activity and have shown major benefits in PC therapy.\textsuperscript{3,12,52,61} However, the affinity of these compounds for the AR is relatively low,\textsuperscript{62} leaving an estimated 5% to 10% of DHT free to continue to stimulate the AR and prostate cancer growth.\textsuperscript{63} Thus, there is a need to discover and develop novel antiandrogens with higher affinity for the AR to take optimal advantage of the well demonstrated high responsiveness of PC to androgen blockade.

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**Figure 4.** Human steroid biosynthesis pathways in adrenal glands and peripheral intracrine tissues. Adrenals produce DHEA, which is converted into active androgens, including most potent natural androgen dihydrotestosterone, by prostate and peripheral tissues via illustrated biosynthetic pathways.\textsuperscript{48} CYP17A1, steroid 17α-dydroxylase/17/20 desmolase. HSD, hydroxysteroid dehydrogenase. 4-dione, androstenedione. 5-diol, androst-5-ene-3β,17β-diol. Source: Labrie,\textsuperscript{73}

**Figure 5.** Meta-analysis comparing combined androgen blockade with medical or surgical castration. Combined androgen blockade consisted of medical (GnRH agonist) or surgical castration vs castration alone as first treatment. Antiandrogen was usually added to castration at time of progression. PCTCG, Prostate Cancer Trials Collaborative Group. NSAA, nonsteroidal antiandrogen. Caubet: NSAA (3732), Caubet: NSAA (1978) and Caubet: NSAA (2397), Caubet JF: Urology 1997; 49: 71. Debruyne: nilutamide, Debruyne FM: Eur Urol, suppl. 1996; 30: 264. Bennett: flutamide, Bennett CL: Prostate Cancer Prostatic Dis 1998; 2; 4. Asterisk indicates 2p <0.05. Dagger indicates 2p <0.01. Source: Labrie,\textsuperscript{73} adapted from Klotz.\textsuperscript{72}
Third Generation Antiandrogens

**Enzalutamide.** Enzalutamide is a selective antagonist of the AR which inhibits AR translocation to the cell nucleus, recruitment of AR cofactors and AR binding to DNA. As previously reported enzalutamide was developed using the nonsteroidal agonist RU59063 as a starting chemical scaffold based on its high affinity and selectivity for the AR as opposed to other nuclear hormone receptors. Enzalutamide has fivefold to eightfold higher binding affinity for the AR compared with bicalutamide. The half-life of enzalutamide is 6 days and like the first and second generation antiandrogens enzalutamide crosses the blood-brain barrier. Clinical trials of enzalutamide confirmed its efficacy in the treatment of patients with metastatic CRPC. Pivotal phase 3 trials, including the PREVAIL Study (ClinicalTrials.gov NCT03260517) in the metastatic CRPC pre-docetaxel setting and the AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy, ClinicalTrials.gov NCT009743111) trial in the post-docetaxel setting of metastatic CRPC demonstrated that adding enzalutamide to castration was superior to adding placebo to castration in terms of overall survival. The AFFIRM study included 1,199 men with CRPC who had previously received chemotherapy and were randomized to enzalutamide 160 mg daily or placebo. Median overall survival was 18.4 months in those treated with enzalutamide vs 13.6 months in the placebo group (HR 0.63, 95% CI 0.53–0.75, p < 0.001). The study was stopped at the time of the planned interim analysis after 520 deaths had occurred.

The prechemotherapy PREVAIL Study was also terminated early when a planned interim analysis was done after 540 deaths were reported. Significant survival and progression-free survival benefits were observed in patients treated with enzalutamide 160 mg daily vs placebo. The risk of disease progression was reduced by 81% (HR 0.19, 95% CI 0.15–0.23) and the risk of death was reduced by 29% (HR 0.71, 95% CI 0.60–0.80, each p < 0.001).

In the randomized phase 2 TERRAIN (A Study of Enzalutamide Versus Bicalutamide in Castrate Men with Metastatic Prostate Cancer, ClinicalTrials.gov NCT01288911) study enzalutamide demonstrated greater activity than bicalutamide 50 mg daily in patients with asymptomatic or mildly symptomatic metastatic CRPC. The primary end point of radiographic progression-free survival was 15.7 months for enzalutamide compared with 5.8 months for bicalutamide (HR 0.44, 95% CI 11.5–19.4, p < 0.0001). Other end points showed improvement, including PSA progression, the PSA response, the objective tumor response and quality of life. The AEs more frequently reported with enzalutamide included fatigue, back pain, hot flush and hypertension whereas nausea, constipation and arthralgia were more common with bicalutamide.

**Apalutamide.** Apalutamide (ARN-509) emerged from the same medicinal chemistry laboratory as enzalutamide, where more potent antiandrogens with no significant agonistic activity were sought. Apalutamide had similar activity in vitro activity but greater in vivo activity in xenograft models compared with enzalutamide. In a first in human, phase 1 study of 30 patients with progressing CRPC treated with apalutamide 46.7% experienced a 50% or greater decline from baseline in PSA. Fatigue was the most frequently reported AE, noted by 47% of patients. The dose limiting toxicity was a single case of grade 3 abdominal pain. The results of a subsequent phase 2 study of apalutamide in patients with CRPC showed that 89% with nonmetastatic disease had a 50% or greater decrease from baseline in PSA with a median time to PSA progression of 24 months. In 46 patients with metastatic CRPC the 12-week PSA response rate was 88% in those naive to abiraterone acetate plus prednisone and 22% in previously treated patients while median time to PSA progression was 18.2 and 3.7 months, respectively. The most common AE was fatigue (mainly grade 1 or 2) and the only grade 3 AEs reported in more than 1 patient receiving apalutamide were anemia and back pain in 2 patients each.
CRPC was performed. Those data showed significantly...

**Figure 6.** Ongoing phase 3 trials with third generation antiandrogens according to disease state. Study of third generation antiandrogens is now moving in direction of hormone naïve patients at earlier disease stages. BCR, biochemical recurrence. nmCRPC, nonmetastatic CRPC.

Based on the activity and favorable toxicity profile of apalutamide in these studies the pivotal phase 3 SPARTAN (Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer, ClinicalTrials.gov NCT01946204) trial of nonmetastatic CRPC was performed. Those data showed significantly longer metastasis-free survival for apalutamide than for placebo (40.5 vs 16.2 months, HR 0.28, 95% CI 0.23–0.35, p < 0.0001).

**Darolutamide.** Another third generation antiandrogen, ODM-201 or darolutamide, is structurally distinct from enzalutamide and apalutamide. Unlike enzalutamide, darolutamide has low penetration of the blood-brain barrier and it is undetectable in the brain 8 hours after a dose. This difference may translate into a lower risk of the central nervous system related events seen with enzalutamide. Other significant differences are that as a single agent darolutamide does not increase testosterone levels in mice and it binds to mutated AR, as a single agent darolutamide does not increase testosterone levels in mice and it binds to mutated AR, including the F876L mutation which confers resistance to enzalutamide and apalutamide.

In an open label, phase 1 study of chemotherapy naïve patients with metastatic CRPC darolutamide 600 mg twice daily demonstrated tumor responses with no central nervous system side effects. Of 30 patients 25 (83%) had a 50% or greater reduction in PSA from baseline at week 12 and 9 of 30 (30%) had a 90% or greater decline in PSA from baseline. Median time to PSA progression was 54 weeks (95% CI 23–not reached). Darolutamide was well tolerated and most AEs were grade 1 or 2. The most common AEs were fatigue, which was grade 1 in all 4 cases (13%), and nausea, which was grades 1 to 3 in 4 (13%). Importantly no seizures have been reported to date. Darolutamide is being studied in the phase 3 ARAMIS (Efficacy and Safety Study of Darolutamide [ODM-201] in Men With High-risk Nonmetastatic Castration-resistant Prostate Cancer, ClinicalTrials.gov NCT02200614) trial in nonmetastatic CRPC cases. There are numerous ongoing trials of the third generation antiandrogens in early stages of PC (supplementary Appendix 1, http://jurology.com/).

**FUTURE THERAPEUTIC OPTIONS**

Despite the progress to date in the discovery of newer and more effective antiandrogens to treat PC eventually clinical evidence of resistance to this treatment develops in virtually all patients with advanced disease. This observation possibly results from starting treatment at too advanced a stage of disease. In the last decade we have gained better understanding of the mechanisms involved in intracrine and paracrine androgen production, and in the appreciation that AR signaling remains active and continues to drive the growth of PC following the androgen depletion used to date for advanced disease.

Further demonstrations of the mechanisms of AR resistance have led to new approaches to drug development. For example, AR overexpression was established as a principal driver of CRPC and a drug screen of antiandrogens that could retain activity even when AR was over expressed led to the discovery of enzalutamide. Several AR dependent mechanisms are recognized as drivers of CRPC, including AR over expression with or without...
amplification, AR mutations, AR variants, intra-tumor production of testosterone and DHT, over expression of the glucocorticoid receptor and AR loss. Drugs that target these resistance mechanisms are in development. However, administering these agents earlier in the disease process seems likely to yield improved results.

Drug resistance through AR independent pathways in response to enzalutamide has included the acquisition of neuroendocrine characteristics which may lead to highly aggressive and lethal tumors. Therapeutic modalities with novel combinatorial agents along with antiandrogens could lead to improved outcomes in the treatment of patients with distinct resistance pathways. Additionally, specific approaches to target biological pathway might offer advantages. One such potential pathway is noncanonical activation of the Hedgehog oncogenic signaling pathway by the interaction of transcriptionally active AR proteins with Gli3, leading to prostate cancer cell growth and progression.

**ONGOING ANTIANDROGEN PHASE 3 TRIALS**

Most antiandrogen data are on patients with metastatic and primarily castration resistant disease.

**APPENDIX 1**

Generations of antiandrogen treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>First Synthesized/Discovered</th>
<th>FDA Approval for Use in Prostate Cancer</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td><strong>Steroidal antiandrogens</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>First patent filing in 1962</td>
<td>No</td>
<td>Full antagonist of androgen receptor, also has progesterone-like effects and is able to activate progesterone receptor</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>1958</td>
<td>No</td>
<td>Agonist of androgen receptor</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>1959 (synthesized from medroxyprogesterone acetate)</td>
<td>No</td>
<td>High affinity antagonist/weak partial agonist of androgen receptor, binds with similar affinity to progesterone receptor</td>
</tr>
<tr>
<td><strong>Nonsteroidal antiandrogens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First generation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>1967</td>
<td>1989</td>
<td>Selective, competitive antagonist of androgen receptor, binds to androgen receptor and inhibits nuclear translocation</td>
</tr>
<tr>
<td>Nilutamide</td>
<td>1980s</td>
<td>1996</td>
<td>Selective competitive antagonist of androgen receptor, affinity for androgen receptor similar to that of flutamide</td>
</tr>
<tr>
<td><strong>Second generation</strong> (bicalutamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1980s</td>
<td>1995</td>
<td>Selective competitive antagonist of androgen receptor, fourfold greater affinity for androgen receptor vs flutamide and fivefold higher affinity vs nilutamide</td>
</tr>
<tr>
<td><strong>Third generation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>2008</td>
<td>2012</td>
<td>Inhibitor of androgen receptor translocation to cell nucleus, recruitment of androgen receptor cofactors and androgen receptor binding to DNA, selective antagonist of androgen receptor, fivefold to eightfold higher binding affinity for androgen receptor vs bicalutamide</td>
</tr>
<tr>
<td>Apalutamide</td>
<td>2007</td>
<td>2018</td>
<td>Selective competitive androgen receptor inhibitor; fivefold to tenfold greater binding affinity for androgen receptor vs bicalutamide</td>
</tr>
<tr>
<td>Darolutamide</td>
<td>2009</td>
<td>Not yet submitted</td>
<td>Selective antagonist of androgen receptor, higher affinity for androgen receptor vs enzalutamide and apalutamide</td>
</tr>
</tbody>
</table>

However, the evolving, previously summarized information illustrates that the development of these compounds is now moving in the direction of hormone naive patients at earlier stages of disease (Appendix 2 and fig. 6). Currently use of the newer, third generation antiandrogen darolutamide remains investigational and efforts should be made to enroll patients in clinical trials.

**CONCLUSIONS**

The evolution of antiandrogens from agents with minimal or no clinical benefit to those that result in significantly prolonged survival demonstrates the power of rational drug development based on improved understanding of the underlying biology of androgen regulated growth and the mechanisms of resistance to AR inhibition. It remains to be determined whether using more potent inhibition of the AR axis alone or combined with other drugs can cure prostate cancer when applied earlier in the course of disease.

**ACKNOWLEDGMENTS**

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APPENDIX 2

Clinical profile of nonsteroidal antiandrogens studied to date for prostate cancer treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patient Population</th>
<th>Efficacy Profile</th>
<th>Key Toxicities</th>
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<tbody>
<tr>
<td>Flutamide</td>
<td>Newly diagnosed, previously untreated metastatic hormone sensitive prostate cancer</td>
<td>Improved overall survival when added to leuproline vs leuproline alone&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Diarrhea, hepatotoxicity, including fatal&lt;sup&gt;12,25,26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nilutamide</td>
<td>Advanced metastatic, hormone sensitive prostate cancer</td>
<td>Improved survival when combined with surgical castration&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Nausea, dark light accommodation, alcohol intolerance, hepatotoxicity&lt;sup&gt;28,29&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stage D, previously untreated prostate cancer</td>
<td>Moderate activity as monotherapy; Partial response rate 41.6%;&lt;sup&gt;28&lt;/sup&gt; Median progression-free survival 9 months and overall survival 23 months&lt;sup&gt;29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>Locally advanced and metastatic prostate cancer</td>
<td>No survival benefit compared with castration, statistically significant benefit for bicalutamide for quality of life measures including sexual interest&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Gastrointestinal and hepatotoxicity&lt;sup&gt;30,31&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Nonmetastatic prostate cancer</td>
<td>Less effective than castration in patients with metastatic disease, statistically significant improvement in subjective response rate (70%) vs castration (58%)&lt;sup&gt;24&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPC (Early Prostate Cancer) trial overall no survival benefit of bicalutamide compared with placebo. However, bicalutamide improved overall survival significantly in patients with locally advanced disease undergoing radiotherapy. In watchful waiting patients with localized disease there was survival trend in favor of placebo (p = 0.064)&lt;sup&gt;23&lt;/sup&gt;</td>
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<tr>
<td>Enzalutamide</td>
<td>Metastatic prostate cancer</td>
<td>37% Reduction in risk of death (p &lt;0.001)&lt;sup&gt;27&lt;/sup&gt; (post-chemotherapy)</td>
<td>Fatigue, hypertension and anemia&lt;sup&gt;36,37&lt;/sup&gt; Seizures&lt;sup&gt;36,37&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>81% Reduction in risk of radiographic progression and 29% reduction in risk of death vs placebo (each outcome p &lt;0.001)&lt;sup&gt;28&lt;/sup&gt; (prechemotherapy)</td>
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<td></td>
<td>Significantly improved progression-free survival vs bicalutamide (15.7 vs 5.8 months, p &lt;0.0001)&lt;sup&gt;29&lt;/sup&gt;</td>
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<td>Nonmetastatic castration resistant prostate cancer</td>
<td>76% Reduction in risk of progression or death vs bicalutamide (p &lt;0.001)&lt;sup&gt;30&lt;/sup&gt;</td>
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<td>Phase 3 study showing significantly prolonged median metastasis-free survival vs placebo (36.6 vs 14.7 months, HR 0.29, 95% CI 0.24–0.35, p &lt;0.0001)&lt;sup&gt;31&lt;/sup&gt;</td>
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<tr>
<td>Apalutamide</td>
<td>Metastatic castration resistant prostate cancer</td>
<td>Phase 1 study in 30 patients, 46.7% of patients with 50% or greater reduction from baseline in prostate specific antigen at 12 weeks&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Fatigue, anemia and gastrointestinal disturbance&lt;sup&gt;36–40&lt;/sup&gt;</td>
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<td>Phase 2 study 12-week prostate specific antigen response rate 88% in patients previously treated with abiraterone acetate and 22% in those previously untreated&lt;sup&gt;33&lt;/sup&gt;</td>
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<tr>
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<td>Nonmetastatic castration resistant prostate cancer</td>
<td>Phase 2 study in 51 patients with 89% prostate specific antigen response rate at 12 weeks&lt;sup&gt;34&lt;/sup&gt;</td>
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<td>Phase 3 study showing significantly longer metastasis-free survival (40.5 vs 16.2 months, HR 0.82, 95% CI 0.73–0.91, p &lt;0.001)&lt;sup&gt;35&lt;/sup&gt;</td>
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<tr>
<td>Darolutamide</td>
<td>Chemotherapy naïve metastatic castration resistant prostate cancer</td>
<td>Prostate specific antigen and tumor responses 83% prostate specific antigen response rate at 12 weeks and median 66 weeks to radiographic tumor progression&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Fatigue and nausea&lt;sup&gt;41&lt;/sup&gt;</td>
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APPENDIX 3

Ongoing phase 3 clinical trials of antiandrogen therapy

<table>
<thead>
<tr>
<th>Study (ClinicalTrials.gov identifier)</th>
<th>Target Population</th>
<th>Primary Efficacy Survival Outcome</th>
<th>Comparator Arms</th>
<th>Primary Completion Date</th>
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<tbody>
<tr>
<td>Apalutamide: ATLAS (NCT02531516)</td>
<td>High risk prostate cancer receiving primary radiation therapy</td>
<td>Metastasis-free</td>
<td>Apalutamide plus luteinizing hormone-releasing hormone analog vs luteinizing hormone-releasing hormone analog plus bicalutamide (cycles 1-4)</td>
<td>12/2022</td>
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<td>ACIS (NCT02257736)</td>
<td>Chemotherapy naïve metastatic castration resistant prostate cancer</td>
<td>Radiographic progression-free</td>
<td>Apalutamide and abiraterone acetate plus prednisone vs abiraterone acetate plus prednisone</td>
<td>12/2018</td>
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<td>TITAN (NCT02489318)</td>
<td>Metastatic hormone sensitive prostate cancer</td>
<td>Radiographic progression-free and overall</td>
<td>Apalutamide plus luteinizing hormone-releasing hormone analog vs luteinizing hormone-releasing hormone analog</td>
<td>11/2020</td>
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<tr>
<td>Darolutamide: ARAMIS (NCT02208614)</td>
<td>High risk nonmetastatic castration resistant prostate cancer</td>
<td>Metastasis-free</td>
<td>Darolutamide vs placebo</td>
<td>4/2018</td>
</tr>
</tbody>
</table>

(Continued on next page)
Enzalutamide: References


or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int 2010; 105: 1074.


