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Anti-Tumour Treatment

Androgen receptor in triple negative breast cancer: A potential target for the targetless subtype

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ABSTRACT

Triple negative breast cancer (TNBC) represents the 15–20% of all breast cancers (BC) and is characterized by a very aggressive behavior. Recent data suggest that TNBC is not a single disease, but it is rather an umbrella for different ontology-profiles such as basal like 1 and 2, mesenchymal, and the luminal androgen receptor (LAR). The LAR subtype is characterized by the expression of the Androgen Receptor (AR) and its downstream effects. Notwithstanding the role of the AR in several signaling pathways, its impact on a biological and clinical standpoint is still controversial. The LAR subtype has been associated with better prognosis, less chemotherapy responsiveness and lower pathologic complete response after neoadjuvant treatment. Clinical evidence suggests a role for anti-androgen therapies such as bicalutamide, enzalutamide and abiraterone, offering an interesting chemo-free alternative for chemo-unresponsive patients, and therefore potentially shifting current treatment strategies.

Introduction

Androgen receptor (AR) is a steroid hormonal receptor that belongs to the nuclear receptors family together with estrogen (ER), glucocorticoid, progesterone (PR) and mineralcorticoid receptor. It links a transcription factor that controls specific genes involved in different, sometimes opposite, cellular processes: it can stimulate or suppress both cell proliferation and apoptosis, depending on the concurrent signaling pathways activated [1–6]. Androgen receptor is expressed in about 70–90% of breast cancers and its expression varies from 10% to 50% in triple negative breast cancer (TNBC) [7–11].

AR seems to play a major role in TNBC carcinogenesis. However, its impact on patient prognosis and its predictive role in patients with TNBC are still controversial. The present review focuses on AR biology and covers the current clinical evidences on both predictive and prognostic implications of AR in TNBC.

The biological role of AR

The AR gene is located on chromosome Xq11-12 and encodes for a 110 kDa cytoplasmic polypeptide comprising four distinct functional regions: a N-terminal region involved in transcriptional activation, a regulatory domain at the amino terminal (AF-1 site), a DNA binding domain composed of two zinc fingers, a hinge region with a nuclear localization signal and a C-terminal ligand-binding domain (AF-2 site) (Fig. 1) [12]. The role of AR in breast cancer carcinogenesis is complex. Without its ligand, AR is found in the cytoplasm kept inactive by a heterocomplex with heat-shock proteins and a chaperone complex (HSP-70, HSP-90). Circulating androgens bind to the C-terminal ligand-binding domain leading to a conformational change which allows AR dimerization. After ligand binding, receptor-hormone complex translocates into the nucleus where it promotes a co-activator-mediated transcription of target genes (transcriptional/genomic modality of AR activation), and an inactivation of AR transcription through a negative feed-back [1,13].

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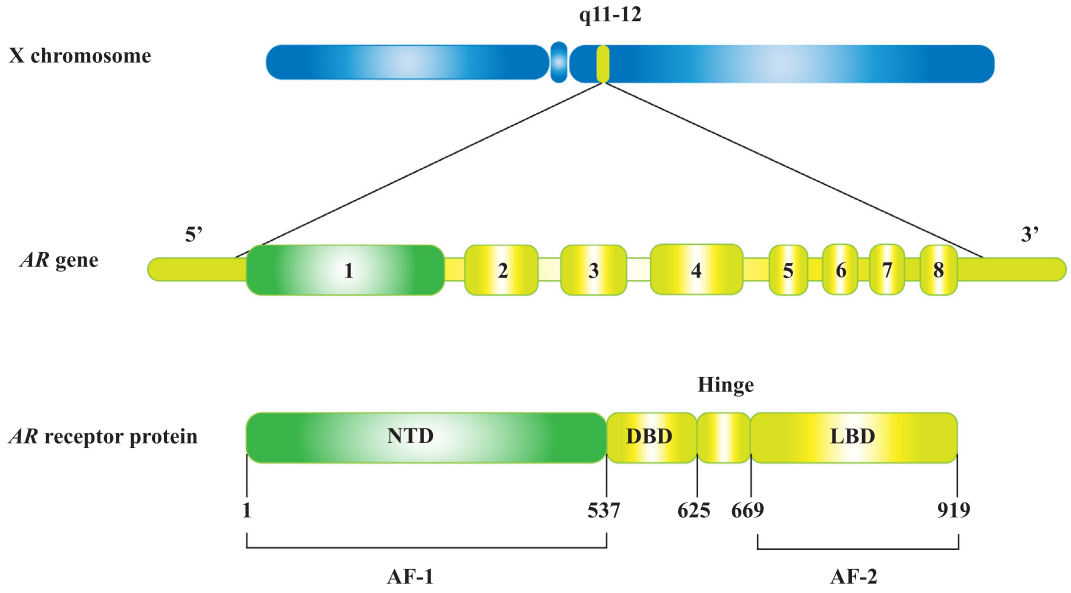


Fig. 1. Androgen receptor gene. Androgen receptor gene is mapped to the long arm of X chromosome (Xq11-12). The androgen receptor protein is encoded by 8 exons (1–8) separated by introns up to 26 Kb in size 8. The protein is composed by distinct functional regions. The exon 1 encoded the N-terminal region (NTD), exons 2 and 3 encoded a DNA binding domain (DBD). The 5′ region of exon 4 encoded for a hinge region, while the 3′ region of exon 4–8 encoded a ligand binding domain (LBD).

However, AR can also be activated through a non-transcriptional/non-genomic mechanism that does not need DNA or RNA interaction and that modulates AR activity by signal transduction in an ERK-dependent or -independent manner. ERK-mediated AR signaling involves cytoplasmic AR which interacts with phosphoinositide 3-kinase (PI3K), Src proteins and Ras GTPase. Non ERK-mediated AR signaling may involve the mammalian target of rapamycin (mTOR) phosphorylation, the forkhead box protein O1 (FOXO1) inactivation, and the protein kinase A (PKA) activation and results in increased cell proliferation (Fig. 2) [6,14].

AR and cell signal transduction pathways

AR enriched TNBC cell lines frequently carry PI3KCA mutations which make them very sensitive to PI3K/mTOR inhibition. The cross-talk between these two pathways have been suggested to promote cancer cell growth [15,16]. Additionally, AR phosphorylation via phosphorylated AKT abolishes AR-induced apoptosis resulting in increased cell survival [17,18]. AR expression may also up-regulate PTEN, due to more frequent mutations of AR in the kinase domain (exon 20), than in the catalytic domain (exon 9) which leads to an increase in PTEN levels [19]. It has been observed that AR expression in ER-negative MDA-MB-453 cells induces PTEN which represses PI3KCA activation and reduces AR activity [20]. At the same time, PTEN acts with the protein killin (KLLN) and induces p53 and p73, resulting in increased apoptosis. These preclinical data explain the anti-proliferative effect of AR that could cause the favorable prognosis in terms of DFS and OS seen among AR-positive TNBC patients [21–23].

GATA-3, a transcription factor involved in mammary gland development and its luminal cell differentiation also seems to interact with AR. It has been demonstrated that GATA-3 may limit the response to chemotherapy by activating the downstream targets of ER signaling, even in ER negative breast cancers, probably under the influence of the AR. Indeed, Naderi at al. found that the activation of AR in ER negative cells induced the expression of FOX1A, which is a downstream target of GATA-3 itself [24]. It was also demonstrated that GATA-3 expression was strongly correlated with AR-positivity especially in apocrine TNBCs [24,25].

Moreover, gene microarray and ChIP-seq analysis showed that AR-positive TNBC presents an up-regulation of the EGFR ligand amphiregulin, involved in tumor proliferation mediated by the EGFR signaling pathway. Enzalutamide seems to decrease this effect in cell lines expressing AR [16].

AR and epithelial-to-mesenchymal transition

Recently, the zinc-finger enhancer binding protein (ZEB1) transcription factor, has been associated with AR positive TNBC subtypes. ZEB1 activation has been associated to an Epithelial to Mesenchymal Transition (EMT) phenotype and predicts for poor patient survival due to a higher metastatic potential [26]. In TNBC, the ZEB1 - AR cross-talk is probably due to a direct binding of ZEB1 to the E-box sequence on the AR promoter [27]. Interestingly, a morphological switch from a mesenchymal to epithelial phenotype was observed after ZEB1 knockdown in TNBC cell lines. ZEB1 suppression in TNBC cell lines was also associated with a decrease of AR mRNA and AR downstream targets and a sensitization to bicalutamide. Consistently, the treatment with bicalutamide reduced the expression of ZEB1 in treated cells [26,28–30].

AR plays a critical role in cancer metastasis development also by promoting migration and invasion, through the extracellular matrix degradation. Preclinical models have demonstrated that AR induces the expression of metalloproteinase (MMP), in particular, MMP2 and MMP9 [31]. The decreased anchorage-independent growth and invasion, and the increased apoptosis reported in clinical trials with enzalutamide in AR-positive TNBC subtypes, including mesenchymal stem-like, mesenchymal-like and basal-like, further support this hypothesis [32].

AR and cell cycle regulators

Noteworthy, AR interacts also with cell cycle regulators and BC susceptibility genes such as Poly-ADP-ribose-polymerase 1 (PARP1) and BRCA1. BRCA1 plays a key role in double-strand breaks repair when a DNA damage occurs, while PARP1 is important in the base excision repair process for DNA single-strand breaks repair. It has been recently reported that BRCA1 and PARP1 act as coactivators of AR and promote AR-targeted gene transcription. Preclinical evidences suggest that PARP1 inhibitors in AR positive TNBC reduce cell migration and

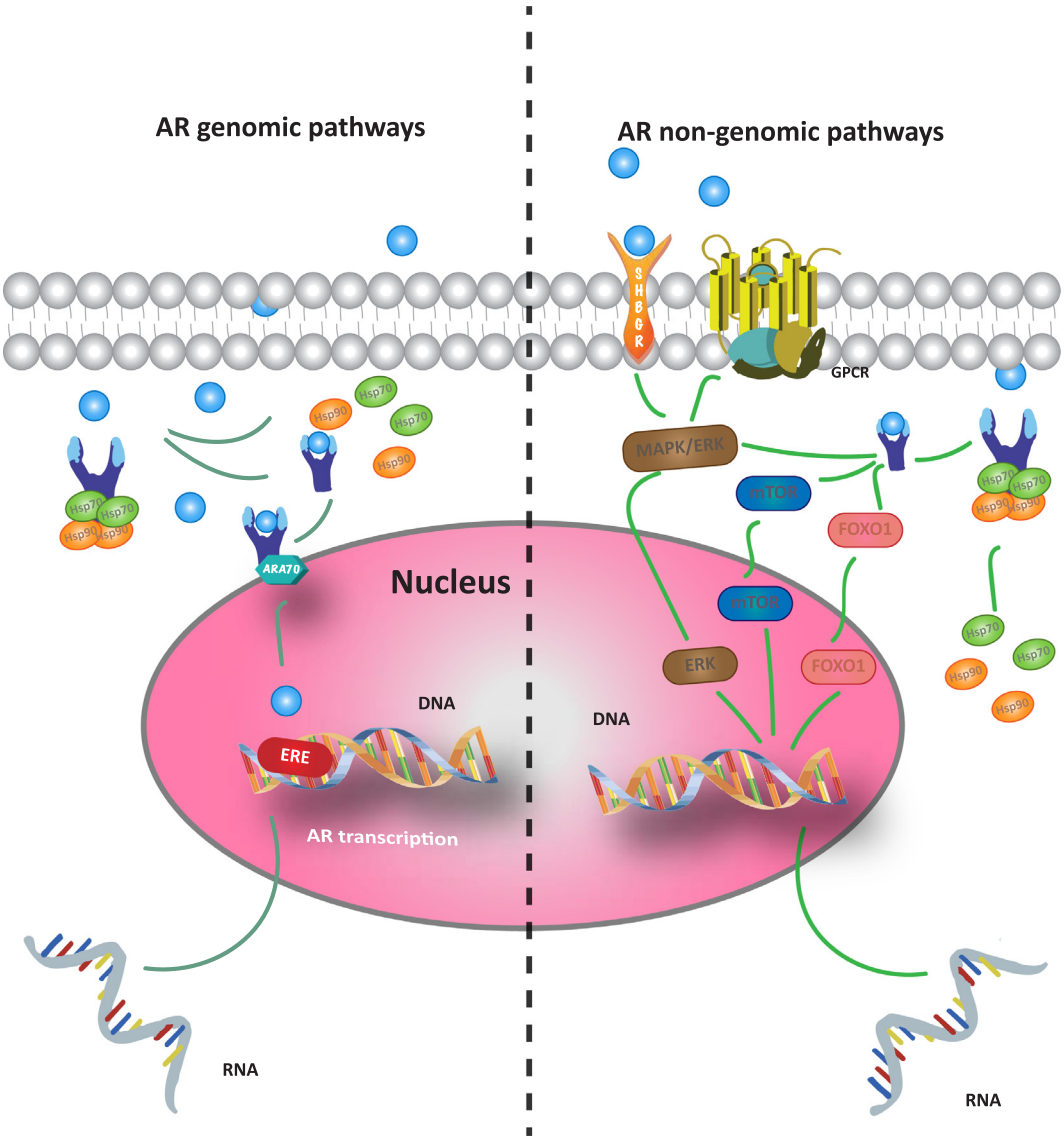


Fig. 2. Androgen receptor activation. Androgen receptor resides in the cytoplasm in an inactive form through a heterocomplex with heat-shock proteins and a chaperone complex (HSP-70, HSP-90). Hormone binding induces a conformational change which allows AR activation. Transcriptional/genomic modality of AR activation: receptor-hormone complex translocates into the nucleus and interacts with co-activators, co-repressor and transcription modulators. As a result, it promotes the transcription of target genes. Non-transcriptional/non-genomic modality of AR activation: ERK-mediated AR signaling involves phosphoinositide 3-kinase (PI3K), Src proteins and Ras GTPase. Non ERK-mediated AR signaling involves the mammalian target of rapamycin (mTOR) phosphorylation, the forkhead box protein O1 (FOXO1) inactivation, and the protein kinase A (PKA) activation.

invasion, thereby preventing DNA repair as well as reducing AR activity. This implies an important role of AR in BRCA1-dependent tumor suppression. Furthermore, BRCA1-mutated BC show a lower expression of AR and preclinical studies have highlighted an increased apoptosis when PARP1 inhibitors were combined with AR inhibitors. However, further studies are required to clarify the crosstalk and the role of these pathways in TNBC cells [22,33,34].

AR, angiogenesis and immune system

Recently, it was observed that AR pathway could be influenced by the hypoxia-inducible factor 1 alfa (HIF-1a) and the vascular endothelial growth factor (VEGF). Preclinical evidence show that the treatment with dutasteride, a dual blocker of both the type-1 and type-2 isoform of the steroid-5 alfa-reductase (SRD5A1), was associated with a reduction in protein expression of VEGF and HIF-1a, resulting in an increased chemosensitivity, and dose- dependent decrease in cell viability of about 40% [35]. If confirmed in clinical prospective trials it could be used in combination with chemotherapy in the treatment of this subgroup of TNBC. Even though nowadays less investigated, the crosstalk between AR and the immune system is not less important. Indeed, treatment with AR inhibitors may increase the recruitment of cytotoxic T cell, which could enhance susceptibility to immunotherapy [15,31].

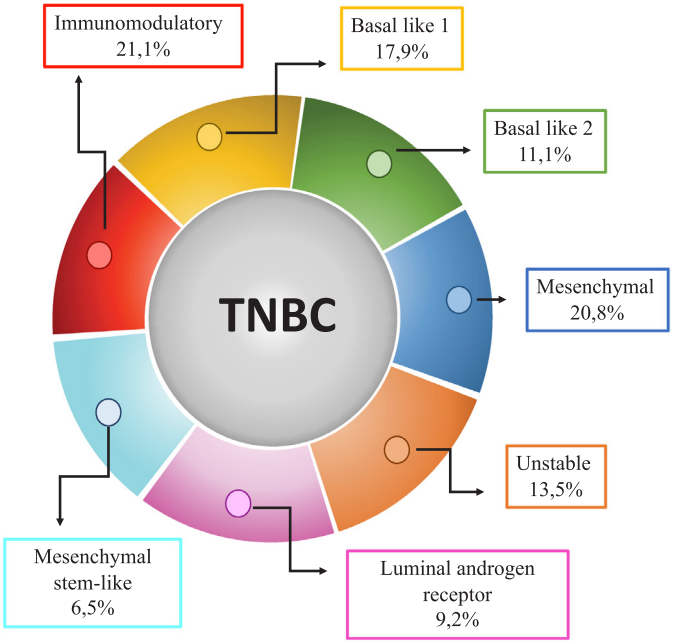
Genomic profiling in TNBC and AR expression

Molecular characteristics of the main gene ontology-based profiles

Genomic profiling strategies have been explored to shed light on the deep heterogeneity which characterize TNBC. The IHC-defined TNBC profile is actually composed by a wide range of molecular profiles that show profoundly different gene ontologies.

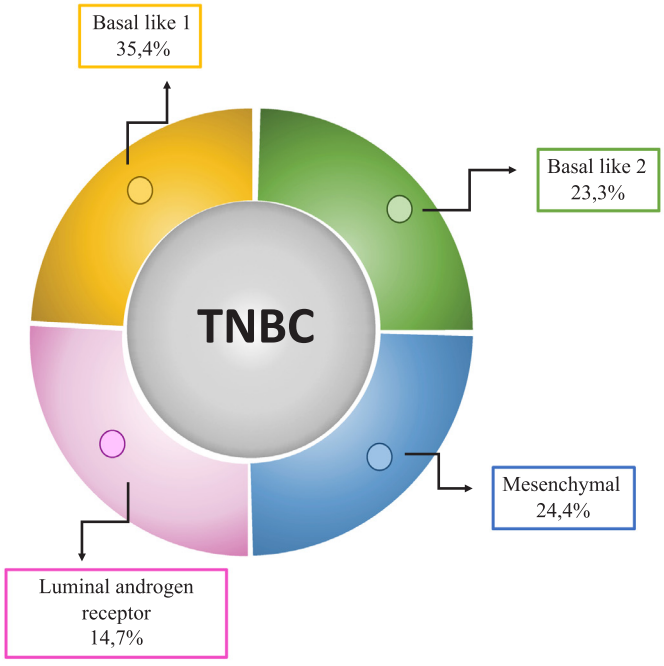
In 2011, Lehmann et al. reported six molecular subtypes of TNBC each characterized by potentially new therapeutic targets: 2 basal like classes (BL1 and BL2), an immunomodulatory (IM), a mesenchymal

A



Sub-types	Characteristics	Molecular Target
BL1	Proliferation drivers such as cell cycle, cell division and DNA replication	PARP1, RAD51, PLK1, TTK, CHEK1, AURKA/B
BL2	Growth factor and metabolic signaling with myoepithelial markers	EGFR, mTOR, MET, EPHA2
M	Epitelial-to-mesenchymal transition and differentiation	PI3K, mTOR, IGF1R, SRC, PDGFR, FGFR
UNS	DNA damage responses and cell proliferation	PARP1, RAD51, PLK1, TTK, CHEK1, AURKA/B
LAR	Hormonale-mediated signaling-androgen receptor	AR, Hsp90, PI3K, FGFR4
MSL	Epitelial-to-mesenchymal transition, differentiation, angiogenesis, stemness, growth factor	SRC, PI3K, MEK1/2, mTOR, PDGFR, NFkB, FGFR, IGFR, TGFBRIII
IM	Immunemediated signaling	JAK ½, LYN, STATs, IRF1/7/8, BTK, NFkB

B



Sub-types	Characteristics	Treatment
BL1	Cell cycle control, DNA damage response and high cell proliferation	Antimitotic agents such as platinum salts and PARP inhibitors
BL2	Expression of EGFR, TP63, MET and activation of glycolysis and gluconeogenesis pathways	Antimitotic agents such as platinum salts and PARP inhibitors
M	Pathways involved in cell motility, extracellular matrix interaction, EMT , growth factor. Mutation of PIK3CA or PTEN deficiency.	TKI, mTOR inhibitor, eribulin mesylate
LAR	Hormonale-mediated signaling-androgen receptor	Anti-androgen therapies

Fig. 3. A and B. Lehmann classification 2011 and 2016. (A) Triple negative breast cancer (TNBC) was classified into main six subgroups: two basal like classes (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem cell (MSL) and the luminal androgen receptor (LAR) class. (B) Triple negative breast cancer (TNBC) was classified into main six subgroups: two basal like classes (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem cell (MSL) and the luminal androgen receptor (LAR) class.

(M), a mesenchymal stem cell (MSL) and the luminal androgen receptor (LAR) class, characterized by AR expression (Fig. 3A) [36,37].

The recently refined version of TNBC molecular classification defined four main subtypes, BL1 and BL2, M, and LAR, with unique ontologies and differential response to therapy [38] (Fig. 3B). Biological pathways involving cell cycle control, DNA damage response and high cell proliferation characterize the BL1 profile. These tumors respond to antimitotic agents such as platinum salts and PARP inhibitors. The BL2 subtype is characterized by the expression of EGFR, TP63, MET and activation of glycolysis and gluconeogenesis pathways. The M group includes more than half of the metaplastic carcinomas and is characterized by EMT and frequent PIK3CA mutations or PTEN deficiency. These tumors respond to tyrosine kinase (TKI) and mTOR inhibitors. Interestingly, eribulin mesylate could be particularly

beneficial in this subtype since it is capable to suppress EMT. Notably, although AR mainly characterizes the LAR profile, it seems to play an important role also in non-LAR subtypes, such as M, BL1 and BL2 [15,32,39]. The LAR subtype is closely linked to histological apocrine type tumors and was so termed because it can be defined as TNBC by IHC but histologically and genetically is similar to ER-positive BC. Gene ontologies defining the LAR subtype are enriched in hormonally regulated pathways including steroid synthesis and androgen/estrogen metabolism [37]. Because of this, phase II and III clinical trials reported encouraging results in term of clinical benefit after treatment with both bicalutamide and enzalutamide among patients with AR-positive TNBC [40,41]. PI3K inhibitors in addition to an AR antagonist seems to be more effective in treating AR-positive TNBC because PIK3CA mutations are frequently activated in these tumors. Further studies testing the clinical effect of concurrent treatment of PI3K inhibitors and AR blockades are ongoing [5,36].

LAR TNBC have lower proliferation rates compared to the other TNBC subtypes, resulting in a partial chemoresistance; consistently, a retrospective analysis of 130 patients treated with neoadjuvant chemotherapy has shown a lower pCR rate in LAR (10%) in respect to BL1 tumors (52%) [42].

Among the different gene ontology-based classification systems, the LAR definition seems one of the most solid. A newly published classification system based on both RNA and DNA profiling, identified 4 molecularly defined TNBC subtypes: LAR, Mesenchymal (MES), Basal-Like Immune-Suppressed (BLIS), and Basal-Like Immune-Activated (BLIA), characterized by different prognosis and potential therapeutic targets [43]. Interestingly, DNA analysis highlighted profile-specific gene amplifications and targetable molecular expression. LAR was found to be particularly characterized by both AR and MUC1 markers, remarking the strategic importance of anti-AR therapy but also the potential role of MUC1 vaccines as an effective treatment for this subtype. Interestingly, in contrast with other profiles, LAR subtype identified by this new classification system share the same genetic and biologic characteristics of those identified by Lehmann/Pietenpol el al [37,43].

New approaches and future applications

New, alternative, approaches have been explored to enable transferability of molecular profiling to the clinic.

A recently published transcriptome analysis identified 4 distinct TNBC clusters according to RNA expression. Among these, the LAR cluster was characterized by gene ontology enriched in hormone-dependent pathways. Spearman's correlation analysis highlighted a significant association between the LAR subtype defined according to the Lehmann/Pietenpol classification and the LAR cluster identified by the transcriptome-driven profiles. In detail, an upregulated estrogen dependent signaling pathway was highlighted in the LAR cluster defined by RNA analyses, confirming the pivotal role of the anti-androgen therapy but also suggesting a potential impact of traditional anti-estrogen therapies [44].

Recently, some efforts have been made to integrate gene-expression profiles with MicroRNAs (miRNAs) expression levels [45]. miRNAs are short non-coding RNAs that regulate the function of target genes at the post-transcriptional phase and are involved in cancer progression and metastasis. In particular, miR-363 seem to be a promising target, but results are still limited [46].

Parker et al. developed a treatment-focused approach based on Next-Gen RNA-sequencing analysis using a "from bedside back to bench" strategy. An initial training set was built by analyzing 80 samples of patients treated with enzalutamide and 42 from untreated patients and was used as a basis to develop a gene expression model of biological subtype according to treatment response. This new approach was capable to predict a 16-weeks clinical benefit from enzalutamide and therefore better identify androgen-sensitive tumors among TNBC with a 80% sensitivity and 65% specificity [47].

Prognostic implications of AR in TNBC

The prognostic impact of AR among TNBC patients is controversial. Several studies have highlighted the favorable prognosis of LAR TNBC given the lower Ki-67 and mitotic index and the lower tumor grade and clinical stage at diagnoses [20,48,49]. In detail, a recent meta-analysis by Wang et al. analyzed data from 2826 women with TNBC from 13 trials conducted between 2007 and 2015 and showed that AR, expressed in the 24.4% of the overall TNBC study cohort, was significantly associated with post-menopausal status (26.9% of patients with AR expressing tumors were postmenopausal and 13.4% were premenopausal), low tumor grade (40.8% of patients with AR expressing tumors were G1-2 and 23% were G3) and with a high risk of nodal involvement (28.8% of patients with AR expressing tumors were node positive and the 22.6% were node negative) [50]. Consistently, Maeda et al. reported an association between AR and both low clinical stage and nuclear grade, among 23 patients with TNBC and Gasparini et al showed that high grade TNBC presented lower AR expression ($p < 0.01$) [48,49]. In a cohort of 203 asian patients, AR positive TNBC showed a lower Ki67 proliferation index [51,52].

Sutton and al. suggested a higher incidence of distant metastases in AR-negative tumors [51,52]. A single study exploring the prevalence of AR expression in 88 patients with inflammatory breast cancer (IBC) showed that only 5 of the 17 TNBC were AR-positive. Interestingly, women with AR-negative TNBC had inferior 5-year survival rates compared with the AR-positive TNBC and the other histologic subgroups ($p < 0.03$) [53].

Three recent meta-analyses have shown longer disease-free survival (DFS) in AR-positive versus AR-negative breast cancer patients. In detail, Qu et al reviewed 12 studies including 5270 patients with breast cancer. The overall rate of AR expression in these studies was 65.2%. The combined hazard ratio (HR) of DFS for all 12 eligible studies was 0.52 (95% CI 0.43–0.64), suggesting that AR expression in breast tumors was an indicator of low risk of recurrence. The HR of overall survival (OS) for all studies was 0.66, but it was not statistically significant [54]. Similarly, Kim et al. selected 16 articles published between 1992 and 2013. With DFS data available for 521 TNBC patients, AR-positive tumors had a significant lower risk of relapse compared to the other TNBC subgroups (OR for DFS 0.44, p 0.002) [55]. Finally, an additional meta-analysis by Wang et al. confirmed that women with AR-positive TNBC display a 20% lower risk of recurrence compared with AR-negative TNBC (HR 0.8, $p < 0.05$). While DFS findings in all these analyses were concordant, both Qu and Wang found no association between AR status and overall survival, whereas the study by Kim et al. showed an overall survival benefit for AR-positive TNBC patients (OR 0.26, p 0.001) [50,54,55]. Results of a recent prospective study by Asano et al corroborate these latest findings as 59 of 190 TNBC patients (29.5%) who displayed AR-positive status had a significantly favorable Cancer Specific Survival ($p = 0.0034$) [56]. In summary, despite initial studies suggested a potential negative prognostic role for AR in TNBC [57–60], a growing body of evidences indicates that AR expression is associated with a favorable prognosis. Data concerning OS are still weak and will need further prospective studies.

Predictive value of AR in TNBC

Despite its clinical aggressive behavior, TNBC is commonly considered more sensitive to chemotherapy compared to others histological subtypes given the higher expression of proliferation-related genes in this subgroup of BC [59]. However, the molecular tumor features associated with LAR TNBC may result in a less responsive phenotype to chemotherapy.

Several studies, particularly in the neoadjuvant setting [16,42], have investigated whether AR positivity is a chemo-resistance marker

in TNBC. Using samples from patients enrolled in the GeparTrio phase III neo-adjuvant trial, Loibl et al evaluated AR expression and its impact on outcome [60]. Overall, 637 core biopsies from primary breast cancer patients treated with neoadjuvant docetaxel/doxorubicin/cyclophosphamide (TAC) chemotherapy were analyzed and AR was detected in 53.2% of tumors. In AR-positive tumors, pathological complete response (pCR) rate was 12.8% compared to 25.4% in AR-negative tumors ($P < 0.0001$). Among the TNBC subgroup AR expression predicted a better DFS (AR-positive 85.7% vs. AR-negative 65.5% log-rank $P = 0.0544$) and OS (95.2% vs. 76.2%; log-rank $P = 0.0355$). Within the non-pCR subgroup, AR positivity selected a group with a significant better DFS ($P = 0.045$) and OS (0.021) but not within the pCR group [60]. Masuda et al. retrospectively classified 146 TNBC tumors according to their gene expression profile and found that LAR tumors had a lower pCR rate as none of the 20 LAR patients achieved pCR after neoadjuvant chemotherapy [42]. Similarly, pCR was significantly less frequent in AR-positive compared with AR-negative TNBC in a prospective trial conducted on 117 Japanese women [56]. Recently, a study investigating the efficacy of neoadjuvant cisplatin plus paclitaxel with or without everolimus in 145 TNBC patients, demonstrated that low levels of AR expression (< 10%) were more likely to be associated with pCR than higher AR levels. These findings were consistent in both control and experimental arm. Interestingly, authors observed no significant modifications in AR levels in serial samples, obtained before, during and after the treatment, suggesting that AR expression is not affected by chemotherapy. Taken together, these results seem to suggest a negative predictive role of AR in the neo-adjuvant chemotherapy setting, being AR positivity correlated with a lower pCR rate. Nonetheless, women displaying an AR positive TNBC had a better DFS and OS, indicating that in LAR pCR may not be an appropriate surrogate marker of survival. Testing AR status at diagnosis could lead to a better selection of patients who are likely to benefit from a more aggressive neo-adjuvant treatment. New therapeutic strategies, such are the combination of chemotherapy with an anti-androgen (i.e. NCT02689427), could lead to a de-esclation of chemotherapy in this subtype.

Notably, AR expression seems to reduce TNBC radiosensitivity too, although preliminary evidence suggests that bicalutamide might restore the effect of therapeutically directed ionizing radiation in these patients [61]. More studies are required to further confirm these findings.

In addition, other markers have been explored in order to further refine AR's predictive potential, such as GATA-3 in the neoadjuvant setting or CK5/6 and p53 [46,62,63].

Androgen receptor as a therapeutic target in TNBC: Clinical evidence

The first clinical trial reporting activity of antiandrogen therapy in advanced breast cancer was published by Gucalp et al in 2013 and conducted by the Translational Breast Cancer Research Consortium (TBCRC). It was an open-label, single-arm study testing the AR antagonist bicalutamide at the dose of 150 mg administered orally on a continuous daily schedule, for the treatment of women with metastatic AR-positive TNBC. Primary endpoint was the clinical benefit rate (CBR) defined as the total number of patients who show a complete response (CR), partial response (PR), or stable disease (SD) > 6 months, while secondary endpoints were progression-free survival (PFS), safety and toxicity. Twenty-six patients were evaluable for the primary endpoint out of the 452 screened [40] (Table 1). Clinical benefit rate was 19% with a median PFS of 12 weeks (range 6.25–57.5 months), giving a proof of concept of the potential clinical role of targeting AR in TNBC treatment. Overall, the treatment was well tolerated and the most common treatment-related adverse events (AEs) were fatigue, hot flashes, limb edema, and elevation of liver function tests.

Data from a phase II trial evaluating a new generation AR antagonist, enzalutamide, in AR positive TNBC, were presented at the 2015 ASCO meeting [61]. Primary endpoint of the trial was CBR defined as CR plus PR plus SD at 16 weeks (Table 1). CBR at 24 weeks, response rate (RR) and safety were evaluated as well. As in the Gucalp study, evaluable patients were defined as having AR IHC ≥ 10% and a response assessment. Outcomes were evaluated according to an androgen-driven gene signature (Dx). Out of the 404 samples tested for AR IHC, 79% had AR > 0% and 55% had at least AR = 10%, suggesting a higher AR prevalence than previously reported. Among the 75 evaluable patients, this trial showed a CBR at 16 and 24 weeks of 35% and 29%, respectively. Median PFS was higher in Dx-positive patients (32 vs 9 weeks), two CR and 5 PR were reported. The most frequent adverse events were fatigue, decreased appetite and nausea.

Table 1
Antiandrogen therapy in LAR-TNBC: clinical trials.

	N	Treatment	CBR	CI
Gucalp et al. [40]	452	Bicalutamide 150 mg continuous daily schedule	19%	95%
Traina et al. [41]	118	Enzalutamide 160 mg continuous daily schedule	35%	95%
Bonnefoi et al. [62]	30	Abiraterone 1000 mg + prednisone 5 mg twice/day continuous daily schedule	20%	95%
Gucalp et al. [63]	33	Bicalutamide 100 mg continuous daily schedule + Palbociclib 100 mg daily 3 weeks on 1 week off	Ongoing analysis	

Another phase II trial tested the potential role of abiraterone, given the mechanism of action of this drug as selective inhibitor of CYP17 [61] (Table 1). Abiraterone was administered orally on a continuous daily schedule at the dose of 1000 mg in heavily pretreated women with AR-positive TNBC, adding five milligrams of prednisone twice a day to avoid adverse effects correlated to increased mineralocorticoid levels. Primary endpoint of the study was CBR at 6 months. Objective response rate, duration of response, PFS and safety were secondary endpoints. Starting from 146 patients screened, 30 patients were considered eligible. Overall, 6 patients showed a clinical benefit at 6 months (20%), with CR in 1 patients and SD more than 6 months in 5 patients and an objective response rate of 6.7%. Median PFS was 2.8 months. Fatigue, hypertension, hypokalemia and nausea were the most common adverse events, predominantly grade 1 and 2. Two patients had a treatment-related serious adverse event, 1 with grade 3 hypokalemia and the other with grade 3 adrenal insufficiency [62].

An ongoing trial presented at ASCO 2016, is currently evaluating the combination of bicalutamide and palbociclib: preliminary pharmacokinetic results showed a good safety profile, while efficacy data have yet to be released (Table 1) [63]. Several clinical trials are currently ongoing in both the (neo)-adjuvant (NCT02689427; NCT01889238) and the metastatic settings (NCT01889238) testing enzalutamide alone and in combination with other drugs (Table 2).

Moreover, the PI3K/mTOR pathway has been explored in order to enhance anti-AR endocrine therapy, similarly to the ER targeted strategy. Preclinical evidence showed that AR-positive TNBC cell lines are sensitive to PI3K/mTOR inhibitors in association with bicalutamide. An additional study found that the combination of the mTOR inhibitor Rapamycin and Enzalutamide has anti-proliferative effects against LAR xenograft models in mice [64]. Recently a combination of taselisib (PI3Kα inhibitor) and Enzalutamide was launched, but recruitment has been suspended (NCT02457910) (Table 1).

Conclusion

The AR is an emerging and promising therapeutic target in breast cancer and, in particular, in the TNBC subtype, both because of the lack of a well-established targetable feature and the presence of a solid molecular subtype with different prognosis and clinical behavior.

Notwithstanding the effectiveness of an endocrine therapy-based

Table 2
Ongoing clinical trials.

Agent	Study population	Study design	Patients (n)	Primary end point	Status	ClinicalTrials.gov Identifier
Bicalutamide 150 mg vs chemotherapy	AR+ metastatic TNBC	Randomized, open-label, Phase III	262 estimated	CBR	Recruiting	NCT03055312
Bicalutamide 150 mg	AR+ metastatic TNBC	Single center, Phase II	1	CBR	Terminated	NCT02348281
Bicalutamide Ribociclib	AR+ metastatic or locally advanced TNBC	Nonrandomized, open-label, Phase I/II	58 estimated	Safety/tolerability, CBR	Recruiting	NCT03090165
Bicalutamide	AR+ metastatic TNBC	Randomized, open-label, Phase II	60 estimated	CBR, PFS	Not yet recruiting	NCT02353988
Bicalutamide	AR+/ER−/PR − metastatic BC	Nonrandomized, open-label, Phase II	26	CBR	Results reported	NCT00468715
Bicalutamide Palbociclib	AR+ metastatic breast cancer	Nonrandomized, open-label, Phase I/II	51	Safety/tolerability, PFS	Recruiting	NCT02605486
Enzalutamide Paclitaxel	AR+ TNBC, stage I–III breast cancer	Nonrandomized, open label, Phase IIB	37 estimated	pCR, RCB-I	Recruiting	NCT02689427
Enzalutamide	AR + TNBC, stage I–III	Nonrandomized, open-label, Phase II	200 estimated	1-year dose compliance rate	Recruiting	NCT02750358
Enzalutamide	AR+ advanced TNBC	Nonrandomized, open-label, Phase II	118	CBR	Active, not recruiting	NCT01889238
4-OH-testosterone	AR+ TNBC or ER+/PR+/HER2− or ER+/PR−/HER2− advanced BC	Nonrandomized, open-label, Phase II	90 estimated	CBR	Recruiting	NCT02067741
AZD5312	Solid carcinomas with AR expression	Nonrandomized, open-label, Phase I	32	Safety, tolerability	Completed	NCT02144051
Enobosarm	AR+ advanced TNBC	Nonrandomized, open-label, Phase II	55 estimated	CBR	Recruiting	NCT02368691
Enobosarm Pembrolizumab	AR+ metastatic TNBC	Nonrandomized, open-label, Phase II	29 estimated	Safety, tolerability, ORR	Recruiting	NCT02971761
Abiraterone acetate plus prednisone	AR+ metastatic or locally advanced TNBC	Nonrandomized, open-label, Phase II	31 estimated	CBR	Active, not recruiting	NCT01842321
Abiraterone acetate AZD8186 AZD2014	Advanced CRPC, SqNSCLC, advanced TNBC	Nonrandomized, open-label, Phase I	180 estimated	Safety, tolerability	Recruiting	NCT01884285
Abiraterone acetate	Postmenopausal women with ER+ or AR+ metastatic or locally advanced BC	Nonrandomized, open-label, Phase I/II	77	Safety, toxicity, CBR	Completed	NCT00755885
Orteronel	AR+ metastatic BC	Nonrandomized, open-label, Phase II	86 estimated	CBR	Recruiting	NCT01990209
Seviteronel	AR+ metastatic TNBC	Nonrandomized, open-label, Phase II	48 estimated	CBR	Recruiting	NCT02130700
Seviteronel	Advanced AR+ TNBC or ER+ BC	Nonrandomized, open-label, Phase I/II	110 estimated	Safety, tolerability, CBR	Recruiting	NCT02580448

Clinical benefit rate (CBR), Minimal Residual Disease (RCB-I), Progression-free survival (PFS), overall response rate (ORR).

strategy, which could enhance both outcome and quality of life, exploiting the interlink between AR and EMT could be a potentially new approach in the treatment of this subtype.

Conflict of interest

The authors declare that there are no conflicts of interest.

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