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Targeting the androgen receptor in prostate and breast cancer – several new agents in development

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Abstract

Prostate cancer and breast cancer share similarities as hormone-sensitive cancers with a wide heterogeneity of both phenotype and biology. The androgen receptor (AR) is a hormone receptor involved in both benign and malignant processes. Targeting androgen synthesis and the AR pathway has been and remains central to prostate cancer therapy. Recently, there is increased interest in the role of the AR in breast cancer development and growth, with data suggesting AR co-expression with estrogen, progesterone and human epidermal growth factor receptors, across all intrinsic subtypes of breast cancer. Targeting the AR axis is an evolving field with novel therapies in development which may ultimately be applicable for both tumor types. In this review, we offer an overview of available agents which target the AR axis in both prostate and breast cancer and provide insight into the novel drugs in development for targeting this signaling pathway.

Keywords

androgen receptor; hormone receptor; breast cancer; prostate cancer

INTRODUCTION

The androgen receptor (AR) is a member of the steroid-hormone family involved in regulation of normal growth and development within a broad array of target organs. It is in the family of steroid receptors that includes the glucocorticoid, progesterone, and

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mineralocorticoid receptors. AR transcription is age- and cell-type-dependent, modulated by the presence of circulating androgens (Gelmann 2002). The 8-exon gene, located on the X chromosome (Xq11–12), encodes for a 110 kDa protein with 4 functionally distinct regions (Fig. 1) (Gelmann 2002). The N-terminal domain (NTD) (exon 1) is involved in transcriptional activation involving interaction with co-regulatory proteins. The DNA binding domain (DBD) (exons 2+3) is a highly conserved region, which folds into a two zinc-finger motif critical to DNA binding. The ligand binding domain (LBD) on the C-terminus (exons 4–8) is responsible for the binding of androgens. The hinge region links the DBD and LBD and is responsible for nuclear localization (Chang *et al.* 1995; Claessens *et al.* 2008; Gelmann 2002; Heinlein and Chang 2004; Lee and Chang 2003).

The normal function of the AR is dependent on ligand binding and interaction with co-activators and chaperone proteins. In the absence of ligand, the AR is present in the cytoplasm bound to heat shock proteins (i.e., hsp90) and other co-chaperones retaining an inactive conformation. Upon exposure and binding to androgen (testosterone or dihydrotestosterone [DHT]), phosphorylation and conformational changes occur. Binding of ligand to the hormone binding site leads to the formation of a co-activator binding site (AF-2 site) and reconfiguration of the components of the helical protein structure (H3, H4 and H12) (Osguthorpe and Hagler 2011). Transcription of target genes is prompted by the dissociation of chaperone proteins, receptor dimerization and exposure of the nuclear localizing signal which leads the 2 zinc fingers of the DBD to bind to the genomic androgen response elements (Claessens *et al.* 2008; Gelmann 2002; Lee and Chang 2003).

In normal tissue, androgen-responsive genes are important for normal prostate architecture, homeostasis and physiologic function. In prostate cancer (PCa) cells, these genes lead to the proliferation and survival of tumor cells. In breast tissue the relationship is less clear. In normal breast tissue, androgens are involved in inhibiting breast development (Dimitrakakis and Bondy 2009). In breast cancer (BCa), androgens have been shown to induce proliferative changes in breast tissue and promote growth of some BCa cell lines (Wong and Xie 2001; Xie *et al.* 1999).

PROSTATE CANCER

The Role of the Androgen Receptor in Prostate Cancer

Since 1941 when Huggins and Hodges first demonstrated that hormonal manipulation could result in antitumor activity in PCa (Huggins *et al.* 1941), androgen deprivation therapy (ADT) has been an essential component of the treatment of advanced disease. However, as the disease evolves, castration-sensitive PCa initially responding to ADT eventually develops mechanisms of resistance leading to PCa growth and the devolvement to a castration-resistant disease state. However, even in castration-resistant PCa (CRPC), the AR continues to signal and drive disease growth, which fact has formed the biologic basis for the development of two novel agents, enzalutamide and abiraterone acetate.

Androgen Receptor Signaling Through CRPC—Medical or surgical castrating therapy is highly effective in over 80% of patients with newly diagnosed castration-sensitive PCa (Crawford *et al.* 1989). However, over time, PCa develops resistance mechanisms

generally manifested first by a rising prostate-specific antigen (PSA) despite androgen-lowering therapies. This phase of the disease is termed CRPC (Scher and Heller 2000). Mechanisms driving CRPC include upregulation of alternative androgen production pathways (Mostaghel *et al.* 2007; Titus *et al.* 2005), AR gene amplification or protein overexpression (Bubendorf *et al.* 1999; Haapala *et al.* 2007; Visakorpi *et al.* 1995), mutations within the LBD of the AR (Marcelli *et al.* 2000; Taplin *et al.* 2003), and activation of other signal transduction pathways (Carver *et al.* 2011).

CRPC cells have been shown to maintain intratumoral levels of testosterone even in the setting of androgen-lowering agents (Mostaghel *et al.* 2007; Titus *et al.* 2005). Orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists or antagonists have little to no effect on adrenal or intratumoral androgen production. Specifically, in the setting of medical castration, adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione are relatively unaffected. In addition, studies comparing metastatic CRPC (mCRPC) to primary tumor samples showed that within the mCRPC tumor cells, there was an upregulation of enzymes involved in androgen synthesis, most notably those catalyzed by members of the cytochrome P450 family (Holzbeierlein *et al.* 2004; Locke *et al.* 2008; Montgomery *et al.* 2008; Stanbrough *et al.* 2006).

AR gene amplification and protein overexpression is believed to be one of the key mechanisms in CRPC (Bubendorf *et al.* 1999; Haapala *et al.* 2007; Visakorpi *et al.* 1995). Unlike primary untreated PCa samples where AR overexpression is rare (<2%), locally recurrent PCa and metastatic sites in CRPC display AR gene amplification in 23% and 22% of samples, respectively. (Bubendorf *et al.* 1999). Circulating tumor cells taken from patients with mCRPC have also been shown to have AR overexpression in 30−60% of the samples analyzed (Attard *et al.* 2009; Bubendorf *et al.* 1999; Leversha *et al.* 2009). It is believed that AR overexpression leads to increased sensitivity of the AR towards castrate levels of testosterone, allowing the AR axis to continue to drive growth and proliferation even in the castrate state (Visakorpi *et al.* 1995; Waltering *et al.* 2009). *In vitro* models have shown AR overexpression to convert the first-generation AR antagonist bicalutamide to an agonist by altering recruitment of AR co-activator and co-repressor molecules (Chen *et al.* 2004).

Mutations in the AR in early-stage PCa are present but relatively rare (Marcelli *et al.* 2000). However, as the tumor progresses to a castration-resistant state, mutations within the AR can be seen in more than 10% of patients who have received treatment with first-generation antiandrogens (Taplin *et al.* 2003). Currently, over 100 somatic mutations in the AR have been identified and the most clinically relevant are thought to alter co-factor binding and ligand specificity. These mutations have been described as enabling alternative steroidal molecules, including progesterone and AR antagonists, to activate the AR pathway (Culig *et al.* 1993; Zhao *et al.* 2000).

Another potential mechanism leading to CRPC is the activation of other signal transduction pathways which bypass or interact with the AR axis. The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is a commonly identified pathway that has shown an association with the AR in PCa (Carver *et al.* 2011; Thomas *et*

al. 2013). *In vivo* models have revealed that activation of one pathway leads to downregulation of the other due to a reciprocal feedback mechanism, and inhibition of both pathways has led to near-complete cancer regression in a Pten-deficient murine PCa model (Carver *et al.* 2011). It has also been shown, in an *in vitro* model, that combining the AKT inhibitor AZD5363 with the AR antagonist bicalutamide resulted in synergistic inhibition of cell growth and induction of cell death (Thomas *et al.* 2013).

First-Generation Antiandrogens

Bicalutamide, nilutamide and flutamide are first-generation or conventional nonsteroidal antiandrogens that bind to the LBD of the AR with a relatively low affinity compared to androgens. Historically, the indication for first-generation antiandrogens was to prevent a flare phenomenon or a transient rise of a patient's testosterone after the initiation of a gonadotropin-releasing hormone (GnRH) analog (Kuhn *et al.* 1989). Another commonly used indication for first-generation antiandrogens, which remains controversial, is their use with a GnRH agonist, a strategy(?) called combined androgen blockade (CAB). Multiple large phase III clinical trials, as well as multiple large meta-analyses, have compared the efficacy of CAB to a GnRH agonist alone (Bennett *et al.* 1999; Group 1995, 2000; Samson *et al.* 2002). The National Comprehensive Cancer Network (NCCN) PCa guidelines version 1.2015 (Samson *et al.* 2002) acknowledge that CAB provides little to no benefit over ADT alone in patients with metastatic disease and do not recommend antiandrogen monotherapy in that it appears to be less effective than surgical or medical castration. However, the NCCN guidelines also cite a meta-analysis that showed a 5−20% improvement in overall survival (OS) with CAB compared to GnRH agonist alone (Samson *et al.* 2002).

One limitation of the long-term use of first-generation antiandrogens is the well-documented AR-driven antagonist to agonist potential. Identified mutations within the LBD at codon 741 or codons 874 and 877 result in bicalutamide or flutamide, respectively, being transformed from a weak antagonist to an agonist (Hara *et al.* 2003; Tan *et al.* 1997). The agonist potential of first-generation antiandrogens is manifested by a paradoxical decline in PSA upon antiandrogen discontinuation, a phenomenon known as antiandrogen withdrawal (AAWD) (Kelly and Scher 1993; Small and Carroll 1994).

Two large phase III clinical trials conducted by the Southwest Oncology Group (SWOG) and the Cancer and Leukemia Group B (CALGB), respectively, measured the incidence of AAWD in first-generation antiandrogens. SWOG 9426 evaluated 210 patients with progressive prostate cancer for a median follow-up of 5.0 years. Sixty-four percent of the patients were on flutamide, 32% on bicalutamide and 3% on nilutamide. The study found that 21% of patients had a PSA decline ≥50% with a median progression-free survival (PFS) of 3 months after stopping the first-generation antiandrogen. Furthermore, 19% of patients had a 1-year or greater progression-free interval, indicating an overall durable response to stopping treatment (Sartor *et al.* 2008). CALGB 9583 evaluated the therapeutic effect of AAWD versus AAWD with ketoconazole therapy in patients with CRPC. This study found an 11% rate of PSA response in the AAWD-alone arm versus a 27% rate of response with the addition of ketoconazole. However, there was no difference in OS between arms (Small *et al.* 2004).

A Second-Generation Antiandrogen — Enzalutamide

Enzalutamide (formerly MDV3100) is an oral nonsteroidal antagonist of the AR. The preclinical development phase for MDV3100 used multiple cell lines. For example, the LNCaP/AR cell line was constructed to contain higher levels of wild-type AR and subsequently established that MDV3100 had higher binding affinity than bicalutamide. In addition, the VCaP cell line, which expresses endogenous AR gene amplification, was used to compare the efficacy of MDV3100 to that of bicalutamide (Tran *et al.* 2009). Enzalutamide was pursued for clinical development based on the recognition that it binds to the AR with higher affinity than prior antiandrogens, reduces the nuclear translocation, and impairs DNA binding of both androgen response elements and co-activators.

Promising enzalutamide preclinical data led to a phase I/II dose-escalation study of 140 men with progressive CRPC, (75)(54%) of whom had received prior chemotherapy. Most subjects had radiographic evidence of metastatic disease at baseline, including 109 men (78%) with metastases in bone, 75 (54%) in lymph nodes, and 13 (9%) in the viscera. Antitumor activity was seen in all dosing cohorts, with a ≥50% decline in PSA in 78 (56%) of the subjects. Median time to PSA progression, using the Prostate Cancer Working Group 2 definition of a ≥25% increase in PSA from the nadir (Scher *et al.* 2008), was 32 weeks in the entire cohort while median time to radiographic progression was 47 weeks. The most common adverse event (AE) was fatigue that was related to dose and improved with dose reduction. Fatigue (27%), nausea (9%), dyspnea (8%), anorexia (6%) and back pain (6%) were the most common mild (grade 2) AEs. Three potential seizure-related events occurred at dose ≥360 mg/day (Scher *et al.* 2010). Given the overall positive results of this phase I/II study, enzalutamide was then evaluated in two phase III studies, AFFIRM and PREVAIL.

AFFIRM, which evaluated men with CRPC previously treated with chemotherapy, randomized subjects in a 2:1 ratio between enzalutamide at 160 mg/day and placebo, with the primary endpoint of OS. A total of 1199 patients were enrolled and, following a planned interim analysis, the study was stopped due to efficacy, demonstrating a statistically significant median OS benefit: 18.4 months in the enzalutamide group compared to 13.6 months in the placebo group (hazard ratio [HR] 0.63; 95% confidence interval [CI], 0.53−0.75; $P<0.001$). Secondary endpoints all favored the enzalutamide arm, including a PSA decline of ≥50%, soft-tissue response rate, quality-of-life measures, time to PSA progression, radiographic PFS (rPFS) and time to the first skeletal-related event (SRE). Fatigue (34%), diarrhea (21%), and hot flashes (20%) were all higher in the enzalutamide arm. There were also 5 (0.6%) seizure events in the enzalutamide arm (vs 0 in the placebo arm) that were thought to be related to potential predisposing factors including brain metastasis (Beer *et al.* 2014; Scher *et al.* 2012). However, given the concern for seizure activity, a phase IV multicenter, single-arm, open-label clinical trial is ongoing to evaluate the risk of seizure among patients with mCRPC at high risk for seizure activity (UPWARD trial [NCT01977651]).

PREVAIL evaluated chemotherapy-naïve men with mCRPC in a 1:1 randomization to enzalutamide 160 mg/day or placebo. The primary endpoints of the trial were rPFS and OS. A total of 1717 patients were evaluated (872 enzalutamide, 845 placebo). At 12 months of

follow-up, the rate of rPFS was 65% in the enzalutamide arm versus 14% in the placebo arm (HR 0.19; 95% CI 0.15−0.23; $P<0.001$). At the time of the interim analysis, 72% of patients were alive in the enzalutamide arm compared to 63% in the placebo arm which correlated to a significant 29% reduction in the risk of death in the enzalutamide arm (HR 0.71; 95% CI 0.60−0.84; $P<0.001$). In addition, all prespecified secondary endpoints favored the treatment arm, including time until the start of chemotherapy, time to first SRE, complete or partial soft-tissue response, time to PSA progression, and rate of ≥50% PSA. Fatigue and hypertension were the most common grade 3 or higher AEs. Two seizure events occurred on trial, one in each treatment arm (Beer *et al.* 2014).

Enzalutamide is now being investigated in a variety of combinatorial trials. These include a phase III clinical trial in first-line mCRPC comparing the combination of enzalutamide plus abiraterone acetate and prednisone to enzalutamide alone (led by the Alliance for Clinical Trials in Oncology [NCT01949337]). Enzalutamide is also being compared to placebo in patients with nonmetastatic CRPC in the PROSPER trial (NCT02003924).

Mechanism of Resistance to Enzalutamide—Notwithstanding the promising results from the AFFIRM and PREVAIL trials, most men on enzalutamide will develop progressive disease and therefore identification of resistance mechanisms is critical (Beer *et al.* 2014; Scher *et al.* 2012). A mutation within the LBD of the AR, F876L, has been shown to be a driver of enzalutamide resistance (Balbas *et al.* 2013). Similar to the LBD mutations that result in resistance to first-generation antiandrogens, F876L has been shown to convert enzalutamide as well as ARN-509, another second-generation AR antagonist, from an antagonist to an agonist (Balbas *et al.* 2013).

Upregulation of the glucocorticoid receptor (GR) has also been identified as a mechanism of resistance towards enzalutamide. Acute AR inhibition leads to GR upregulation and when the GR, a nuclear receptor in the same family (NR3C) as the AR, binds to its ligand (dexamethasone), an enzalutamide-resistant phenotype is maintained. However, when a GR antagonist is introduced, enzalutamide sensitivity is reestablished, implying an important mechanistic relationship between the AR and the GR in enzalutamide resistance (Balbas *et al.* 2013). In addition, a post-hoc analysis of the AFFIRM trial showed that patients who were on corticosteroids during the study had a reduction in OS and higher rates of grade 3/4 toxicity independent of their treatment. (Scher *et al.* 2013).

The PI3K/AKT/mTOR signaling pathway has also been shown to be a potential mechanism of resistance towards enzalutamide. As stated previously, preclinical models have revealed that the AR and the PI3K pathways cross-regulate each other through a reciprocal feedback mechanism and there are currently ongoing clinical trials evaluating the safety and efficacy of inhibiting both pathways (Table 3) (Carver *et al.* 2011).

Finally, the AR splice variant (AR-V), specifically AR-V7, has recently been shown to be a potential mechanism of resistance and a predictive marker of response to enzalutamide in both preclinical and clinical models. One study evaluated 31 men treated with enzalutamide, of whom 38.7% had a detectable AR-V7 measured by circulating tumor cells. Compared to subjects without a detectable AR-V7, patients with AR-V7 had inferior PSA response rates

(0% vs 53%, *P*=0.004), time to PSA progression (median, 1.4 months vs 6.0 months; *P*<0.001), clinical and radiographic PFS (median, 2.1 months vs 6.1 months; *P*<0.001) and OS (median, 5.5 months vs not reached; *P*=0.002) (Antonarakis *et al.* 2014). Preclinical data have shown that AR-V expression is increased in a castrate state and potentially suppressed by testosterone. It is believed by some that the AR-V is an acute biochemical response to castration rather than a mutation associated with a gain of function or clonal expansion to enzalutamide. These findings will need to be validated clinically but could provide insight into the AR-V resistance pattern (Watson *et al.* 2010). Further trials are ongoing to validate the AR-V7 assay as a potential predictive biomarker for AR-directed therapy in patients with CRPC.

An Androgen Biosynthesis Inhibitor — Abiraterone Acetate

Abiraterone acetate (AA) (formerly known as CB7630), a prodrug of abiraterone, is a potent, orally available, selective inhibitor of both 17α-hydroxylase/c17,20-lyase which targets adrenal and tumor intracrine androgen biosynthesis. Preclinical and early-phase clinical studies displayed promising efficacy with AA for patients with mCRPC; these led to two large phase III clinical trials (COU-AA-301 and COU-AA-302) (de Bono *et al.* 2011; Ryan *et al.* 2013).

COU-AA-301 enrolled 1195 patients with mCRPC previously treated with docetaxel and randomized them in a 2:1 ratio to AA 1,000 mg/day with prednisone 5 mg twice daily or to placebo plus prednisone 5 mg twice daily (de Bono *et al.* 2011). At a median follow-up of 20.2 months, median OS in the AA group was 15.8 months versus 11.2 months in the placebo group (HR 0.74, 95% CI 0.64−0.86; *P*<0.0001) (Fizazi *et al.* 2012). The most common grade 3 and 4 AEs in the AA group were fatigue (9%), anemia (8%), back pain (7%) and bone pain (6%) (Fizazi *et al.* 2012). On the basis of the survival advantage demonstrated, AA plus prednisone was FDA approved in April 2011 for men with CRPC who progressed after docetaxel-based therapy.

COU-AA-302 randomly assigned 1088 patients with chemotherapy-naïve mCRPC to AA plus prednisone or placebo plus prednisone. After a median follow-up of 22.2 months, median OS in the placebo group was 27.2 months compared to the AA group where median OS was not reached (HR 0.75; 95% CI 0.61−0.93; *P*=0.01) (Ryan *et al.* 2013). In addition, recently presented data at the European Society for Medical Oncology 2014 annual meeting showed, after a median follow-up of 49.4 months, a significantly prolonged median OS in the AA plus prednisone arm compared to the prednisone-only arm (34.7 vs 30.3 months; HR 0.80; 95% CI 0.69−0.93; *P*=0.0027) (Ryan *et al.* 2015). In the initial analysis, the other co-primary endpoint, rPFS, also showed benefit for the AA group with median rPFS of 16.5 months compared to 8.3 months for placebo (HR 0.53; 95% CI 0.35−0.52; *P*<0.001) (Ryan *et al.* 2013). Key secondary endpoints also favored the AA group; these included time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status. AEs associated with mineralocorticoid excess and liver function test abnormalities, seen in previous AA trials, were again displayed (de Bono *et al.* 2011; Ryan *et al.* 2013). AA received FDA approval in December 2012for patients with chemotherapy-naïve mCRPC (National Cancer Institute 2013).

Mechanisms of Resistance Towards Abiraterone Acetate—Similar to enzalutamide, patients with mCRPC on AA plus prednisone will eventually develop resistance(de Bono *et al.* 2011; Ryan *et al.* 2013). In 31 patients treated with AA, AR-V7 was also associated with inferior PSA response rates (0% versus 68%; P=0.004), shorter time to PSA progression (median, 1.3 months versus not reached; P<0.001), clinical or radiographic PFS (median, 2.3 months versus not reached; P<0.001) and OS (median, 10.6 months versus not reached, P=0.006) (Antonarakis *et al.* 2014).

Another proposed predictive biomarker for AA response in CRPC is the TMPRSS2-ERG fusion gene. Samples taken from the initial phase I/II clinical trial evaluating AA identified 15 patients who had ERG rearrangement, 12 (80%) of whom had a PSA decline of ≥90% (Attard *et al.* 2009). In COU-AA-302, 117 patients with evaluable samples were identified as having the ERG rearrangement. Upon ERG subtype analysis, patients with a unique ERG subtype were found to have a non-significant trend towards rPFS and time to PSA progression compared to the ERG non-rearrangement cohort (Attard *et al.* 2015). However, this biomarker remains controversial given that another study did not find the presence of the TMPRSS2-ERG fusion on circulating tumor cells to be associated with AA response (Danila *et al.* 2011).

In addition, recent case reports have noted a paradoxical decline in PSA in patients who stopped abiraterone acetate due to disease progression, similar to the AAWD phenomenon. The underlying mechanism for this observation is unknown at this time (Caffo *et al.* 2013; Gauthier *et al.* 2012).

BREAST CANCER

Unlike PCa, the antiandrogen narrative in BCa is in its infancy, despite knowledge of AR expression in BCa reaching back almost 50 years (1973; Engelsman *et al.* 1974).

The AR in Breast Cancer

Historically, androgens were considered beneficial for the treatment of BCa. Prior to the 1970s, BCa was treated with DHT, testosterone, and fluoxymesterone with some clinical efficacy (Adair and Herrmann 1946; Kennedy 1958; McNamara *et al.* 2014). However, androgen therapy fell out of favor due to concerns of aromatization to estrogen, virilizing effects, and the availability of the estrogen-targeted therapy tamoxifen (Garay and Park 2012; Kennedy 1958; Narayanan *et al.* 2014; Peters *et al.* 2012; Santagata *et al.* 2014). With recognition of BCa heterogeneity, increased knowledge of the androgen signaling pathway, and better models of anti-estrogen resistance mechanisms, there has been renewed interest in the role of androgens and AR targeting for the treatment of BCa.

Early epidemiologic studies alluded to an association between BCa incidence and higher levels of circulating androgens (Berrino *et al.* 1996; Dorgan *et al.* 2010). Retrospective analyses show an increased risk of BCa in pre- and post-menopausal women with higher levels of estrogens, testosterone, and adrenal androgens (Berrino *et al.* 1996; Dorgan *et al.* 2010; Eliassen *et al.* 2006; Key *et al.* 2002; Page *et al.* 2004). Animal models reveal that combined testosterone and estrogens induce proliferation in breast tissue, overexpression of

AR, and activation of estrogen-responsive genes, all of which are reversed by antiandrogen therapy (Nantermet *et al.* 2005; Wong and Xie 2001; Xie *et al.* 1999). *In vitro*, differing responses to androgen administration are observed for different BCa cell lines. Growth for MCF-7 (estrogen receptor [ER]-positive and human epidermal growth factor receptor 2 [HER2]-negative) and MDA-MB-453 (ER-HER2 -/+) cells were promoted by presence of androgens (DHT and non-metabolized synthetic mibolerone), whereas T47-D (ER+HER2-) and ZR-75-1 (ER+HER2+) cells were inhibited by androgens. These changes were reversed by the AR antagonist, hydroxyflutamide (Birrell *et al.* 1995). The differing response to androgens in breast cell lines implies variable factors involved in AR signaling.

Clinically, AR is highly expressed in both normal and malignant breast tissue, with positive expression defined as immunohistochemical (IHC) nuclear staining ≥1% or ≥10%, depending on the study (Gucalp *et al.* 2013; He *et al.* 2012; Ogawa *et al.* 2008; Safarpour *et al.* 2014; Tang *et al.* 2012). The proportion of tumors co-expressing AR varies depending on the intrinsic subtype of BCa. For example, in ER+, HER2+, and triple-negative BCa (TNBC), prevalence of AR by IHC is 70−95%, 50−81%, and 12.5−35%, respectively (Agoff *et al.* 2003; Choi *et al.* 2015; Cochrane *et al.* 2014; Hu *et al.* 2011; Micello *et al.* 2010; Park *et al.* 2010; Safarpour *et al.* 2014). When classifying BCa by gene expression-derived intrinsic subtype, luminal A represents the highest proportion of AR+ tumors (91%) and basal-like (32%) demonstrates the lowest, with luminal B (68%) and HER2 (59%) measuring between the two (Agoff *et al.* 2003; Collins *et al.* 2011; Isola 1993; Lehmann *et al.* 2011; Loibl *et al.* 2011; Safarpour *et al.* 2014).

While AR is expressed across all subtypes of BCa, the prognostic role is not fully established and evidence is occasionally conflicting. The association between AR expression and survival appears to be linked to tumor subtype, nature of treatment, and stage of disease. In a series of 215 women, co-expression of ER and AR conferred a survival advantage (AR+ 94% vs AR- 75%, P=0.0002), but AR expression had no effect on survival in the ER- tumors (AR+ 60% vs AR- 70%, P=0.32) (Peters *et al.* 2009). In a separate series of 347 women, improved OS was seen with AR expression independent of ER/progesterone receptor (PR) status (79% in AR+ vs 64% in AR-, P=0.004) (Gonzalez-Angulo *et al.* 2009). Although AR is often associated with improved clinicopathologic features compared to AR non-expressing tumors, that is not universal and in some series AR expression was linked to poorer OS or no improvement in OS (Agoff *et al.* 2003; Park *et al.* 2010). In a cohort of 492 women with TNBC (17.7% AR+), AR expression correlated with older age (P<0.001), poor OS (P=0.008) and decreased DFS (P=0.011). In the stratified analysis, DFS and OS were driven by patients with early-stage disease not related to lymph node involvement or metastatic disease (Choi *et al.* 2015). In an earlier study of BCa patients treated with tamoxifen, lack of AR expression was associated with poorer response to therapy and a trend toward decreased survival compared to AR+ tumors (Bryan *et al.* 1984). In women treated with neoadjuvant chemotherapy, AR expression was associated with improved disease-free survival (DFS) and OS, compared to tumors not expressing AR (Loibl *et al.* 2011). Post-treatment stratified analysis demonstrated that AR expression predicted better DFS (85.7% vs 65.5%) and OS (95.2% vs 76.2%) in the TNBC group, but not in the other predefined subgroups including luminal A, luminal B and HER2 (Loibl *et al.* 2011). In

women with TNBC, decreased rates of pathologic complete response were observed after neoadjuvant anthracycline-based chemotherapy (10% in a new TNBC subtype called "luminal AR" [LAR] vs 52% in other TNBC subtypes) (Lehmann *et al.* 2011; Masuda *et al.* 2013). Conversely, there is evidence that AR expression is predictive of chemotherapy responsiveness in ER+ disease, with improved 5-year event-free survival in tumors with high AR mRNA expression (74% vs 57%, P=0.013) and shorter event-free survival when AR mRNA expression was low (odds ratio [OR] 2.86, 95% CI 1.29−6.35, P= 0.01), adjusted for HER2, Ki67, tumor size, age and tumor grade (Witzel *et al.* 2013).

It is likely that AR has a role across all BCa subtypes, yet its value as a prognostic marker remains unclear. In fact, the significance of AR may vary across subtypes as a result of its varying relationship to ER in the different subtypes. We will first review AR in the context of TNBC, where the first androgen-dependent BCa growth was identified and subsequently exploited as an investigational therapeutic target.

Triple-Negative Breast Cancer

Doane *et al.* identified a subset of ER- breast tumors with a gene expression profile similar to that of ER+ BCa, including genes that are targets of or responsive to androgen (Doane *et al.* 2006). In a separate series of 587 TNBC tumors, 6 distinct subgroups were recognized based upon their molecular profiles; one of these confirmed the previously described ER-AR + subtype and was termed luminal androgen receptor (LAR) (Lehmann *et al.* 2011). Compared to other TNBC subtypes, the LAR tumors reveal a >10-fold (P<0.004) protein expression of AR and are enriched for hormone-regulated pathway genes including genes involved in steroid synthesis, porphyrin metabolism, and androgen/estrogen metabolism. The most highly expressed genes are downstream of AR and classify a luminal gene expression profile (Doane *et al.* 2006; Lehmann *et al.* 2011). The LAR subtype demonstrated similarities to a previously identified histologically distinct subtype, molecular apocrine (Birrell *et al.* 1998; Farmer *et al.* 2005). When tumors were selected based on histologic apocrine features, gene expression profile highly correlated with the LAR subtype, suggesting the LAR TNBC group includes tumors classified with molecular apocrine histology (Lehmann *et al.* 2011).

Doane and colleagues went on to find a cell line, MDA-MB-453, which recapitulated the molecular profile of the LAR subtype with profile of AR+/ER-/PR-/HER2 -/+(low), depending on the testing laboratory (Vranic *et al.* 2011). In preclinical experiments, these cells exhibit androgen-dependent growth and are inhibited by the AR antagonist, flutamide, in an estrogen-independent manner (Doane *et al.* 2006; Farmer *et al.* 2005). These data were hypothesis-generating and led to the first, proof of concept trial for androgen blockade in patients selected by AR status with metastatic ER/PR- BCa.

Bicalutamide as Treatment for AR+ TNBC—Bicalutamide shows enhanced cell death in the AR+ MDA-MB-453 BCa cell line with reduction of HER3 and pAKT signaling (Ni *et al.* 2011). The Translational Breast Cancer Research Consortium (TBCRC) led the first, proof of concept, phase II trial testing the antitumor activity of bicalutamide 150 mg daily in women with metastatic TNBC, selected by AR status. TBCRC011 screened >450 patients

for AR status using IHC testing of primary or metastatic tumors. Twelve percent of patients tested AR+, defined as >10% nuclear staining. This trial met its prespecified endpoint of clinical benefit rate (CBR; defined as complete response, partial response, or stable disease >24 weeks) of 19% (95% CI 5−42%) with a median PFS of 12 weeks (Gucalp *et al.* 2013). Bicalutamide was well tolerated with no grade 4 or 5 AEs. Grade 3 toxicities were limited to elevated liver function tests in 3 patients. Grade 1 events that occurred in >10% of patients (n=28) included AST/ALT elevation (n=10), hot flashes (n=6), limb edema (n=6), and fatigue (n=5) (Gucalp *et al.* 2013). The antitumor activity demonstrated by bicalutamide is highly compelling and comparable to that seen in chemotherapy trials for treatment of TNBC unselected by AR status.

Moreover, the benefit of an anti-AR approach in AR+ TNBC was recently published in a case report describing the experience of a woman with AR 100%, ER-/PR-/HER2- metastatic BCa who had progressive disease despite 6 lines of cytotoxic chemotherapy. She achieved a complete response after 4 months of treatment with bicalutamide and remained disease-free for >12 months at the time of publication (Arce-Salinas *et al.* 2014). Although anecdotal, this is the first report of a response with the utilization of AR-targeted therapy in a carefully selected population with androgen-driven disease.

Enzalutamide in AR+ TNBC—Building upon the promise of next-generation AR antagonists developed for the treatment of PCa, investigators have begun to study these agents in AR+ BCa. In a phase I dose-escalation trial in patients with advanced BCa, enzalutamide was found to be well tolerated at 160 mg daily with common (>10%) treatment-related AEs including nausea, vomiting and fatigue; no treatment-related AEs ≥ grade 3 were reported (Schwartzberg *et al.* 2014; Traina *et al.* 2013). For patients with AR+ metastatic TNBC, a phase II trial of single-agent enzalutamide has completed accrual (NCT01889238) and stage 1 results were recently presented (Traina *et al.* 2014; Traina *et al.* 2013). IHC testing showed ≥10% AR-positivity in ~55% of tumors screened. The primary endpoint is CBR ≥16 weeks; secondary endpoints include CBR ≥24 weeks, PFS, response rate and toxicity. In 26 evaluable patients, CBR at 16 weeks was 42% (11/26) and CBR at 24 weeks was 35% with 1 partial response and 1 complete response. The stage 2 data continue to mature, but statistical boundaries for efficacy were already achieved such that the null hypothesis was rejected (Traina *et al.* 2014). Additionally, correlatives were an important part of this trial design, and progress has been made in defining a companion biomarker of response to enzalutamide.

Estrogen Receptor-Positive Breast Cancer

The AR is highly co-expressed in ER-positive cells, ranging between 70−95% (Agoff *et al.* 2003; Collins *et al.* 2011; Isola 1993; Lehmann *et al.* 2011; Loibl *et al.* 2011; Safarpour *et al.* 2014). Although the functional relationship of the AR and ER is not completely understood, ER/AR crosstalk has been suggested by preclinical data. The domains of AR and ERα can physically interact, leading to transcriptional consequences. For example, in the presence of E2 (estradiol), the N-terminus of the AR can interact with the LBD of ERα, leading to a transcriptional inhibitory interaction in both receptors (Panet-Raymond *et al.* 2000). Transfection of the AR DBD in BCa cells is sufficient to inhibit ERα activity,

inferring a direct competition for binding sites. ARA70, an AR cofactor, also interacts with ERα and AR has demonstrated the ability to bind to estrogen response elements (Fioretti *et al.* 2014; Panet-Raymond *et al.* 2000; Peters *et al.* 2009).

Understanding the relationship between ER and AR signaling pathways may be most relevant when discussing its role in anti-estrogen therapy. In patients with previously treated ER+ disease, increased androgen production is considered a potential indicator for resistance to anti-estrogen therapy and a possible pathway for growth and survival of tumor in treated patients. Androgens are converted by aromatase to estrone and estradiol. Aromatase inhibitors (AIs) block the conversion of androgens to estrogens by inhibiting this enzyme, resulting in an increase in androgens (Cochrane *et al.* 2014). Mouse models treated with an AI demonstrate markedly elevated intratumoral testosterone concentrations (Wong and Xie 2001). In women treated on AI therapy, circulating testosterone, androstenedione and DHEA-S levels are increased and high levels of adrenal androgen prior to treatment can predict a propensity for AI failure (Morris *et al.* 2001). Transfection of AR into ER+ cells confers resistance to both AI therapy and tamoxifen (De Amicis *et al.* 2010). Exogenous overexpression of AR renders the ER+ MCF-7 BCa cell lines resistant to inhibitory effects of tamoxifen in growth assays and in xenograft models (De Amicis *et al.* 2010; Peters *et al.* 2012). Furthermore, the AR-overexpressing cells remain sensitive to growth with DHT and inhibition with bicalutamide (De Amicis *et al.* 2010). To further delineate this relationship, Peters *et al.* looked at AR:ER ratio. The results showed that a high ratio of AR:ER, rather than absolute AR expression level, may be more predictive of tamoxifen failure. *In vitro* studies show that E2-induced proliferation of T-47D and ZR-75-1 BCa cell lines was decreased when cells demonstrated an increased AR:ER ratio (Peters *et al.* 2009). Overall, AR expression in ER+ cancers is associated with good prognostic indicators including improved OS and DFS, lower grade, smaller tumor size and lack of lymph node involvement at diagnosis (Castellano *et al.* 2010; Gonzalez-Angulo *et al.* 2009; Niemeier *et al.* 2010; Peters *et al.* 2009; Schwartzberg *et al.* 2014; Tokunaga *et al.* 2013). However, AR appears to predict resistance or decreased activity to anti-estrogen therapy (Bryan *et al.* 1984; D'Amato *et al.* 2013; De Amicis *et al.* 2010). These observations make combined AR and ER targeting appealing.

Enzalutamide in ER+ Breast Cancer—In BCa cell lines, enzalutamide abrogated androgen-mediated proliferation of ER+ (MCF-7, BCK4, T47D and ZR-75-1) and ER- BCa cell lines (MDA-MB-453). Specifically, in cell lines MCF-7 and BCK4 (AR+ER+) and MDA-MB-543 (AR+ER-), proliferation was stimulated by DHT and DHT-mediated growth was blocked by enzalutamide (Cochrane *et al.* 2014). Xenograft models exhibited similar results with reduction in tumor size when oral enzalutamide was administered. This occurred in a dose-dependent fashion (Cochrane *et al.* 2014).

The previously described phase I trial included expansion cohorts which tested enzalutamide in combination with exemestane, anastrozole or fulvestrant. Of note, enzalutamide induces CYP3A4, an enzyme involved in metabolism of exemestane and anastrozole. Concurrent treatment with enzalutamide reduced exemestane exposure by ~40% due to this interaction. Doubling the dose, as recommended by the US product label, when combined with potent CYP3A4 inducer appears to restore the exemestane exposure (Schwartzberg *et al.* 2014).

Anastrozole exposure was reduced by nearly 90% with concurrent enzalutamide, therefore the combination is not being further developed. The cohort of enzalutamide and fulvestrant is ongoing (NCT01597193) but not expected to encounter similar drug interactions. A randomized, placebo-controlled, phase II trial is evaluating exemestane with or without enzalutamide in 240 patients with ER/PR+/HER2- advanced BCa (Schwartzberg *et al.* 2014). The co-primary endpoint is PFS in all patients and in patients with AR+ disease. Cross-over is allowed following RECIST 1.1 progression. Secondary endpoints include CBR at ≥24 weeks, response rate, duration of response, safety and tolerability.

Abiraterone Acetate in ER+ Breast Cancer—Based on the mechanism of action of AA as a CYP17 inhibitor, there was a rationale for studying its potential benefit in ER+ BCa, as reduced levels of estradiol are expected from upstream inhibition of the steroid synthesis pathway. A large, prospective, phase II trial randomized 300 postmenopausal women with ER+ metastatic BCa to one of 3 treatment arms: 1) exemestane, 2) exemestane with AA and prednisone or 3) AA and prednisone. The primary endpoint of the study was PFS. An interim analysis led to early closure of the AA plus prednisone arm due to futility. At the final analysis, there was no significant difference in median PFS between the combination arm and the exemestane-alone arm (HR 0.96; 95% CI 0.70–1.32; P=0.795) or for the AA plus prednisone arm compared with exemestane-alone (HR 1.1, 95% CI 0.82–1.60; P=0.437). Treatment was relatively well-tolerated and no unexpected AEs occurred. Grade ≥3 AEs including hypokalemia, hypertension, and AST/ALT elevation were mitigated by concurrent prednisone yet were numerically more common in the AA treatment arms (O'Shaughnessy *et al.* 2014).

The failure of abiraterone to significantly improve outcome in this patient population may be related to pathways already discussed. First, the importance of the GR should not be underestimated. It has been hypothesized that the concurrent requirement for prednisone with abiraterone may activate signaling through the GR, thereby potentiating tumor growth. Second, although abiraterone effectively reduced estradiol levels in pharmacokinetic correlatives associated with this trial, progesterone levels were significantly increased, above that of typical physiologic levels (O'Shaughnessy *et al.* 2014). Third, CYP17A1 inhibition simultaneously decreases testosterone with stimulatory estradiol; in certain cell lines (ie, T47-D and ZR-75-1), the androgen has demonstrated protective effects which may be lost with CYP17 inhibition (Birrell *et al.* 1995). The complex cross-talk between AR- and ER- pathways may counter the benefits of reduced estradiol levels. Ongoing correlative analyses are anticipated which may clarify the role, if any, for AA in the treatment of BCa.

HER2-Positive Breast Cancer

AR is enriched in ER-/HER2+ BCa, with 77% of HER2-amplified tumors expressing AR, compared to 30% in HER2- (Micello *et al.* 2010). Preclinical observations indicate that hyperactivation of HER2 enhances AR and that AR upregulation is involved in a positive feedback loop with HER2 (Ni *et al.* 2011). AR mediates ligand-dependent activation of wnt and HER2 signaling pathways, through direct transcription of WNT7B and HER3 and collaboration between AR and FOXA1 transcriptional activation (Ni *et al.* 2011). In some series, survival appears unaffected by AR status whereas others suggest more favorable

morphology when HER2 and AR are co-expressed (Arslan *et al.* 2012; Gonzalez-Angulo *et al.* 2009; Lin *et al.* 2012; Micello *et al.* 2010). Further understanding regarding the role of AR in HER2+ disease is warranted (Niemeier *et al.* 2010). Trials for the combination of HER2 blockade with androgen blockade using enzalutamide and trastuzumab are ongoing (NCT02091960).

NOVEL AGENTS

Despite hormone deprivation therapy, tumors eventually progress to a castrate-resistant state in PCa through either AR overexpression and gene amplification, increased intratumoral androgen synthesis, aberrant AR expression (either by mutation or splice variants) and activation of alternative pathways (Chen *et al.* 2004; Ford *et al.* 2003; Montgomery *et al.* 2008; Stanbrough *et al.* 2006). Resistance to anti-estrogen therapy similarly occurs for patients with ER-driven advanced BCa and likewise for AR-driven BCa. An increased recognition of the mechanism utilized by the AR in a castrate state has led to the development and subsequent approval of enzalutamide and AA, both shown to improve OS for men with mCRPC (Beer *et al.* 2014; Fizazi *et al.* 2012; Scher *et al.* 2012). Investigations in women with BCa are ongoing but offer hope for a potential, highly effective strategy for endocrine manipulation.

Novel therapies in various stages of development inhibiting aspects of the AR pathway include: LBD inhibitors (ARN-509, ODM-201), androgen synthesis inhibitors (TOK-001, TAK-700, VT-464), selective AR downregulators (AZD-3514), selective AR modulators (GTx-024), and target chaperone inhibitors (OGX-427, AT13387, STA-9090). These are described below and in Tables 1 and 2 and illustrated in Figure 2.

Next-Generation AR Antagonists — Targeting the LBD

ARN-509 is a second-generation AR antagonist with a mechanism of action similar to that of enzalutamide in that after binding to the LBD of the AR, it inhibits AR nuclear translocation and AR binding to androgen response elements. However, ARN-509 preclinical data have shown lower steady-state brain levels than with enzalutamide, suggesting a lower seizure potential with ARN-509 (Clegg *et al.* 2012; Scher *et al.* 2012). Phase I data suggest a linear pharmacokinetic profile and potential efficacy of the drug with a PSA decline defined as ≥50% from baseline in 46.7% of patients at 12 weeks. Treatment was well tolerated in the phase I trial, with the most frequent AEs reported being grade 1/2 fatigue in 47% of patients. Notably, no seizure activity occurred at any dosing level in the phase I study (Rathkopf *et al.* 2013a; Rathkopf *et al.* 2013b).

A phase II clinical trial of ARN-509 is currently ongoing in three cohorts of patients with CRPC including 1) treatment-naïve high-risk non-metastatic CRPC, 2) treatment-naïve mCRPC, and 3) AA-exposed mCRPC. Preliminary data showed a PSA response rate (based on the Prostate Cancer Working Group 2 criteria) at 12 weeks of 91% in the high-risk treatment-naïve non-metastatic CRPC arm, 88% in the treatment-naïve mCRPC arm, and 29% in the AA-exposed mCRPC population (Rathkopf *et al.* 2013a; Smith *et al.* 2013). ARN-509 is now being studied in a phase III randomized placebo-controlled clinical trial in men with non-metastatic CRPC (SPARTAN; NCT01946204) as well as in a phase I clinical

trial in combination with AA in men with mCRPC (NCT02123758). ARN-509 preclinical data also exhibit antitumor effects in BCa cell line MDA-MB-453 cells (Clegg *et al.* 2012) though the study has not advanced past the preclinical stage.

ODM-201 is a next-generation AR inhibitor which demonstrates binding of wild-type AR with higher affinity than enzalutamide, blocks nuclear translocation, and does not demonstrate agonist activity when AR is overexpressed nor experienceCNS penetration thus decreasing or eliminating its potential seizure activity (Moilanen *et al.* 2013). The phase I/II data from the ARADES trial supports its use as monotherapy in men with mCRPC, showing a tolerable safety profile. The most common AEs included fatigue (12%), hot flashes (5%) and decreased appetite (4%). A single grade 3 AE was reported, fatigue, with no grade 4 AEs. PSA response at 12 weeks (defined as ≥50% decrease from baseline) was obtained in 13/15 (87%) patients. All patients achieved partial response or stable disease by RECIST v1.1 criteria (Fizazi *et al.* 2013). The phase II data demonstrated PSA response at 12 weeks in 29%, 33%, and 33% of the dosing cohorts of 200 mg, 400 mg and 1400 mg, respectively (Fizazi *et al.* 2014). Currently, a phase III randomized placebo-controlled clinical trial is ongoing in patients with high-risk non-metastatic CRPC, the ARAMIS trial (NCT02200614).

Novel Androgen Synthesis Inhibitors

In contrast to targeting the LBD of the AR, inhibition of androgen synthesis with novel agents remains another viable strategy. TOK-001 (galeterone) is a semi-synthetic steroid analog which inhibits PCa cell growth by functioning as a CYP17 lyase inhibitor, AR antagonist for both wild-type and mutant AR as well as degrading AR protein. Results of the phase I trial, ARMOR 1, showed PSA reduction ≥30% in 24 patients (49%), including 11 (22%) who had ≥50% reduction in PSA (Taplin *et al.* 2012). The phase II trial, ARMOR2 (NCT01709734), is ongoing. (Taplin *et al.* 2014). Preliminary data from the phase II trial showed that the drug was well tolerated with most AEs (94%) being grade 1 or 2 and including nausea, diarrhea, fatigue and pruritus.

TAK-700 (orteronel) is a nonsteroidal oral androgen synthesis inhibitor, with affinity for 17,20-lyase over 17α-hydroxylase. Development of TAK-700 in PCa has been halted given that two large phase III trials in chemotherapy-naïve (ELM-PC 4) and chemotherapy-exposed (ELM-PC 5) patients with mCRPC both had negative results and showed no OS benefit (De Wit *et al.* 2014; Fizazi *et al.* 2015; Takeda 2013) A potential hypothesis explaining these negative findings is that TAK-700 was tested in a patient population exposed to a number of currently available agents including AA that could have influenced the phase III results.

TAK-700 is currently under investigation in metastatic BCa (NCT01808040, NCT01990209). Preclinical activity of TAK-700 provided the basis of this investigation; TAK-700 does not directly inhibit aromatase activity, but at a dose of 300 mg/kg it appears to suppress serum estradiol, testosterone, androstenedione and 17-hydroxyprogesterone to a similar degree as 0.1 mg/kg of anastrozole. In animal models, TAK-700 appears to suppress serum estradiol concentrations in hypophysectomized female rats and monkeys through

inhibition of CYP17A1 activity, suggesting a possible role for this agent in hormone-dependent BCa (Yamaoka *et al.* 2013).

VT-464, currently under investigation in PCa, is an oral nonsteroidal selective inhibitor of CYP 17,20 lyase with less activity towards CYP17 hydroxylase, therefore eliminating the need for concurrent steroid administration (Eisner *et al.* 2012; Figg *et al.* 2012). Preclinical data have shown that cell lines treated with VT-464 had significantly lower levels of testosterone and DHT compared to abiraterone-treated cells, suggesting a greater effect on AR pathway suppression with VT-464 (Toren *et al.* 2015). Both a phase I and a phase II clinical trial are actively recruiting patients (NCT02012920, NCT02130700).

Selective Androgen Receptor modulators (SARMs)

SARMs are a class of drugs in development; unlike androgen synthesis inhibitors, they act as selective androgen agonists and show promise as a potential therapeutic strategy in BCa. Enobosarm (GTx-024) is the farthest along in clinical development and demonstrates an agonist effect that in some populations inhibits BCa growth. Preclinical data show antitumor activity of GTx-024 in AR+ stably expressing cell lines MCF-7 (ER+) and MDA-MB-231 (TNBC) implanted subcutaneously into nude mice. Tumor growth was reduced >75% in MDA-MB-231-AR cells and 50% in MCF-7-AR cells compared to vehicle-treated tumors, demonstrating benefit (Dalton *et al.* 2013).However, it is uncertain how to best select the patients who may benefit from this therapeutic strategy. A phase II trial is open to accrual for the treatment of women with ER+ metastatic BCa (NCT01616758). The primary endpoint is clinical benefit at 6 months as measured by RECIST, with secondary objectives including objective response rate, PFS, and response in the AR+ subset.

Chaperone Inhibitors

As seen in figure 2, targeting the AR chaperone is another rational target currently under development. Heat shock proteins (hsp) are stress proteins functioning as molecular chaperones that play a variety of roles in hormone signaling pathways and transcription. They are transcriptionally upregulated in heat and stress, helping to protect cells from damage (Hong *et al.* 2013; Taipale *et al.* 2010). In AR signaling, molecular chaperones such as hsp90 assist in protein folding, trafficking, activation and transcription of AR. Hsp90 maintains AR in high affinity ligand-binding conformation to facilitate efficient response to its ligand (DHT). Clinical trials evaluating hsp90 inhibitors AT13387 and STA-9090 and an hsp27 inhibitor, OGX-427, are under development in both PCa (Table 1) and BCa (Table 2).

Preclinical activity of ganetespib (STA-9090) demonstrated decreased viability of PCa cell lines, independent of androgen sensitivity or AR status (He *et al.* 2013). However, the phase II trial of single-agent ganetespib in heavily pretreated men with CRPC failed to reach its primary endpoint of 6-month PFS, The trial was halted early due to 6-month PFS of 1.9 months (90%CI 1.7–2.7 months) with median OS of 10.2 months (90% CI: 2.3−18.3 months). The compound is no longer in development for PCa (Heath *et al.* 2013). In BCa, ganetespib preclinical data suggest activity in hormone receptor-positive (MCF-7, T47D), HER2-overexpressing (BT-474, Sk-BR3), TNBC (MDA-MB-231, OCUB-M) and inflammatory (SUM 149) BCa cell lines, with the HER2+ cell line BT-474 being the most

sensitive. Treatment of hormone receptor-positive cell lines led to potent dose-dependent destabilization of ER and PR, accompanied by increased hsp70 expression, a surrogate marker for hsp90 inhibition. In HER2+ cell lines, activated HER2 was degraded after exposure to ganetespib. In MCF-7 and MDA-MB-231 xenografts, ganetespib suppressed tumor growth and led to tumor regression in a BT-474 model (Friedland *et al*. 2014). Clinical trials are ongoing in breast cancer; however, these have primarily focused on patients with HER2+ tumors based on the preclinical data (NCT01273896; NCT02060253).

Dual Inhibition of AR and Other Signaling Pathways

In understanding the AR pathway, additional signaling pathways have been identified with potential implications in mediating AR downstream activity. Pathways include PI3K/AKT/MAPK, PTEN, p53, and cell-cycle regulators. Several novel therapies are in development with the hypothesis that dual inhibition of these companion pathways will be superior to single-agent anti-androgen therapy.

Enzalutamide and Abiraterone Acetate—Dual AR pathway inhibition is currently being evaluated by combining enzalutamide and AA in men with mCRPC. Interim results of an early-phase clinical trial found this combination approach to be well tolerated, with grade 3 AEs being elevated ALT, hypertension, and increase in alkaline phosphatase, arthralgias and bone pain. PSA decline (defined as ≥50% decline from baseline) was seen in 76% (37/49) of patients, of which 22/49 (45%) had a ≥90% decline in PSA (Efstathiou *et al.* 2014). A phase III randomized trial of enzalutamide versus enzalutamide plus AA and prednisone in men with mCRPC is currently ongoing (NCT01949337).

PI3K/AKT/mTOR—There is much attention given to alternative pathway activation in CRPC, particularly the PI3K/AKT/mTOR pathway. Early-phase clinical trials in CRPC are ongoing to simultaneously target the AR and PI3K/AKT/mTOR pathways. For example, an ongoing phase I trial in men with progressive mCRPC following treatment with AA (NCT02106507) is evaluating the safety, PK properties and maximum tolerated dose of ARN-509 and everolimus, an FDA-approved mTOR inhibitor used in other malignancies. In addition, abiraterone with a pan-PI3K inhibitor (BKM120) and a pan-Akt inhibitor (GDC-0068) are being investigated in mCRPC (NCT01634061, NCT01741753 and NCT01485861).

In BCa, this pathway has been a particular focus within the AR+ TNBC population, as it is enriched for PIK3CA-activating mutations (10/25, 40%; $P<0.002$) compared to AR- TNBC (1/25, 4%). AR+ TNBC cell lines stimulated by DHT demonstrated increased PI3K pathway activation. When treated with pan-PI3K inhibitors (GDC-0941, NVP-BKM120) and dual PI3K/mTOR inhibitors (GDC-0980, NVP-BEZ235), the TNBC cell lines expressing PIK3CA mutations showed the greatest sensitivity. An additive inhibitory effect was observed in cell lines that were more sensitive to single-agent bicalutamide, including MDA-MB-453, CAL148 and SUM185 cells, when an AR antagonist (bicalutamide) was used in combination with PI3K inhibitors (GDC-0941, GDC-0980) (Lehmann and Pietenpol 2014). Clinical trials are in development.

CONCLUSION

Androgen signaling has been the primary target for the treatment of PCa. Many novel therapies are in development to overcome the mechanisms that invariably create resistance to our currently available AR antagonists and strategies for androgen deprivation. Exploiting next-generation methods for inhibiting androgen signaling offers hope for improved outcomes in patients with advanced PCa. For patients with BCa, the role of the AR and its pathway effectors is less well understood. However, we have shown for the first time that androgen inhibition has clinical benefit for women with AR-driven ER/PR-negative BCa, thus it may offer an additional target to exploit in BCa. However, the relative importance of AR may depend upon the molecular subtype of BCa. Nevertheless, antiandrogen therapies for both prostate and breast cancers are exciting area with many novel drugs in development.

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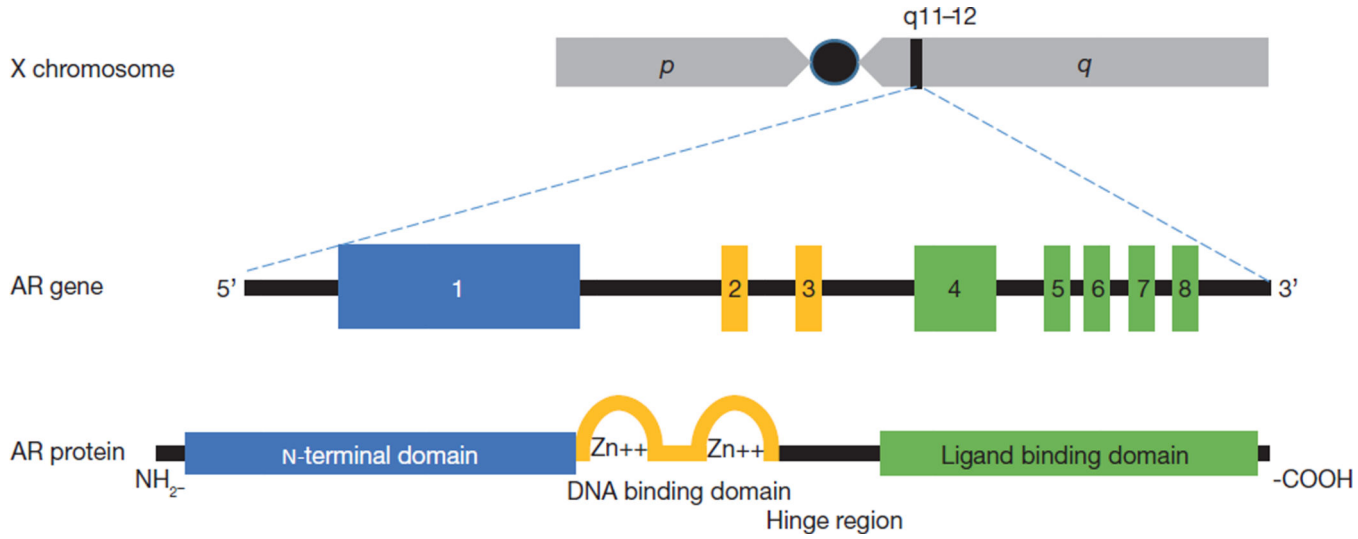

Figure 1.
Androgen Receptor Structure

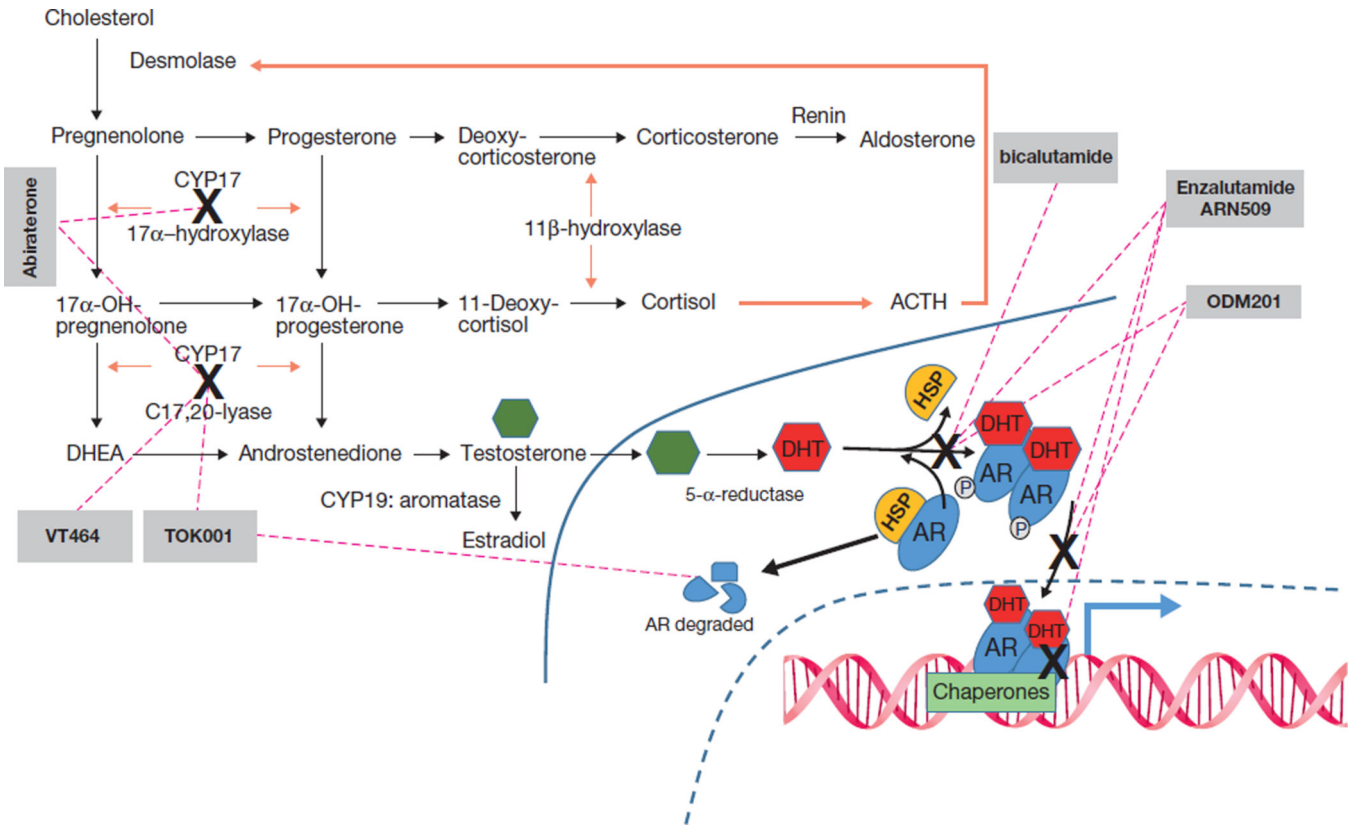

Figure 2.
Androgen

Endocr Relat Cancer. Author manuscript; available in PMC 2016 January 15.

Table 1

Novel agents targeting the AR axis in late-stage development for castration-resistant prostate cancer

	Agent	Phase	Population	Notes	References/clinicaltrials.gov
AR antagonist					
	ARN-509	III	Non-metastatic CRPC	SPARTAN. Randomized, double-blinded, placebo controlled	Rathkopf 2013 (Rathkopf *et al*. 2013b)/ NCT01946204 (recruiting)
	ODM-201	III	Non-metastatic CRPC	ARAMIS. Randomized, double-blinded, placebo controlled	Fizazi 2014 (Fizazi *et al.* 2014)/ NCT02200614 (recruiting)
	Enzalutamide	III	Non-metastatic CRPC	PROSPER. Randomized, double-blinded, placebo controlled	NCT02003924 (recruiting)
	EPI-001	Pre-clinical	CRPC	Small-molecule inhibitor of the AR NTD	Andersen 2010 (Andersen *et al*. 2010) Myung 2013 (Myung *et al*. 2013)
Biosynthesis inhibitor					
	Galeterone (TOK-001)	II	CRPC	ARMOR2, Mechanisms of action: CYP17A1 inhibitor, AR antagonist and may enhance AR degradation	NCT01709734 (recruiting)
	VT-464	I/II	CRPC	Potent inhibitor of CYP17,20-lyase	NCT02012920 (recruiting)
Targeting the AR carrier molecule					
	AT13387	I/II	CRPC, post-abiraterone	Resorcinol inhibitor	Shapiro 2014 (Shapiro *et al.* 2014)/NCT01685268 (active, not recruiting)
	Apatorsen (OGX-427)	II	mCRPC with concurrent AA and prednisone use	Antisense inhibitor of HSP27. Preliminary data from NCT01120470 showed promising results	NCT01681433(recruiting)
Targeting the AR and PI3K/Akt/mTOR pathways					

	Agent	Phase	Population	Notes	References/clinicaltrials.gov
	GDC-0068	II	CRPC, post-docetaxel	AKT inhibitor, with and without AA	NCT01485861(recruiting)
Combination trials					
	Enzalutamide plus AA	III	mCRPC	Randomized (enzalutamide plus AA vs. enzalutamide alone)	NCT01949337 (recruiting)

AR, androgen receptor; CRPC, castration-resistant prostate cancer; NTD, N-terminal domain; mCRPC, metastatic castration-resistant prostate cancer; AA, abiraterone acetate; HSP, heat shock protein; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin.

Table 2

Novel agents targeting the AR axis in late-stage development for breast cancer

	Agent	Phase	Population	Notes	References/clinicaltrial.gov
AR antagonistz					
	Bicalutamide	II	AR+ mTNBC	(Gucalp *et al.* 2013)	NCT00468715 (active, not recruiting)
	Enzalutamide (MDV3100)	II	AR+ mTNBC		NCT01889238 (active, not recruiting)
Biosynthesis inhibitor					
	Abiraterone acetate	I/II	ER+ or AR+ mBCa, post-menopausal		NCT00755885 (recruiting)
	Abiraterone acetate	II	AR+ TNBC, molecular apocrine		NCT01842321 (recruiting)
	Orteronel (TAK-700)	Ib	HR+ mBCa	(prostate) (Dreicer *et al.* 2014)	NCT01808040 (recruiting)
	Orteronel (TAK-700)	II	HR+ mBCa		NCT01990209 (recruiting)
Targeting the AR carrier molecule					
	Ganetespib (STA-9090)	II	mBCa	Small molecule Hsp90 inhibitor	NCT01273896 (completed results pending)
	Ganetespib (STA-9090)	II	mBCa (TNBC, ER+, HER2+)	Small molecule Hsp90 inhibitor	NCT01677455 (active, not recruiting)
Selective AR modulators (SARMs)					
	Enobosarm (GTx-024)	II	mBCa		NCT01616758 (active, not recruiting)
Combination trials					
	Trastuzumab + enzalutamide	II	mBCa, AR+,HER2+		NCT02091960 (recruiting)

	Agent	Phase	Population	Notes	References/clinicaltrial.gov
	Fulvestrant + enzalutamide	II	ER+AR+ mBCa		NCT01597193 (recruiting)
	Exemestane + abiraterone	II	mBCa, ER+	(O'Shaughnessy *et al*. 2014)	NCT01381874 (active, not recruiting)

AR, androgen receptor; mTNBC, metastatic triple-negative breast cancer; ER, estrogen receptor; mBCa, metastatic breast cancer; TNBC, triple-negative breast cancer; HR, hormone receptor; hsp, heat shock protein.

Table 3

Novel agents targeting the AR axis: early-phase trials and future directions

	Agent	Phase	Population	Notes	References/clinicaltrial.gov
AR-targeted					
	AZD3514	I	mCRPC		NCT01162395 (active, not recruiting)
	AZD3514	II	solid tumor with AR+		NCT02144051 (recruiting)
Combination trials					
	ARN-509 + AA	I	mCRPC	AR targeting	NCT02123758 (recruiting)
	BEZ235 or BKM120 + AA	I	mCRPC	Pan class PI3K inhibitor	NCT01634061 (active, not recruiting)
	BMK120 + AA	I	mCRPC	Pan class PI3K inhibitor	NCT01741753 (recruiting)
	GDC-0068 or GDC-0980 + AA	I	mCRPC	Pan-Akt	NCT01485861 (recruiting)
	Dasatinib or sunitinib + AA	I	mCRPC	ABL, SRC or VEGFR, EGFR tyrosine kinase inhibitor	NCT01254864 (recruiting)
	Alisertib + AA	I/II	mCRPC	Small molecule inhibitor of serine/threonine protein kinase, aurora A kinase	NCT01848067(recruiting)
	Tivozanib + enzalutamide	I	mCRPC	Antisense to clusterin	NCT01885949 (recruiting)
	Temsirolimus + ARN-509	Ib	mCRPC	mTOR inhibitor	NCT02106507 (recruiting)

AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; AA, abiraterone acetate; HSP, heat shock protein; PI3K, phosphatidylinositol 3-kinase; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.