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

E. David Crawford,*,† Paul F. Schellhammer, David G. McLeod, Judd W. Moul,‡ Celestia S. Higano, Neal Shore, Louis Denis, Peter Iversen, Mario A. Eisenberger and Fernand Labrie

From the University of Colorado-Denver (EDC), Aurora, Colorado, Eastern Virginia Medical School (PFC), Norfolk, Virginia, Center for Prostate Disease Research, Uniformed Services University of the Health Sciences (DGM), Bethesda and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (MAE), Baltimore, Maryland, Duke Cancer Institute, Duke University (JWM), Durham, North Carolina, Fred Hutchinson Cancer Research Center, University of Washington (CSH), Seattle, Washington, Carolina Urologic Research Center (NS), Myrtle Beach, South Carolina, Europa Uomo, Oncology Centre Antwerp (LD), Antwerp, Belgium, Copenhagen Prostate Cancer Center, University of Copenhagen (PI), Copenhagen, Denmark, and Endoceutics (FL), Quebec City, Quebec, Canada

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.

Abbreviations and Acronyms

ADT = androgen deprivation therapy
AE = adverse event
AR = androgen receptor
CPA = cyproterone acetate
CRPC = castration resistant prostate cancer
DHT = dihydrotestosterone
FDA = Food and Drug Administration
PC = prostate cancer
PSA = prostate specific androgen

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Janssen Scientific Affairs (IM).

* Correspondence: Urologic Oncology, University of Colorado, Denver, Mail Stop F 710, P. O. Box 6510, Aurora, Colorado 80045 (telephone: 720-848-0195; e-mail: edc@edavidcrawford.com).

† Financial interest and/or other relationship with Tolmar, Bayer, MDx, Genomic Health, Janssen, Dendreon and Ferring.

‡ Financial interest and/or other relationship with Janssen and Pfizer.

Supplementary references 51-73 for this article can be obtained at http://jurology.com/.

0022-5347/18/2005-0001/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2018.04.083
Vol. 200, 1-12, November 2018
Printed in U.S.A.

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 further 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

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.[6–9] 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] [F1]

MATERIALS AND METHODS

We searched PubMed® 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 (anti-apoptotic 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

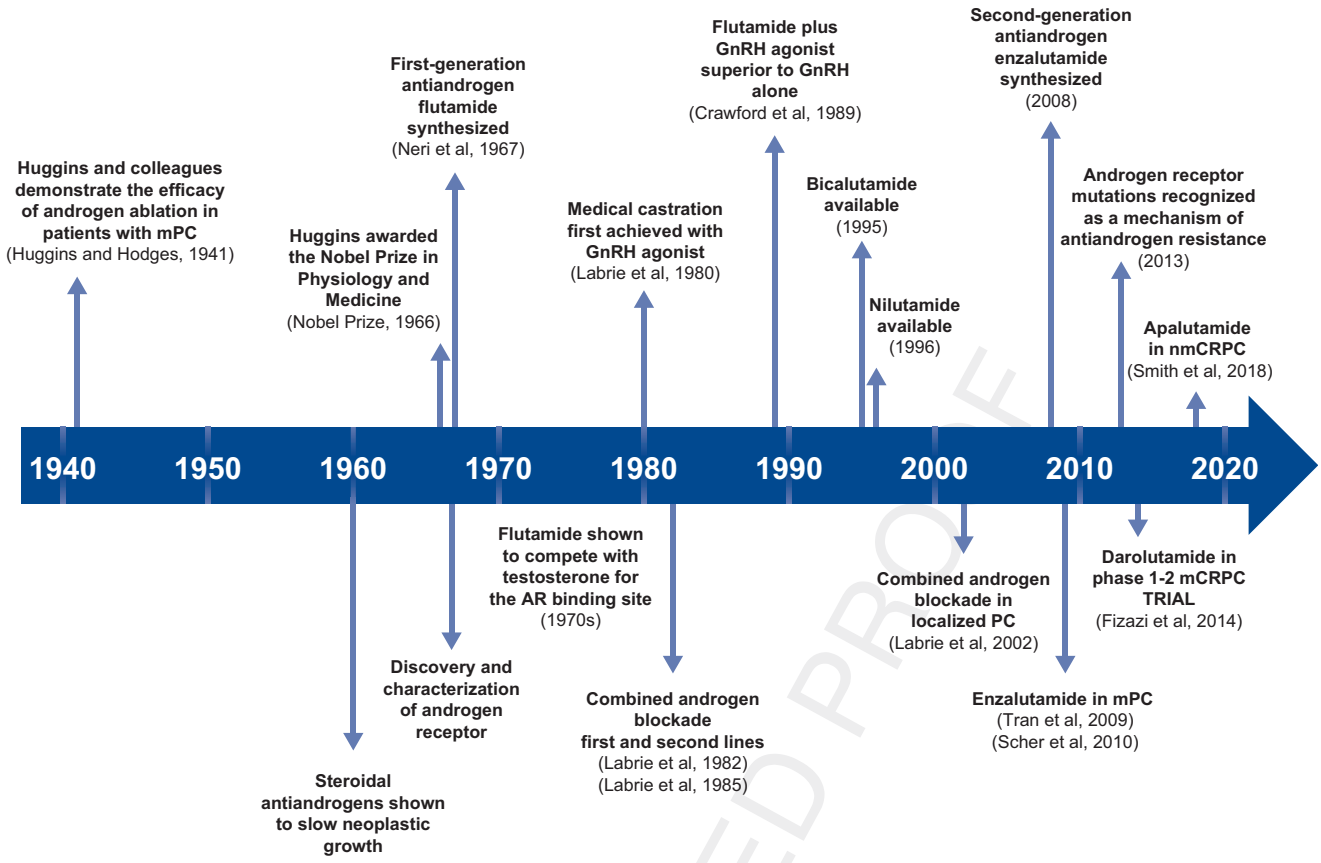

Figure 1. Timeline of the development of antiandrogen therapy for prostate cancer shows significant events and key studies associated with clinical development path of antiandrogens, including work by Huggins and Hodges,[1] Neri et al,[10] Labrie et al 1980,[11] 1982,[4] 1985[3] and 2002,[13] and Crawford,[12] Smith,[16] Tran,[14] Scher[15] and Fizazi[17] et al.

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 [F2] locally derived androgens to the AR (fig. 2).[21–23] Antiandrogens are globally classified as steroidal or nonste- [F3] roidal (Appendix 1 and fig. 3).[24] They differ in chemical structure, pharmacological effects and safety profiles (supplementary Appendix 1, http://jurology.com/).[12,16,25–41] 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.[42,43]

Antiandrogens

Steroidal. Steroidal antiandrogens preceded the development of nonsteroidal compounds to treat patients with advanced disease (Appendix 1). CPA, the first steroidal antiandrogen, competitively blocked DHT and testosterone from binding to the AR. When used as single agent, CPA was as effective as medical castration or diethylstilbestrol for treating advanced PC.[44] 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.[43] 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.[42,43] 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.

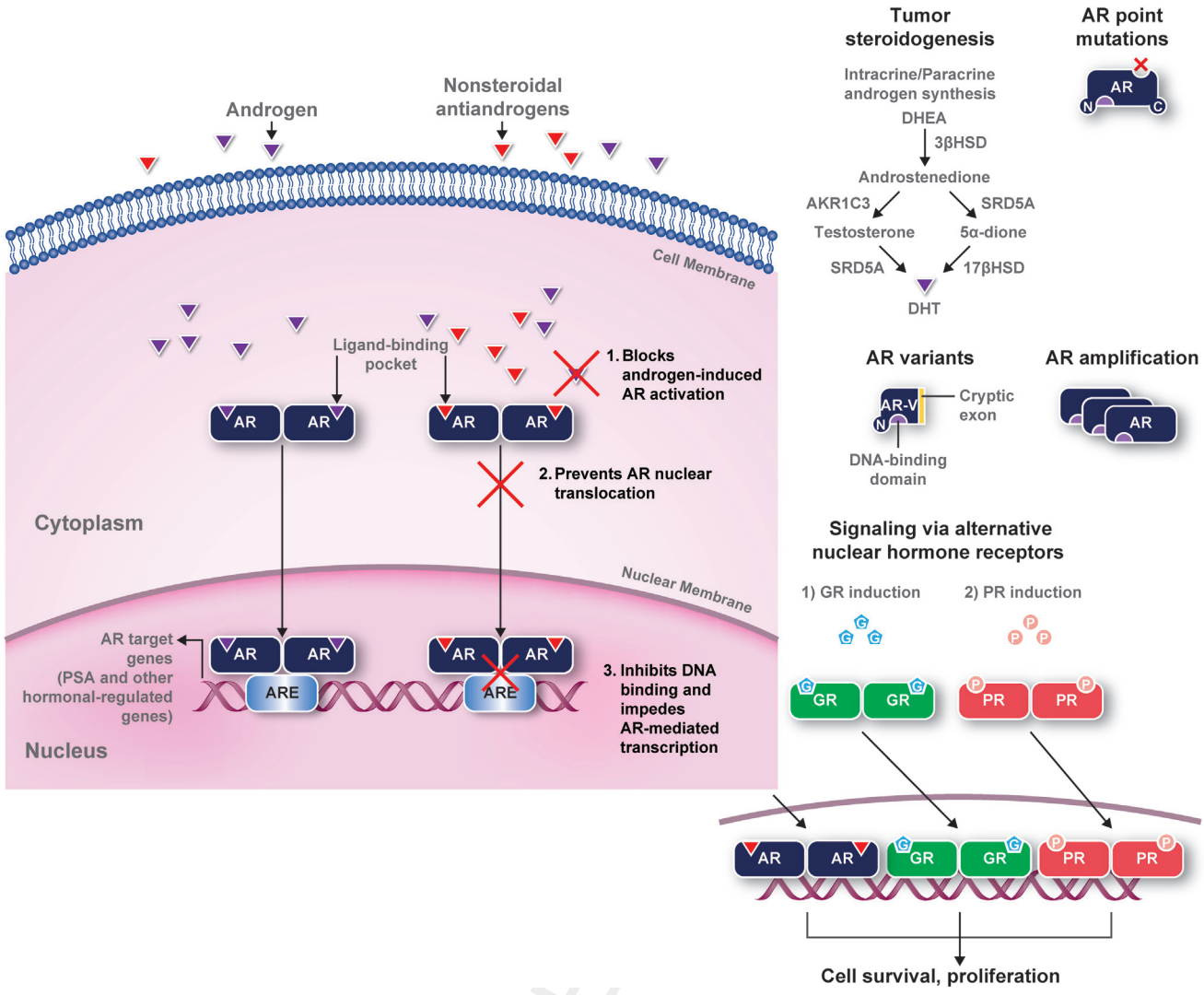

Figure 2. Antiandrogen mechanism of action with focus on newer generation antiandrogens, including blockade of androgen induced AR activation, prevention of AR nuclear translocation and inhibition of DNA binding and impeded AR mediated transcription as well as potential resistance pathways, including AR point mutations, variants and amplification. Adapted from Nelson,[21] and Siberstein[22] and Tan[23] et al.

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.[45]

Flutamide

Flutamide was first described in 1967 by Neri et al as a bacteriostatic agent.[42] However, subsequent animal studies demonstrated its antiandrogenic activity.[46] 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.[3,4,18,19,47] 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).[48–50] This was the [F4] first combination of drugs[3,4,12,18,19] approved by health authorities in Canada in 1984 and in 1989 in the United States. The concept of combined androgen blockade was based on the observation that after castration androgens of adrenal origin could continue to stimulate PC growth based on the mechanism of intracrinology (supplementary Appendix 3, http://jurology.com/).

The pivotal trial of flutamide in the United States compared daily subcutaneous administration of leuprolide acetate with flutamide or an identical placebo (double blinded) in men with newly diagnosed metastatic PC. The combination of flutamide and leuprolide resulted in improved median overall survival of 36 vs 28 months with leuprolide alone and in 1989 led to FDA approval.[12] Toxicities seen in this pivotal trial included diarrhea and anemia[25,26] but hepatotoxicity was also noted in the

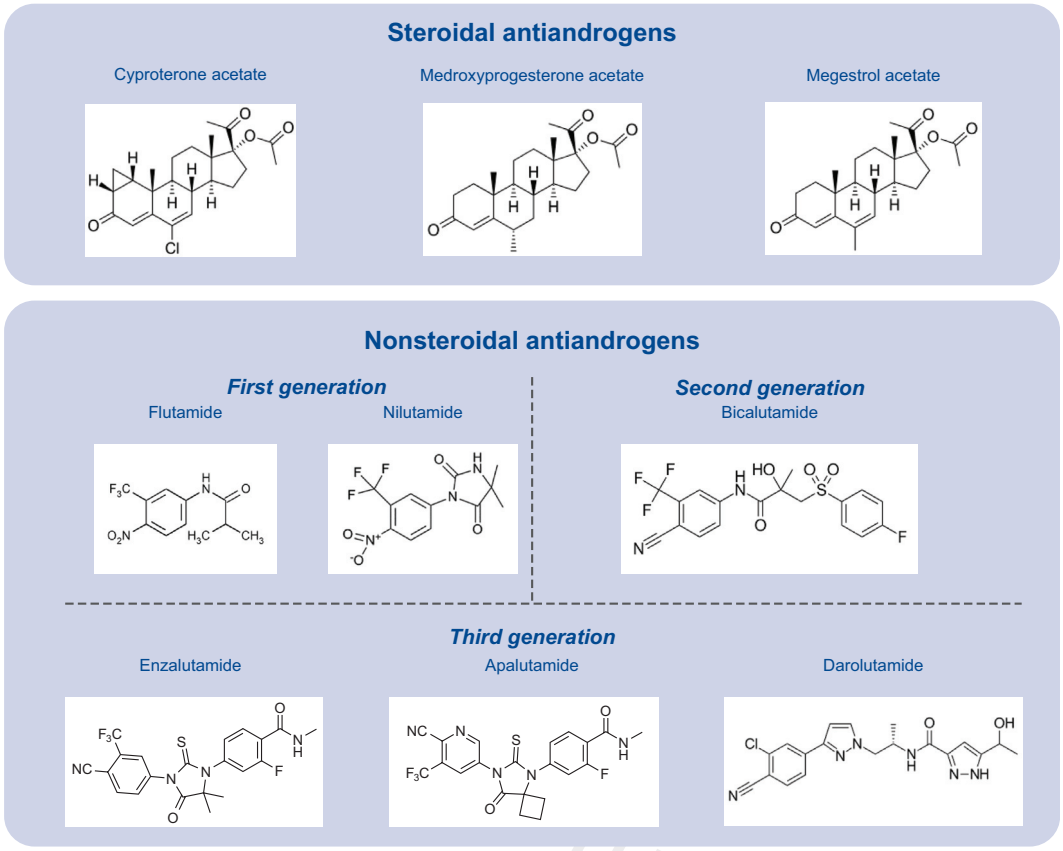

Figure 3. Molecular structures of antiandrogens, including steroidal antiandrogens cyproterone acetate, medroxyprogesterone acetate and megestrol acetate, and nonsteroidal antiandrogens. Nomenclature of nonsteroidal antiandrogens is differentiated as first generation—flutamide and nilutamide, second generation—bicalutamide and third generation—enzalutamide, apalutamide and darolutamide.

post-marketing setting, necessitating the FDA mandate that liver enzymes should be monitored.[51]

Analysis of all studies performed with flutamide and nilutamide associated with castration compared with castration plus placebo showed that overall survival was [F5] 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.[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).[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%.[28,29] Interstitial pneumonitis was experienced by 1% of patients[53] and elevated liver enzymes were noted in 8%.[52] Other toxicities associated with nilutamide include hot flashes, breast pain and gynecomastia, which are also associated with low serum androgen levels.[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.[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.[56]

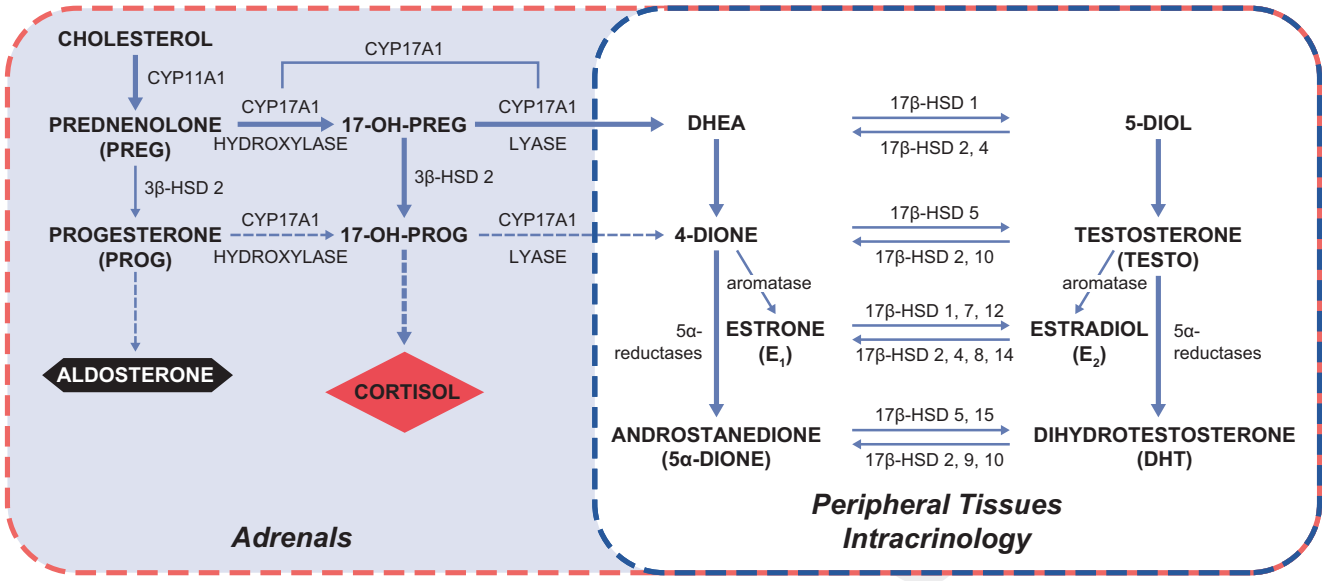

Figure 4. Human steroid biosynthesis pathways in adrenal glands and peripheral intracrine tissues. Adrenals produce DHEA, which is converted into active androgens, including most potent natural androgen dihydrotestosterone, by prostate and peripheral tissues via illustrated biosynthetic pathways.[48–50] *CYP11A1*, cholesterol side-chain cleavage enzyme. *CYP17A1*, steroid 17α-dydroxylase/17/20 desmolase. *HSD*, hydroxysteroid dehydrogenase. *4-dione*, androstenedione. *5-diol*, androst-5-ene-3β,17β-diol. Source: Labrie.[73]

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.[30,31,57] No significant difference in survival could be found in men with locally advanced PC, although the criteria for equivalence were not met.[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.

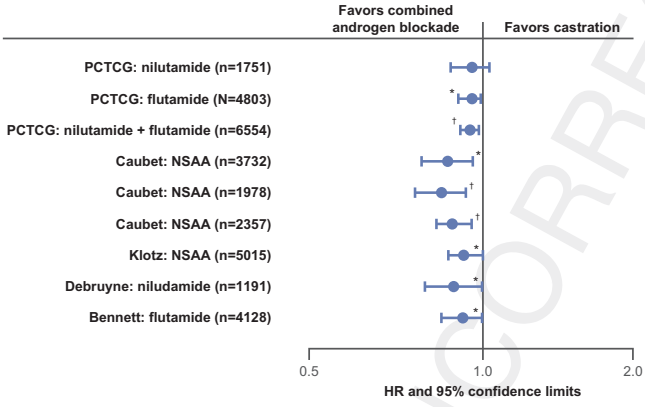

Figure 5. Meta-analysis comparing combined androgen blockade with medical or surgical castration. Combined androgen blockade consisted of medical (GnRH agonist) or surgical castration vs castration alone as first treatment. Antiandrogen was usually added to castration at time of progression. *PCTCG*, Prostate Cancer Trialists Collaborative Group. *NSAA*, nonsteroidal antiandrogen. *Caubet: NSAA (3732)*, *Caubet: NSAA (1978)* and *Caubet: NSAA (2357)*, Caubet JF: Urology 1997; **49:** 71. *Debruyne: nilutamide*, Debruyne FM: Eur Urol, suppl, 1996; **30:** 264. *Bennett: flutamide*, Bennett CL: Prostate Cancer Prostatic Dis 1999; **2:** 4. Asterisk indicates 2p <0.05. Dagger indicates 2p <0.01. Source: Labrie,[73] adapted from Klotz.[72]

The classically available antiandrogens flutamide, bicalutamide and nilutamide exert pure AR antagonistic activity and have shown major benefits in PC therapy.[3,12,52,61] However, the affinity of these compounds for the AR is relatively low,[62–64] leaving an estimated 5% to 10% of DHT free to continue to stimulate the AR and prostate cancer growth.[65] 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.

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.[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.[58] In men with localized PC (T1-2, M0) assigned to watchful waiting the addition of bicalutamide resulted in poorer survival,[58] which may have been attributable to cardiovascular events.[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.[60]

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.[14,66] 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.[67]

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 predocetaxel 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 NCT00974311) 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.[36,37] 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).[37] 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.[36] 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.[33] 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.

STRIVE (Safety and Efficacy Study of Enzalutamide versus Bicalutamide in Men with Prostate Cancer, ClinicalTrials.gov NCT01664923) is another randomized, phase 2 study of patients with asymptomatic or mildly symptomatic metastatic CRPC and nonmetastatic CRPC.[34] In that study progression-free survival was also improved by enzalutamide compared with bicalutamide (19.4 vs 5.7 months, HR 0.24, 95% CI 0.18−0.32, p <0.001).[34] The more frequently reported AEs of enzalutamide similarly included fatigue, back pain and hot flushes. Constipation, diarrhea, anemia and urinary tract infection were more frequent with bicalutamide.

Most recently promising enzalutamide monotherapy activity has been reported in patients with hormone naïve PC in a phase 2 trial.[68] The global, phase 3 EMBARK (Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients with Nonmetastatic Prostate Cancer, ClinicalTrials.gov NCT02319837) trial comparing leuprolide plus enzalutamide, leuprolide plus placebo and enzalutamide monotherapy in men with biochemical relapse who are at high risk for metastatic disease is currently recruiting. In the PROSPER (Safety and Efficacy Study of Enzalutamide in Patients with Nonmetastatic Castration-Resistant Prostate Cancer) study of patients with nonmetastatic CRPC metastasis-free survival was significantly prolonged with enzalutamide vs placebo (36.6 vs 14.7 months, HR 0.29, 95% CI 0.24−0.35, p <0.0001).[35]

The most common AE associated with enzalutamide is fatigue. Other AEs include hypertension, falls and seizures. In the recently published UPWARD (A Study to Evaluate the Potential Increased Risk of Seizures among Metastatic Castration-Resistant Prostate Cancer Patients Treated with Enzalutamide, ClinicalTrials.gov NCT01977651) trial of men with at least 1 risk factor for seizure the seizure rate was 1.1% during the first 4 months of therapy, indicating that enzalutamide could be safely administered in that population.[69] A rare but related toxicity is posterior reversible encephalopathy syndrome, which manifests clinically as headache, altered mental status, seizures and loss of vision, and is diagnosed by magnetic resonance imaging. In such cases enzalutamide should be permanently discontinued.

Apalutamide. Apalutamide (ARN-509) emerged from the same medicinal chemistry laboratory as enzalutamide, where more potent antiandrogens with no significant agonistic activity were sought.[66] Apalutamide had similar in vitro activity but greater in vivo activity in xenograft models compared with enzalutamide.[14]

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.[39] 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.[39] 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.[40] In 46 patients with metastatic CRPC the 12-week PSA response rate was 88% in those naïve 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.[38] 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.

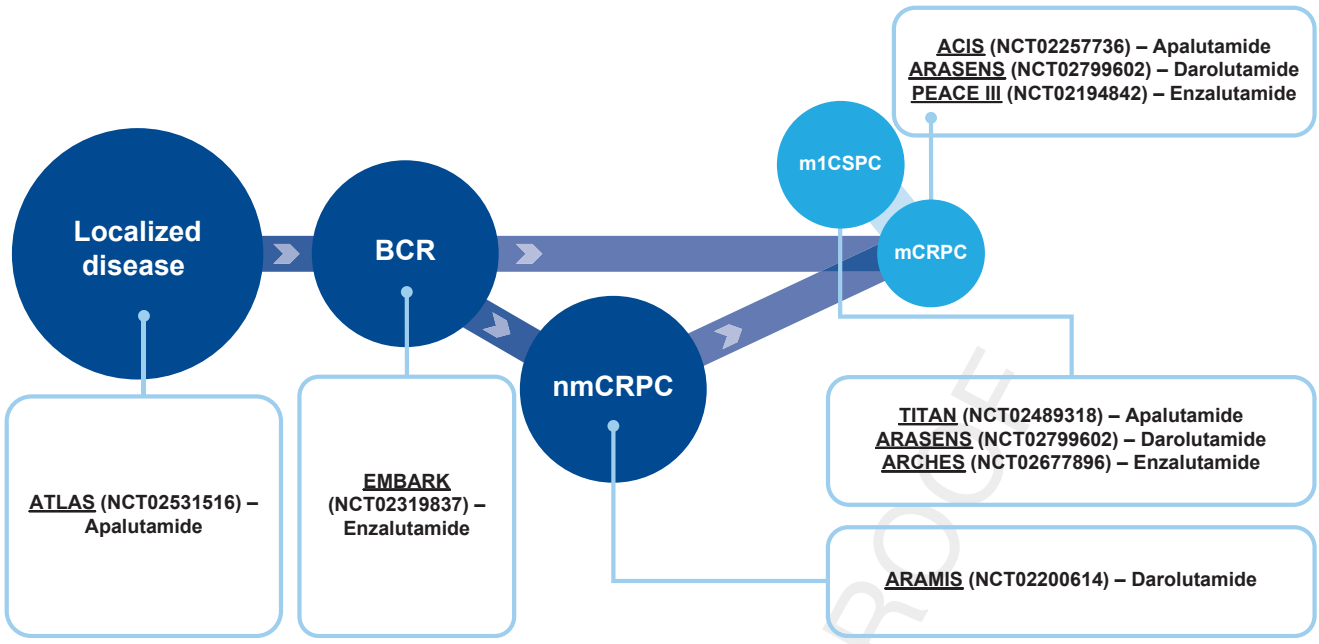

Figure 6. Ongoing phase 3 trials with third generation antiandrogens according to disease state. Study of third generation antiandrogens is now moving in direction of hormone naïve patients at earlier disease stages. *BCR,* biochemical recurrence. *nmCRPC,* nonmetastatic CRPC.

Based on the activity and favorable toxicity profile of apalutamide in these studies[38–40] 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.[16] 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.[70] 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, including the F876L mutation which confers resistance to enzalutamide and apalutamide.[71]

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.[41] 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/).[12,16,25–41]

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 over expression 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, intratumor 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.[72] 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.[72]

ONGOING ANTIANDROGEN PHASE 3 TRIALS

Most antiandrogen data are on patients with metastatic and primarily castration resistant disease. However, the evolving, previously summarized information illustrates that the development of these compounds is now moving in the direction of hormone naïve 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

Dr. Ira Mills, PAREXEL®, Waltham, Massachusetts, assisted with writing.

APPENDIX 1

Generations of antiandrogen treatments

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

APPENDIX 2

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

Agent	Patient Population	Efficacy Profile	Key Toxicities
		1st Generation	
Flutamide	Newly diagnosed, previously untreated metastatic hormone sensitive prostate cancer	Improved median overall survival when added to leuprolide vs leuprolide alone[12]	Diarrhea, hepatotoxicity, including fatal[12,25,26]
Nilutamide	Advanced metastatic, hormone sensitive prostate cancer	Improved survival when combined with surgical castration[27]	Nausea, dark light accommodation, alcohol intolerance, hepatotoxicity[28,29]
	Stage D, previously untreated prostate cancer	Moderate activity as monotherapy: Partial response rate 41.6%[28] Median progression-free survival 9 months and overall survival 23 months[29]	
		2nd Generation	
Bicalutamide	Locally advanced and metastatic prostate cancer	No survival benefit compared with castration, statistically significant benefit for bicalutamide for quality of life measures including sexual interest[30] Less effective than castration in patients with metastatic disease, statistically significant improvement in subjective response rate (70%) vs castration (58%)[31]	Gastrointestinal and hepatoxicity[30,31]
	Nonmetastatic prostate cancer	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 ($p = 0.054$)[32]	
		Third generation	
Enzalutamide	Metastatic prostate cancer	37% Reduction in risk of death ($p < 0.001$)[37] (post-chemotherapy) 81% Reduction in risk of radiographic progression and 29% reduction in risk of death vs placebo (each outcome $p < 0.001$)[36] (prechemotherapy) Significantly improved progression-free survival vs bicalutamide (15.7 vs 5.8 months, $p < 0.0001$)[33]	Fatigue, hypertension and anemia[36,37] Seizures[36,37]
	Nonmetastatic castration resistant prostate cancer	76% Reduction in risk of progression or death vs bicalutamide ($p < 0.001$)[34] 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, $p < 0.0001$)[35]	
Apalutamide	Metastatic castration resistant prostate cancer	Phase 1 study in 30 patients, 46.7% of patients with 50% or greater reduction from baseline in prostate specific antigen at 12 weeks[39] Phase 2 study 12-week prostate specific antigen response rate 88% in patients previously treated with abiraterone acetate and 22% in those previously untreated[38]	Fatigue, anemia and gastrointestinal disturbance[38—40]
	Nonmetastatic castration resistant prostate cancer	Phase 2 study in 51 patients with 89% prostate specific antigen response rate at 12 weeks[40] Phase 3 study showing significantly longer metastasis-free survival (40.5 vs 16.2 months, HR 0.28, 95% CI 0.23—0.35, $p < 0.0001$)[16]	
Darolutamide	Chemotherapy naïve metastatic castration resistant prostate cancer	Prostate specific antigen and tumor responses 83% prostate specific antigen response rate at 12 weeks and median 66 weeks to radiographic tumor progression[41]	Fatigue and nausea[41]

APPENDIX 3

Ongoing phase 3 clinical trials of antiandrogen therapy

Study (ClinicalTrials.gov identifier)	Target Population	Primary Efficacy Survival Outcome	Comparator Arms	Primary Completion Date
Apalutamide:				
ATLAS (NCT02531516)	High risk prostate cancer receiving primary radiation therapy	Metastasis-free	Apalutamide plus luteinizing hormone-releasing hormone analog vs luteinizing hormone-releasing hormone analog plus bicalutamide (cycles 1-4)	12/2022
ACIS (NCT02257736)	Chemotherapy naïve metastatic castration resistant prostate cancer	Radiographic progression-free	Apalutamide and abiraterone acetate plus prednisone vs abiraterone acetate plus prednisone	12/2018
TITAN (NCT02489318)	Metastatic hormone sensitive prostate cancer	Radiographic progression-free and overall	Apalutamide plus luteinizing hormone-releasing hormone analog vs luteinizing hormone-releasing hormone analog	11/2020
Darolutamide:				
ARAMIS (NCT02200614)	High risk nonmetastatic castration resistant prostate cancer	Metastasis-free	Darolutamide vs placebo	4/2018

(Continued on next page)

Continued

Study (ClinicalTrials.gov identifier)	Target Population	Primary Efficacy Survival Outcome	Comparator Arms	Primary Completion Date
ARASENS (NCT02799602)	Metastatic hormone sensitive cancer	Overall	Darolutamide and androgen deprivation therapy and docetaxel vs androgen deprivation therapy and docetaxel	8/2022
Enzalutamide:				
EMBARK (NCT02319837)	Nonmetastatic cancer with biochemical recurrence	Metastasis-free	Enzalutamide plus luteinizing hormone-releasing hormone analog vs enzalutamide vs luteinizing hormone-releasing hormone analog	3/2021
ARCHES (NCT02677896)	Metastatic hormone sensitive cancer	Radiographic progression-free	Enzalutamide and androgen deprivation therapy vs androgen deprivation therapy	4/2020
PEACE III (NCT02194842)	Asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer (bone)	Radiographic progression-free	Enzalutamide and ^{223}Ra vs enzalutamide	11/2019

REFERENCES

1. Huggins C and Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; **1:** 293.
2. Feldman BJ and Feldman D: The development of androgen-independent prostate cancer. Nat Rev Cancer 2001; **1:** 34.
3. Labrie F, Dupont A and Belanger A: Complete androgen blockade for the treatment of prostate cancer. In: Important Advances in Oncology 1985. Edited by VT DeVita Jr, S Hellman and SA Rosenberg. Philadelphia: Lippincott Williams & Wilkins 1985; pp 193—217.
4. Labrie F, Dupont A, Belanger A et al: New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. Clin Invest Med 1982; **5:** 267.
5. Alva A and Hussain M: The changing natural history of metastatic prostate cancer. Cancer J 2013; **19:** 19.
6. Anderson KM and Liao S: Selective retention of dihydrotestosterone by prostatic nuclei. Nature 1968; **219:** 277.
7. Bruchovsky N and Wilson JD: The intranuclear binding of testosterone and 5-alpha-androstan-17-beta-ol-3-one by rat prostate. J Biol Chem 1968; **243:** 5953.
8. Bruchovsky N and Wilson JD: The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. J Biol Chem 1968; **243:** 2012.
9. Mainwaring WI: A soluble androgen receptor in the cytoplasm of rat prostate. J Endocrinol 1969; **45:** 531.
10. Neri RO, Monahan MD, Meyer JG et al: Biological studies on an anti-androgen (SH 714). Eur J Pharmacol 1967; **1:** 438.
11. Labrie F, Bélanger A, Cusan L et al: Antifertility effects of LHRH agonists in the male. J Androl 1980; **1:** 209.
12. Crawford ED, Eisenberger MA, McLeod DG et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989; **321:** 419.
13. Labrie F, Candas B, Gomez JL et al: Can combined androgen blockade provide long-term control or possible cure of localized prostate cancer? Urology 2002; **60:** 115.
14. Tran C, Ouk S, Clegg NJ et al: Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; **324:** 787.
15. Scher HI, Beer TM, Higano CS et al: Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010; **375:** 1437.
16. Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378:** 1408.
17. Fizazi K, Massard C, Bono P et al: Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. Lancet Oncol 2014; **15:** 975.
18. Labrie F, Dupont A, Belanger A et al: New approach in the treatment of prostate cancer: complete instead of partial withdrawal of androgens. Prostate 1983; **4:** 579.
19. Tombal B and van Soest RJ: Prostate cancer: STAMPEDE, LATITUDE and Fernand Labrie's legacy. Nat Rev Urol 2017; **14:** 588.
20. Maughan BL and Antonarakis ES: Androgen pathway resistance in prostate cancer and therapeutic implications. Expert Opin Pharmacother 2015; **16:** 1521.
21. Nelson PS: Targeting the androgen receptor in prostate cancer—a resilient foe. N Engl J Med 2014; **371:** 1067.
22. Silberstein JL, Taylor MN and Antonarakis ES: Novel insights into molecular indicators of response and resistance to modern androgen-axis therapies in prostate cancer. Curr Urol Rep 2016; **17:** 29.
23. Tan MH, Li J, Xu HE et al: Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacol Sin 2015; **36:** 3.
24. Crawford ED: Hormonal therapy in prostate cancer: historical approaches. Rev Urol, suppl., 2004; **6:** S3.
25. Eisenberger MA, Blumenstein BA, Crawford ED et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998; **339:** 1036.
26. Ornstein DK, Beiser JA and Andriole GL: Anaemia in men receiving combined finasteride and flutamide therapy for advanced prostate cancer. BJU Int 1999; **83:** 43.
27. Namer M, Amiel J and Toubol J: Anandron (RU 23908) associated with orchiectomy in stage D prostate cancer. Preliminary results of a randomized, double-blind study. Am J Clin Oncol, suppl., 1988; **11:** S191.
28. Boccardo F, Decensi AU, Guarneri D et al: Anandron (RU 23908) in metastatic prostate cancer: preliminary results of a multicentric Italian study. Cancer Detect Prev 1991; **15:** 501.
29. Decensi AU, Boccardo F, Guarneri D et al: Monotherapy with nilutamide, a pure nonsteroidal antiandrogen, in untreated patients with metastatic carcinoma of the prostate. The Italian Prostatic Cancer Project. J Urol 1991; **146:** 377.
30. Iversen P, Tyrrell CJ, Kaisary AV et al: Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. J Urol 2000; **164:** 1579.
31. Tyrrell CJ, Kaisary AV, Iversen P et al: A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998; **33:** 447.
32. Iversen P, McLeod DG, See WA et al: Antiandrogen monotherapy in patients with localized

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.

33. Shore ND, Chowdhury S, Villers A et al: Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016; **17:** 153.

34. Penson DF, Armstrong AJ, Concepcion R et al: Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016; **34:** 2098.

35. Hussain M, Fizazi K, Saad F et al: PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). J Clin Oncol, suppl., 2018; **36:** 3, abstract 3.

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

37. Scher HI, Fizazi K, Saad F et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; **367:** 1187.

38. Rathkopf DE, Antonarakis ES, Shore ND et al: Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. Clin Cancer Res 2017; **23:** 3544.

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

40. Smith MR, Antonarakis ES, Ryan CJ et al: Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016; **70:** 963.

41. Massard C, Penttinen HM, Vjaters E et al: Pharmacokinetics, antitumor activity, and safety of ODM-201 in patients with chemotherapy-naive metastatic castration-resistant prostate cancer: an open-label phase 1 study. Eur Urol 2016; **69:** 834.

42. Neri R: Pharmacology and pharmacokinetics of flutamide. Urology 1989; **34:** 19.

43. Plante M, Lapointe S and Labrie F: Stimulatory effect of synthetic progestins currently used for the treatment of prostate cancer on growth of the androgen-sensitive Shionogi tumor in mice. J Steroid Biochem 1988; **31:** 61.

44. Pavone-Macaluso M, de Voogt HJ, Viggiano G et al: Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomized phase III trial of the European Organization for Research on Treatment of Cancer Urological Group. J Urol 1986; **136:** 624.

45. Dupont A, Gomez JL, Cusan L et al: Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 1993; **150:** 908.

46. Baker JW, Bachman GL, Schumacher I et al: Synthesis and bacteriostatic activity of some nitrotrifluoromethylanilides. J Med Chem 1967; **10:** 93.

47. Stoliar B and Albert DJ: SCH 13521 in the treatment of advanced carcinoma of the prostate. J Urol 1974; **111:** 803.

48. Labrie F, Luu-The V, Lin SX et al: Intracrinology: role of the family of 17 beta-hydroxysteroid dehydrogenases in human physiology and disease. J Mol Endocrinol 2000; **25:** 1.

49. Luu-The V: Assessment of steroidogenesis and steroidogenic enzyme functions. J Steroid Biochem Mol Biol 2013; **137:** 176.

50. Luu-The V, Bélanger A and Labrie F: Androgen biosynthetic pathways in the human prostate. Best Pract Res Clin Endocrinol Metab 2008; **22:** 207.