CLINICAL INVESTIGATION

# Elucidating the role of androgen receptor in breast cancer

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The androgen receptor (AR) is expressed in the majority of breast cancers and can be effectively targeted with both AR agonists and anti-androgen therapies. AR expression and its prognostic implications vary according to breast cancer subtype. We will review the prognostic effect of AR expression, and discuss recent preclinical studies that have shed light on AR signaling and its interactions with other signaling pathways according to breast cancer subtype. Finally, we will discuss AR inhibitors that have been evaluated in early-phase clinical trials and that are under development. We will also discuss novel mechanistic insights and combinatorial therapeutic strategies that have been developed in preclinical studies with the potential to translate into effective clinical strategies for AR$^+$ breast cancer.

**Keywords:** androgen receptor • androgen signaling • anti-androgen therapy • breast cancer

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The androgen receptor (AR) and estrogen receptor (ER) are steroid receptors with major roles in development and carcinogenesis. Tumors expressing these receptors are effectively targeted with inhibitors that block the formation of their ligands and direct antagonists. These therapeutic approaches apply to both ER$^+$ breast and AR$^+$ prostate cancer. Although AR is expressed in 50–80% of breast cancers, regardless of expression of ER, progesterone receptor (PR), HER2 and the molecular subtype [1–3], it is currently not routinely used as a biomarker or as a therapeutic target in breast cancer. The ER$^-$/AR$^+$ breast cancer subtype was previously characterized histologically by apocrine features and subsequently termed molecular apocrine breast cancer [4]. Recent gene expression microarray studies have provided novel insights into the heterogeneity of breast tumors, and an increased interest in AR signaling in breast cancers [4–6]. These studies have demonstrated that AR expression varies with, and AR ligands can have opposing effects in, different breast cancer subtypes. Translating AR-targeted agents into clinical practice has been challenging because of the heterogeneity of breast cancer and the differential effects of AR inhibition in the different tumor subtypes *in vitro*. In this review, we will discuss the effect of AR expression on breast cancer outcomes, and review recent preclinical studies that have shed light on the mechanisms of AR signaling according to the different subtypes of breast cancer. Whilst most of the mechanistic data have been obtained using breast cancer cell lines, they provide potentially important insights into the underlying mechanisms of AR signaling and breast tumorigenesis. We will discuss novel therapeutic strategies stemming from these studies, specifically highlighting AR-targeted therapies that are now being evaluated in breast cancer clinical trials.

## Variation of AR expression according to breast cancer subtype

The AR is expressed in approximately 50–80% of breast cancer and in approximately 85% of ductal carcinoma *in situ* lesions [1]. AR is most commonly expressed in ER$^+$ breast cancer, and associated with smaller and lower-grade tumors, fewer

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lymph node metastases and improved survival in patients [3,7,8]. We performed the largest analysis of AR expression in primary breast cancers in the Nurses' Health Study (NHS), and found that 77% of 2000 invasive breast tumors evaluated expressed AR as detected by immunochemistry [1]. In this study, the majority of ER$^+$ tumors were also AR$^+$ and AR expression varied across the different breast cancer subtypes (luminal A: 91%; luminal B: 68%; HER2$^+$: 59%; and basal-like: 32%). Similar distributions of AR across breast cancer subtypes have been reported in other studies [9], including one that measured AR expression by reverse-phase protein lysate microarray [10]. Similar to ER$^+$ breast cancers, gene amplification was not a major underlying genetic change in AR$^+$ breast cancers [11].

The effect of AR expression on prognosis also varies according to the breast cancer subtype. Previous studies have suggested that AR may be both a prognostic factor for survival and a predictive factor for response to endocrine treatment in patients with breast cancer [7,10,12–19]. Of the studies conducted to date, most were small, with only two including more than 350 breast cancer cases. The largest study evaluating the prognostic significance of AR was conducted on 1181 patients with primary breast cancer. However, in this study, the only prognostic factor that was taken into account in the analysis was ER status [16]. In addition, few studies have examined the prognostic value of AR expression according to ER status [7,12,15,16,20] or in triple-negative breast cancer (TNBC) [10].

It has been postulated that AR expression has opposing effects on cell proliferation according to the ER status of breast tumors, acting in an antiproliferative manner in ER$^+$ tumors by antagonizing ER [12,21], and facilitating cell proliferation in an androgen-dependent manner in ER$^-$ tumors [5]. In the subset of postmenopausal patients with stage I–III breast cancer studied in the NHS, AR expression was associated with a 30% reduction in breast cancer mortality in the ER$^+$ subgroup on multivariate analysis (n = 1164; 88% AR$^+$; hazard ratio [HR]: 0.68; 95% CI: 0.47–0.99; p = 0.03). There was, however, a nonsignificant association of AR and breast cancer outcomes in the ER$^-$ subgroup with a poorer overall survival (n = 303; 43% AR$^+$; HR: 1.59; 95% CI: 0.94–2.68; p = 0.08) [3]. Similarly, other studies have found AR expression to be associated with improved outcomes in early-stage ER$^+$ breast cancers following adjuvant endocrine or chemoendocrine therapy [7,10].

The relation between AR expression and prognosis in ER$^-$ breast cancer is unclear. In one study, AR expression was associated with improved survival (HR: 0.33; 95% CI: 0.1–1.0) [15]. However, among women with ER$^-$ tumors in the NHS (42.9% AR$^+$), there was a nonsignificant positive association between AR status and increased risk of breast cancer death (HR: 1.59; 95% CI: 0.94–2.68). In contrast, a recent preoperative study performed by the German GeparTrio group found that AR expression predicted for improved disease-free survival and overall survival in the TNBC compared with other tumor subtypes at a median follow up of 60.5 months (85.7 vs 65.5%; p = 0.054 and 95.2 vs 76.2%; p = 0.036 respectively) [2]. The likely reason for the differences in results across studies is the significant heterogeneity of AR expression within TNBC; whilst the majority has a basal-like molecular profile, there is a significant minority with nonbasal molecular gene signatures, including luminal signatures [6]. These variable results are also likely to be affected by differences in the patient cohorts studied, variability in the use of tissue arrays, methods of measuring AR and cut-offs used. For these reasons, the prognostic effect of AR expression in TNBC has been difficult to elucidate.

## AR signaling & its dependency on patient serum hormonal levels & menstrual status

The effect of AR signaling on breast cancer cell proliferation is not only dependent on the level of AR expression and breast cancer subtype, but also on the patient's menopausal status, as well as circulating and peritumoral androgen levels. Testosterone is the most prominent androgen in women, and a necessary precursor for estradiol and 5α-dihydrotestosterone (DHT) – high-affinity ligands of ER and AR, respectively. These androgens are typically only detectable intracellularly, and circulate at subthreshold levels in the majority of women. In women, androgens are secreted by the ovaries and adrenal glands, and circulate at a similar concentration to pre-ovulatory estradiol levels [22]. There are many similarities between ER and AR signaling. Tissue estrogens and androgens typically diffuse into the cytoplasm of cells, and bind to their respective receptors. The ligand–receptor complex is subsequently stabilized in the nucleus, occupying specific sites across the genome in cooperation with other transcription factors, such as the pioneer factor forkhead box A1 [23,24]. Through the interplay between these nuclear receptors and their coregulators, the transcriptional potential of a given cell lineage is predefined.

The relation between serum hormonal levels and breast cancer risk in AR$^+$ breast cancer is complex. In contrast to estrogens, androgens at physiological concentrations are thought to exert an antiproliferative effect on ER$^+$ breast cancer [21]. High circulating androgen levels, on the other hand, are thought

to increase breast cancer risk, possibly through the aromatization of androgens to estrogens, resulting in ER signaling in ER$^+$ breast cancer and through increased AR signaling in AR$^+$ breast cancer [25,26]. Epidemiologic studies have demonstrated that high circulating androgen and estradiol levels could be associated with an increased risk of developing breast cancer, in particular ER$^+$ breast tumors [27,28]. Within the NHS, a nested case–control study was performed to study the effect of serum hormonal levels on breast cancer risk [29]. The findings were that patients with androgen and estrogen levels in the top quintile had a doubling of postmenopausal breast cancer risk compared with patients with levels in the bottom quintile. These studies were, however, not performed to specifically look at the effects of circulating hormonal levels on the risk of AR$^+$ breast cancer. It has also been hypothesized that peritumoral androgen levels play a role in tumor proliferation. Following menopause, the serum levels of progesterone and estrogen decreases dramatically, whilst serum androgen levels increase. In addition, androgens and estrogens are synthesized primarily in peripheral tissues from precursor hormones of adrenal origin rather than from the adrenal glands. In support of this hypothesis is the higher peritumoral concentration of DHT found within breast cancer and ductal carcinoma *in situ* compared with serum levels [30,31].

## AR signaling in TNBC

### Preclinical rationale for targeting AR in TNBC

Gene expression profiling studies in breast cancer have shed light on the heterogeneity within TNBC and have identified a luminal subset of ER$^-$ tumors with a paradoxical expression of genes known to be either direct targets of ER or genes that are expressed in ER$^+$ breast cancers [4,5]. The luminal subset constituted 8–12% of all breast cancers, approximately 50% of ER$^-$ breast cancers and 35% of TNBC as assessed by clustering analysis [4,5,32]. Although it did not express ER, the luminal TNBC subset had a more similar molecular signature to that of luminal compared with the basal-like breast cancers [5]. Another recent study analyzed the gene expression profiles of 587 TNBC from 21 published data sets and identified six unique TNBC subtypes by cluster analysis (training set, n = 386; validation set, n = 201) [6]. These included a luminal AR (LAR) subtype characterized by gene ontologies heavily enriched for hormonally regulated pathways and high levels of AR mRNA, downstream AR targets and coactivators. The majority of the LAR subtype tumors had the molecular signatures of luminal A and B breast cancer. Patients with LAR-like tumors were significantly older at diagnosis and had a decreased relapse-free survival compared with patients with other TNBC subtypes. The authors in this study identified a number of TNBC cell lines with the most similar gene expression profiles to the LAR TNBC subtype (SUM185PE, CAL-148, MDA-MB-453 and MFM-223 cells), and found these cell lines to be exquisitely sensitive to the AR antagonist bicalutamide [6]. These cell lines also had activating mutations in the *PIK3CA* gene, and treatment with PI3K inhibitors resulted in decreased cell proliferation [6]. These results are consistent with previous studies that have demonstrated an association between higher AR expression and *PIK3CA* mutations in TNBC, and also mirror the higher incidence of *PIK3CA* mutations in ER$^+$ breast cancer [5,10]. Importantly, these findings point to a potential therapeutic approach for this TNBC subtype with AR antagonists and PI3K pathway inhibitors, many of which are currently in clinical development. In another study, ectopic overexpression of AR in nontumorigenic MCF-10A and MDA-MB-231 TNBC cell lines resulted in MAPK activation in the presence of androgens [11]. In contrast to MAPK signaling-induced cell proliferation that resulted from either AR or EGFR pathway activation alone, hyperactivation of MAPK signaling from both pathways paradoxically resulted in a growth inhibitory response. These results are intriguing and point to a complex interaction between the two signaling pathways.

### Clinical trials targeting AR in TNBC

The breast cancer subtype in which targeting the AR has the most mature data is TNBC. Most classical AR antagonists, such as bicalutamide and hydroxyflutamide, were developed in prostate cancer, and inhibit AR signaling by directly competing with testosterone and DHT for binding to AR. These drugs bind AR with a rather low affinity and have been shown to induce escape mechanisms in prostate cancer [33]. Similar to tamoxifen's action on ER, these AR antagonists can also act as partial agonists in the settings of increased AR mRNA and/or altered recruitment of AR coactivators or corepressors [34]. There are recent data from a Phase II multicenter clinical trial of bicalutamide in patients with pretreated ER$^-$/PR$^-$/AR$^+$ metastatic breast cancer [35,101]. In this trial, approximately 12% of the 400 patients with ER$^-$ breast cancer had AR$^+$ tumors. Of the 21 evaluable patients, the clinical benefit rate was encouraging at 19% (95% CI 5–42%) and, importantly, bicalutamide was well tolerated.

## Interaction of AR & HER2 signaling pathways in molecular apocrine breast cancer

We and others have demonstrated a significant association of AR expression and HER2 overexpression in ER$^-$ breast tumors [15,32]. It has been shown that the receptor tyrosine kinase pathway modulates nuclear hormone receptor activity [36]. There is also evidence of functional crosstalk between the AR and HER2 signaling pathways that modulates cell proliferation and expression of steroid response genes in molecular apocrine breast cancer [37]. In our analysis of several primary breast cancer gene expression data sets, we confirmed that AR is highly expressed in ER$^-$ tumors that overexpress HER2 [38].

AR has been shown to promote tumor cell growth in ER$^-$/HER2$^+$ breast cell lines in the presence of androgens such as DHT, and the synthetic androgen R1881, and this stimulatory effect was abrogated with AR antagonists, such as bicalutamide [5,38]. To elucidate the molecular mechanisms behind AR signaling-induced cell proliferation in breast cancer, we sought to determine the direct AR targets that were differentially regulated by androgen stimulation, through the recruitment of AR and its coregulators, such as forkhead box A1, to the *cis*-regulatory elements of AR [24,38]. Chromatin immunoprecipitation combined with next-generation sequencing is a tool used to define the genome-wide binding sites of transcription factors, histone marks and other chromatin associated factors (cistrome) [39]. Our integrated analysis of the cistrome data and of androgen-stimulated gene expression profiles in ER$^-$/HER2$^+$/AR$^+$ MDA-MB-453 breast cancer cells demonstrate that AR signals to the HER2 pathway by inducing the expression of HER3, which is primarily mediated by the WNT signaling pathway. AR induction of *WNT7B* activated the nuclear translocation of β-catenin, which in cooperation with AR stimulated *HER3* gene transcription and resulted in a positive feedback loop between the AR and HER2/HER3 signaling pathways. These data provide strong preclinical rationale for targeting AR in ER-/HER2$^+$ breast cancers (Figure 1A) [38].

Another mechanism in which AR signaling may result in HER2-mediated cell proliferation in molecular apocrine breast cancer is through a positive feedback loop between the AR and ERK signaling pathways [40]. In this study, the combination of AR and MEK inhibitors *in vitro* and *in vivo* demonstrated synergistic therapeutic efficacy in cell line models of molecular apocrine breast cancer. Interestingly, combination therapy with AR and MEK inhibitors overcame trastuzumab resistance in the trastuzumab-resistant AR$^+$/HER2$^+$ MDA-MB-453-R cell line. This is a clinically relevant subgroup as HER2 amplification is present in at least 50% of molecular apocrine tumors, and resistance to trastuzumab is inevitable in the metastatic setting.

## Interaction of AR & ER signaling pathways in luminal breast cancer

Elucidating how AR antagonizes estrogen and ER function is key to understanding the clinical correlation between high AR expression and better outcomes in ER$^+$ breast cancers. In a retrospective study of 856 patients with early-stage ER$^+$ breast cancer, AR expression was shown to be an independent prognostic factor of better outcomes, particularly in patients who received adjuvant chemoendocrine therapy [7]. Although similar results were derived from other independent studies [3,12], the basic mechanism remains largely unknown.

Cistrome analyses have provided a valuable tool to elucidate the cellular mechanisms of hormone receptor signaling [23,39]. It has been proposed that by binding to a subset of estrogen-responsive elements, AR can prevent activation of some ER target genes that mediate the stimulatory effects of estradiol on breast cancer cells [12], implicating a competition between AR and ER for chromatin occupancy at specific ER target genes (Figure 1C). An alternative hypothesis is that ligand-bound AR and ER bind to independent sites in the genome, following which AR exerts its inhibitory effects on ER signaling through either a direct (Figure 1D) or indirect manner, the latter possibly through competition for common coregulators (Figure 1E). In this circumstance, both ER and AR are presumably localized in the nucleus and activated by their respective ligands. These are speculative models and there are currently no definitive data to address which of these mechanisms is correct.

Preclinical studies with hormonal agents have shed some light into the interactions between ER and AR signaling. The growth-inhibitory effect of androgens and aromatase inhibitors (AIs) in ER$^+$ tumors has been demonstrated to be mediated at least in part by AR, and involve the suppression of the prosurvival protein BCL-2 [21]. During aromatase inhibition, precursor androgens such as androstenedione can act directly on AR or be converted to DHT, subsequently exerting their antiproliferative effect by activating AR. Interestingly, AR blockade by bicalutamide or RNA interference abolished the antiproliferative effects of both DHT and the nonsteroidal AI letrozole [21]. These findings suggest that the mechanism underlying the antiproliferative action of AIs on ER$^+$/AR$^+$ breast cancer is both by reducing peripheral production of estrogens and by activating AR, and may explain the lower recurrence rate with adjuvant AIs compared with tamoxifen in postmenopausal women [41]. Novel strategies aimed at altering the balance between

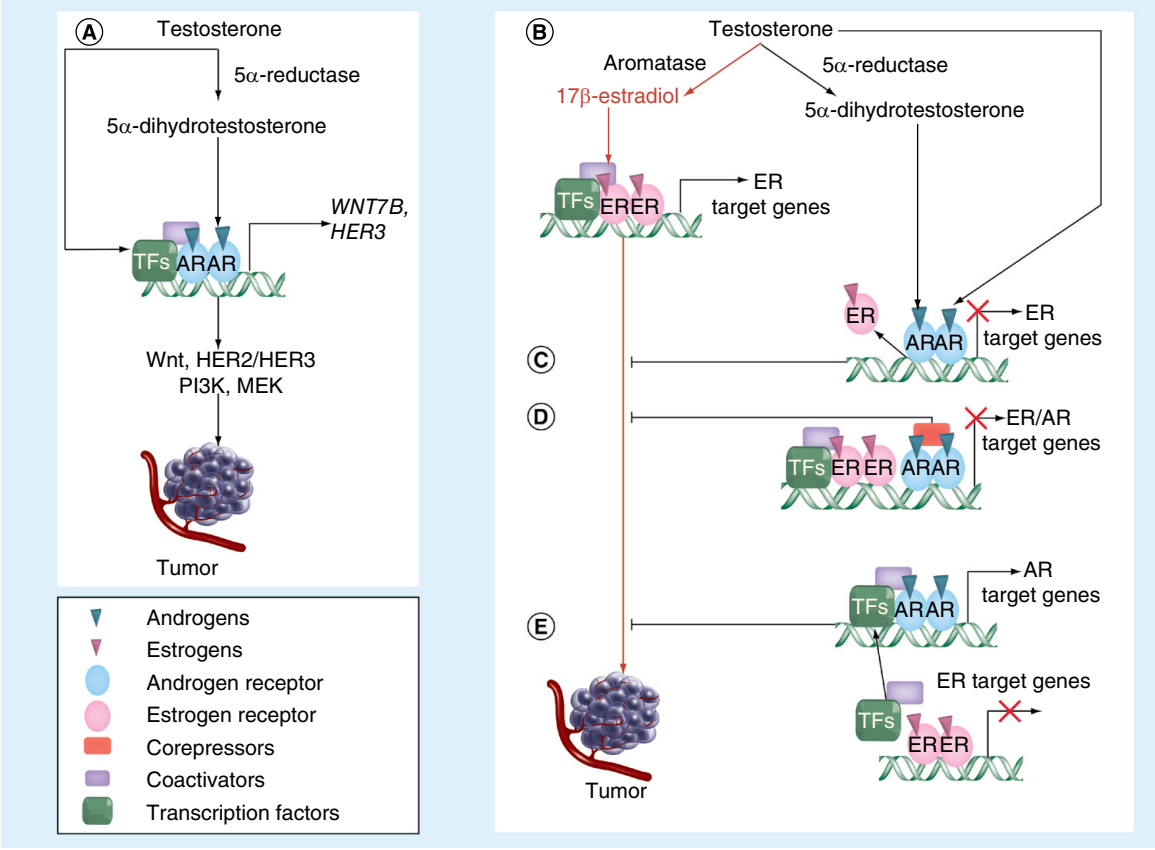


**Figure 1. Summary and hypothesis on the role of androgen receptor in the different subtypes of breast cancer. (A)** Androgen and AR signaling promotes tumor growth in ER$^-$/HER2$^+$ breast tumors by activation of oncogenic signaling pathways. **(B)** A speculative model on the antiproliferative role of AR in ER$^+$ breast tumors by the following mechanisms: **(C)** AR competes with ER for binding at ER target genes; **(D)** AR directly inhibits ER target genes by occupying unique AR binding sites; and **(E)** AR sequesters ER coregulators and abrogates their interaction with ER.
AR: Androgen receptor; ER: Estrogen receptor; TF: Transcription factor.

androgenic and estrogenic influences therefore warrant further investigation in the ER$^+$/AR$^+$ breast cancer. Prior to the routine clinical use of tamoxifen, androgens were used to treat hormone-dependent breast cancers [42]. In addition, androgens in combination with tamoxifen have previously been demonstrated to improve response rates in the treatment of advanced ER$^+$ breast cancer [43,44], although this approach has not been validated in larger randomized control studies and is not standard clinical practice.

Another area of complexity in ER$^+$/AR$^+$ breast cancer is the conflicting data on the effect of AR on anti-estrogen therapy. A recent epidemiological study suggested that high AR expression was a significant predictor for responsiveness to endocrine therapy in ER$^+$ breast cancers [45]. In contrast, another study demonstrated that AR was overexpressed in tamoxifen-resistant MCF-7 breast cancer cells, and the induction of tamoxifen resistance with ectopic overexpression of AR was reversed with bicalutamide, thereby suggesting a possible role for AR in tamoxifen-resistant breast cancer [46]. These controversies surrounding AR function in ER$^+$ breast cancer requires a comprehensive dissection of the molecular mechanisms by which androgens and AR modulate the function of ER in breast cancers that are estrogen-dependent and estrogen-independent, as well as anti-estrogen susceptible and resistant. We envisage the elucidation of the genome-wide binding sites of AR and ER, and their respective target genes specific to these conditions will provide novel insights into understanding the complex action of androgens in ER$^+$ breast cancers.

## Conclusion & future perspective

Androgens and AR clearly have different roles in the

context of different breast cancer subtypes (Figure 1), and a clearer understanding of androgen signaling in the different contexts and subtypes within breast cancer is providing a better foundation in which to better guide the targeting of this signaling pathway. There is a clear balance between androgenic and estrogenic influences on breast cancer proliferation in ER$^+$ breast cancer, and crosstalk between the AR and HER2 signaling pathways in AR$^+$/HER2$^+$ tumors that results in cell proliferation. In ER$^+$ breast cancers, activation of AR appears to have an antiproliferative effect and AR expression predicts improved clinical outcomes, although the precise interaction between AR and ER signaling remains unclear. In TNBC, there is evidence for a luminal subset characterized by the paradoxical expression of genes in the ER signaling pathway, and the clinical association of AR expression and *PIK3CA* activating mutations [6]. We speculate that the lack of ER expression in this subset of TNBC may result in a shift from an ER$^-$ to an AR-mediated transcriptional program in a subset of breast cancers, resulting in the expression of a luminal gene signature and additional unique AR target genes that confer androgen-stimulated tumor growth in molecular apocrine breast

## Executive summary

**Androgen receptor expression varies according to breast cancer subtype**

- Androgen receptor (AR) is expressed most commonly in estrogen receptor (ER)$^+$ tumors, in approximately half of HER2$^+$ and a third of triple negative breast cancers (TNBC).
- AR expression has opposing effects on cell proliferation according to the ER status of breast tumors, acting in an antiproliferative manner in ER$^+$ tumors by antagonizing ER, and facilitating cell proliferation in an androgen-dependent manner in ER$^-$ tumors.
- AR may be both a prognostic factor for survival and a predictive factor for response to endocrine treatment in patients with ER$^+$ breast cancer.
- The relation between AR expression and prognosis in ER$^-$ breast cancer is unclear.

**AR signaling is dependent on the patient's serum hormonal levels & menstrual status**

- Epidemiologic studies have demonstrated that high circulating androgen and estradiol levels are associated with an increased risk of developing breast cancer, in particular ER$^+$ breast tumors.
- Peritumoral androgen levels may also play a role in tumor proliferation.

**AR signaling in TNBC**

- Preclinical rationale for targeting AR in TNBC:
  - TNBC is a heterogeneous group of tumors and a luminal subset of ER$^-$ tumors with a paradoxical expression of genes known to be either direct targets of ER or genes that are expressed in ER$^+$ breast cancers have been identified;
  - The luminal subset of TNBC is associated with AR expression, the presence of PIK3CA mutations, and cell line models of this subset are sensitive to AR inhibitors.
- Clinical trials targeting AR in TNBC:
  - AR inhibitors are now being trialed in the clinical setting and a recent Phase II multicenter clinical trial of bicalutamide in patients with pretreated ER$^-$/progesterone receptor$^-$/AR$^+$ metastatic breast cancer reported an encouraging response rate of 19%.

**AR & HER2 signaling pathways interact in molecular apocrine breast cancer**

- There is evidence of functional crosstalk between the AR and HER2, and AR and ERK signaling pathways. These interactions modulate cell proliferation and expression of steroid response genes in molecular apocrine breast cancer.
- The combination of AR and MEK inhibitors have demonstrated synergistic therapeutic efficacy in cell line models of molecular apocrine breast cancer.

**AR & ER signaling pathways interact in luminal breast cancer**

- The mechanisms in which AR and ER signaling interacts in unclear.
- Potential mechanisms of interaction include:
  - AR binding to a subset of estrogen-responsive elements, resulting in competition between AR and ER for chromatin occupancy at specific ER target genes;
  - Ligand-bound AR and ER bind to independent sites in the genome, following which AR exerts its inhibitory effects on ER signaling through either a direct or indirect manner, the latter possibly through competition for common coregulators.

**Conclusion & future perspective**

- Routine AR testing in breast cancer is not currently recommended for clinical decision-making by the National Comprehensive Cancer Network and American Society of Clinical Oncology outside of a clinical trial setting because of a lack of sufficient clinical evidence to support their use.
- Newer antiandrogens with greater affinity to AR, such as MDV3100, are currently being developed for use in advanced breast cancer.
- Promising preclinical data with AR inhibitors in combination with HER2, PI3K and MEK inhibitors highlights potential opportunities for novel combinatorial treatment approaches for AR$^+$ breast cancer.

cancers [38]. One important caveat of the preclinical data presented in this review is that they have primarily been derived from breast cancer cell lines. The novel therapeutic approaches that have been highlighted in this review should ideally be validated in alternative *in vivo* preclinical models, such as patient-derived tumor xenografts, prior to being evaluated in clinical trials of subtype specific breast cancer.

Routine AR testing in breast cancer is not currently recommended for clinical decision-making by the National Comprehensive Cancer Network and American Society of Clinical Oncology outside of a clinical trial setting because of a lack of sufficient clinical evidence to support their use. In order to move routine AR testing into the clinical arena, an equal effort is required to develop a standardized approach in order to overcome differences in tissue preparation and assay methods, analysis of results, and definitions used for AR positivity across separate studies. Finally, in regards to targeting AR, there are recent data demonstrating an encouraging response in $ER^-$ breast cancer to bicalutamide. It is also important to consider that, like other forms of systemic hormonal therapy, AR inhibitors are not without side effects, such as fatigue, hot flashes and abnormal liver function tests [35]. It remains unclear if the use of AR inhibitors or androgen synthesis inhibitors alone would be sufficient to have a clinical impact in $AR^+$ breast cancers, particularly in light of evidence for multiple other signaling pathways (such as HER2, PI3K and MEK signaling) that have been implicated in cell proliferation in $AR^+$ breast cancer [6,38,40]. Newer antiandrogens with greater affinity to AR, such as MDV3100, are currently being developed for use in advanced breast cancer [102]. MDV3100 is an AR antagonist with a six-fold higher affinity to AR relative to bicalutamide that blocks ligand binding and prevents nuclear translocation and coactivator recruitment of the ligand–receptor complex. In contrast to bicalutamide, MDV3100 has no agonist activity [47]. Another therapeutic approach is to reduce the synthesis of androgens with CYP17 inhibitors, which include agents such as ketoconazole (a nonselective CYP17 inhibitor) and abiraterone (a selective and irreversible inhibitor ten- to 30-fold more potent than ketoconazole) [48]. Looking forward, promising preclinical data with AR inhibitors in combination with HER2, PI3K and MEK inhibitors highlights potential opportunities for novel combinatorial treatment approaches for $AR^+$ breast cancer [6,49].

There is finally renewed interest in targeting AR, and while the routine use of AR inhibitors in breast cancer is still not current practice, there is now promising activity in early-phase clinical trials, and preclinical rationale for novel combinatorial strategies targeting AR signaling.

## Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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