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Newly Developed Targeted Therapies Against the Androgen Receptor in Triple-Negative Breast Cancer: A Review

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***Abstract*——Among different types of breast cancers (BC), triple-negative BC (TNBC) amounts to 15% to 20% of breast malignancies. Three principal characteristics of TNBC cells are (i) extreme aggressiveness, (ii) absence of hormones, and (iii) growth factor receptors. Due to the lack or poor expression of the estrogen receptor, human epidermal growth factor receptor 2, and progesterone receptor, TNBC is resistant to hormones and endocrine therapies. Consequently, chemotherapy is currently used as the primary**

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approach against TNBC. Expression of androgen receptor (AR) in carcinoma cells has been observed in a subset of patients with TNBC; therefore, inhibiting androgen signaling pathways holds promise for TNBC targeting. The new AR inhibitors have opened up new therapy possibilities for BC patients carrying AR-positive TNBC cells. Our group provides a comprehensive review of the structure and function of the AR and clinical evidence for targeting the cell's nuclear receptor in TNBC. We updated AR agonists, inhibitors, and antagonists. We also presented a new era of genetic manipulating CRISPR/Cas9 and nanotechnology as state-of-the-art approaches against AR to promote the efficiency of targeted therapy in TNBC.

***Significance Statement*——The lack of effective treatment for triple-negative breast cancer is a health challenge. The main disadvantages of existing treatments are their side effects, due to their nonspecific targeting. Molecular targeting of cellular receptors, such as androgen receptors, increased expression in malignant tissues, significantly improving the survival rate of breast cancer patients.**

I. Introduction

According to the World Health Organization, in 2021, there were 2.3 million women diagnosed with breast cancer (BC) and 685,000 deaths globally. This makes BC the most prevalent malignancy in women around the world (https://www.who.int/news-room/fact-sheets/detail/breast-cancer; also see Nigam, 2013; Gomari et al., 2021). Heterogenicity and diverse molecular and clinical features are the hallmarks of BC, leading to the need for various drugs to control this type of cancer (Shah et al., 2013). Triple--negative BC (TNBC) is defined as any type of BC that lacks the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) genes. This makes treatment more challenging because most hormone therapies target one of the three receptors (Qiu et al., 2021). Because of its aggressive biologic features and lack of effective therapeutic choices compared with other subtypes of BC, TNBC has been associated with a poor prognosis. As a result, the discovery of innovative TNBC therapeutics is critical. Recently, numerous investigations have revealed that additional types of hormone receptors, such as the androgen receptor, are expressed in TNBC (Gerratana et al., 2018; Traina et al., 2018; Elghazawy et al., 2021; Sridhar et al., 2022).

The design and development of new generation androgen inhibitors for control of and targeting androgen receptors (ARs) have raised hopes for effective targeting of AR-positive TNBC cells. AR-targeted drugs have been approved with positive outcomes in clinical trials for the treatment of TNBC patients (Anestis et al., 2020; Yuan et al., 2021). Molecular and immunohistochemical analyses revealed that AR-expressing TNBC cases were efficiently targeted using AR inhibitors (Liu et al., 2018). The main focus of this review is the new promising targeted therapies against AR-positive (AR+) TNBC subtypes, focusing on monotherapy, combination therapy, CRISPR/Cas9 gene editing, and nanotechnology.

II. TNBC Subtypes and Their Clinical Characteristics

BC is classified into four molecularly distinct subtypes based on genetic profile, treatment response, and disease prognosis (Eroles et al., 2012). These BC malignancy subtypes are distinguished as luminal A, luminal B, HER2+ enriched, and basal-like or TNBC (Ades et al., 2014; Tsang and Tse, 2020). Typically, these three biomarkers, including the ER, PR, and HER2−/neu, are the main indicators to examine the molecular category of BC. Ki-67 is a tumor grade predictor, which is sometimes included in BC classification (Karangadan et al., 2016; Nazari et al., 2021) (Table 1).

TNBC malignancy was first introduced by Brenton et al. (2005) with an incidence rate between 12% to 20% (Howard and Olopade, 2021; Zimmer, 2021). TNBC is the most aggressive type BC with a high risk of recurrence and metastasis (Qin et al., 2019). As its nomenclature implies, the absence or poor expression of BC biomarkers PR, ER, and HER2/neu is commonly considered the main clinical characteristic of TNBC (Afghahi et al., 2017). The lack of expression of these biomarkers strongly correlates with poor clinical prognosis (Elbaz et al., 2015). ER, PR, and HER2 are related to drug resistance and the high rate of cancer-associated death occurrence in TNBC patients; targeting BC cancer cells by employing these receptors has attracted attention in recent years (Anders and Carey, 2008; Dogan and Turnbull, 2012). The latest available data showed that about 83% of the BC-related death belong to TNBC patients; however, this subtype of BC only accounts for

ABBREVIATIONS: AR, androgen receptor; AR-AF-1, androgen receptor activation function subdomain-1; AR-FL full-length androgen receptor; BC, breast cancer; BL1, basal-like 1; BL2, basal-like 2; CDK4/6, cyclin-dependent kinases 4 and 6; CRPC, castration-resistant prostate cancer; CYP17A1, cytochrome P450 c17; DBD, DNA binding domain; DHT, dihydrotestosterone; EMT, epithelial–mesenchymal transitions; Enza, enzalutamide; ER, estrogen receptor; GT, gemcitabine and paclitaxel; HER2, human epidermal growth factor receptor 2; HSD3β1, human 3-beta-hydroxysteroid dehydrogenase/delta5-4 isomerase type 1; HSP90, heat shock protein 90; IM, immunomodulatory; LAR, luminal androgen receptor; LBD, ligand-binding domain; mTOR, mechanistic target of rapamycin; NTD, N-terminal domain; PI3K, phosphatidylinositol-3-kinase; PC, prostate cancer; PR, progesterone receptor; SARMs, selective androgen receptor modulators; siRNA, small interfering RNA RNA; T, testosterone; TAUs, transactivator units; TNBC, triple-negative breast cancer; ZFN, zinc-finger nucleases

TABLE 1
Molecular classification of breast cancer

	ER	PR	HER
Luminal A	+ and/or	+	—
Luminal B	+ and/or	+/–[a] or	—
Luminal B	+ and/or	+/–[b] or	+
HER+	—	—	+
TNBC or basal-like	—	—	—

[a] PR < 20% + Ki 67 > 14%.
[b] Any PR + any Ki 67.

15% to 20% of the BC malignancies (Kim et al., 2014; Wein and Loi, 2017) (Fig. 1).

Chemotherapy medications such as tamoxifen, paclitaxel, cisplatin, and anthracycline are the first prescribed treatments given to patients with TNBC. However, the effectiveness of chemotherapeutics intervention due to rapid early tumor progression and drug resistance was overshadowed in TNBC patients (Kim et al., 2014; Najafi et al., 2014; Elbaz et al., 2015; Takai et al., 2016; Afghahi et al., 2017; Jhan and Andrechek, 2017; Wein and Loi, 2017). Given the high heterogeneity of tumor cells in TNBC, many efforts have been made to develop effective diagnostic and therapeutic approaches to control this type of BC.

Among numerous available systems (Weigman et al., 2012; Abramson et al., 2015; Takai et al., 2016; Gong et al., 2021; Jiang et al., 2021), the model developed by Lehmann et al. (2011) is regarded in our investigation and has employed for TNBC classification. Gene expression analysis and clinicopathological variables help classify TNBC for accurate pathologic diagnosis and therapy selection (Bando et al., 2021). The basic of the Lehmann model was gene expression profile and ontologies. In this model, TNBC was categorized into six distinct subtypes, including basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal, mesenchymal stem-like, immunomodulatory (IM), and luminal androgen receptor (LAR; see Table 2 for their characteristic features) (Lehmann et al., 2011; Abramson et al., 2015). Owing to the intricacy of the many histologic landscapes in tumor tissues, in the second investigation, Lehmann et al. employed histopathological quantification and laser-capture microdissection to demonstrate that IM and mesenchymal stem-like transcripts were provided by infiltrating lymphocytes and tumor-associated stromal cells, respectively. Therefore, they refined TNBC molecular subtypes from six into four tumor-specific subtypes (BL1, BL2, M, and LAR; see Fig. 1 for their incidence rates) (Lehmann et al., 2016).

Both BL1 and BL2 subtypes are distinguished by mutation appearance in BC genes 1 and 2 (BRCA1 and BRCA2). The BRCA1 and BRCA2 are the two known BC susceptibility genes that are actively involved in the sensitivity of malignant cells to platinum-based chemotherapies (Dréan et al., 2017). Investigation has demonstrated that inhibition of B-cell lymphoma/leukemia 11A and histone deacetylase 1 and 2 efficiently induced BL cells to transform into luminal A cells and enhance ER expression, resulting in enhanced sensitivity to tamoxifen. In BC patients, high levels of B-cell lymphoma/leukemia 11A and histone deacetylase 1 and 2 expression

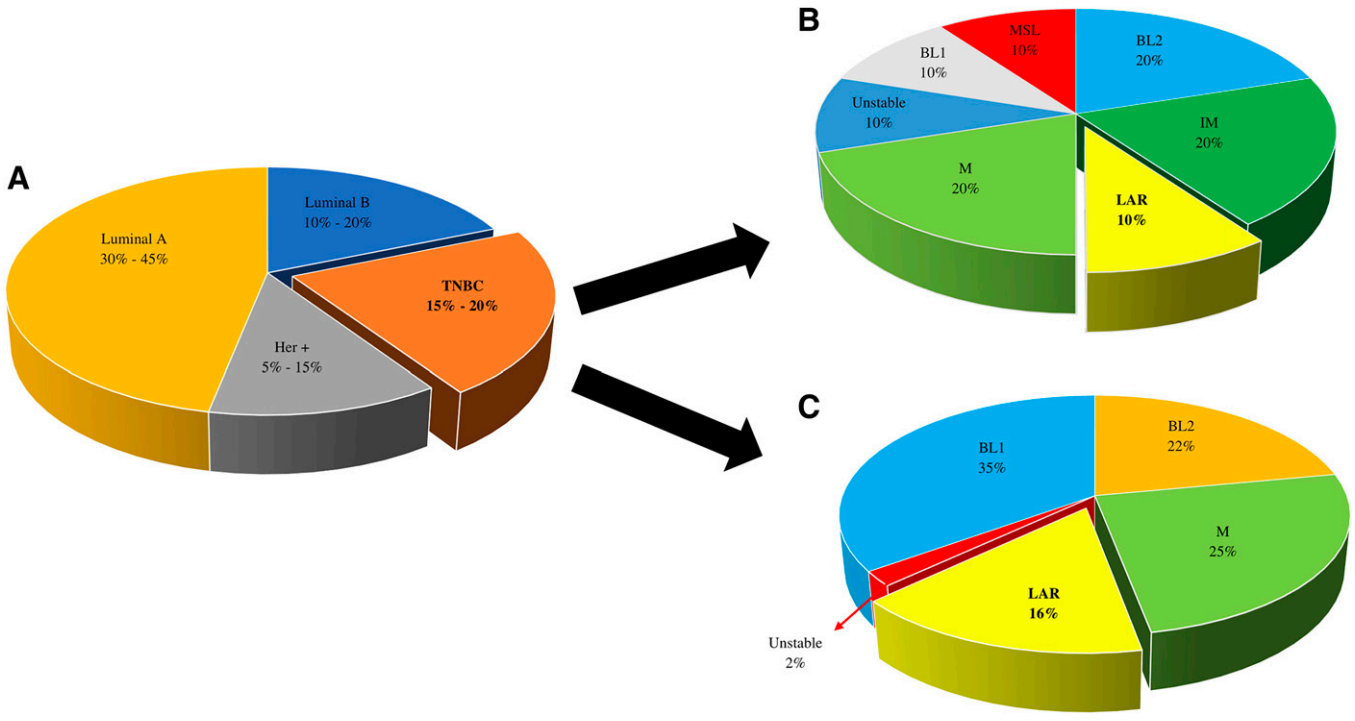

Fig. 1. (A) Incidence rate. BC is classified as luminal A, luminal B, HER2+, and triple-negative based on the status of ER, PR, and HER2; (B and C) TNBC classification by Abramson et al. (2015), Lehmann et al. (2011), and Lehmann et al. (2016), respectively.

TABLE 2
Subtypes of TNBC based on gene expression

Subtypes	Characteristics
Basal-like 1	• Expression of cell cycle, proliferation, and DNA repair genes • High expression of ki-67 gene
Basal-like 2	• Enriched in growth factor signaling pathway (epidermal growth factor receptor; the human gene, also known tyrosine-protein kinase Met; nerve growth factor and insulin-like growth factor-1 receptor) • Glycolysis and gluconeogenesis • Expression of myoepithelial
Immunomodulatory	• Expression of gene involved in immune cell processes (cytotoxic T lymphocyte-associated molecule-4, IL7, interleukin 2, B cell, T cell, and natural killer cells) • Cytokine signaling
Mesenchymal	• High expression gene of cell motility and extracellular matrix • Cell differentiation • Insulin-like growth factor
Mesenchymal stem-like	• Similar to M with enrichment in genes involved in cell motility and extracellular matrix • Height expression of gene involved in stem cells pathway • Janus kinases signal transducers and activators of transcription activation
Luminal androgen receptor	• Androgen receptor signaling • Height expression of gene involved in hormonally regulated signaling (steroid synthesis and metabolism)

were associated with a poor prognosis. These findings highlight systems that regulate BC morphologies and offer the possibility of reprograming basal-like BC cells to increase their targetability (Choi et al., 2022).

The hallmark characteristic of the mesenchymal and mesenchymal stem-like subtypes is the enrichment of genes involved in growth factor-related signaling pathways that trigger epithelial-mesenchymal transitions (EMT). This latter characteristic makes these two BC subtypes sensitive to EMT inhibitors (Hill et al., 2019). The capacity to develop vascular-like networks, known as vascular mimicry, is another feature of the mesenchymal-TNBC subtype that is known to cause metastatic spread (Liu et al., 2013). Furthermore, some evidence suggests that the aggressive character of mesenchymal-TNBC, which correlates with the presence of cancer stem cells, demonstrates a distinct ability for self-renewal, tumor initiation, and resistance to typical cancer therapy (O'Conor et al., 2018). Moreover, it has been observed that the EMT program and cancer stem cell state are tightly linked in numerous carcinomas and are related to treatment failure, metastasis, and cancer relapse (Hill et al., 2019).

LAR subtype accounts for about 16% of TNBC (Lehmann et al., 2016). The remarkable trait of the LAR subtype is its unique gene profile that makes cancer cells sensitive to hormone-based therapeutics, particularly regimen containing AR-targeting agents (Lehmann et al., 2011; Masuda et al., 2013; Lehmann et al., 2016) (Fig. 1). Although AR expression is not restricted to the LAR subtype, this nuclear receptor expression increased in the TNBC subtype. The LAR subtype was sometimes classified with the nonbasal-like TNBC; similar to the nonbasal-like subtype, they do not express basal-like markers. In comparison to the other TNBC subtypes, the LAR subtype was accompanied by a low pathologic grade of malignancy and was more potent for metastasis to the lymph nodes and bone marrow (Caiazza et al., 2016). Regarding the characteristic features of the LAR subtype, this type of TNBC was in the spotlight of the prognosis optimization and treatment development programs (Bratthauer et al., 2002; Gao, 2010; Gerratana et al., 2015; Dogra et al., 2020).

III. Biologic Characteristics of Androgen Receptor

The AR, also known as nuclear receptor subfamily 3 group C, member 4, is a steroid hormone receptor (Song et al., 2021). Steroid hormones interact with four different kinds of hormone receptors, including the glucocorticoid receptor, estrogen receptor-α, estrogen receptor-β, and AR (Norman et al., 2004). Steroid hormone receptors act as ligand-activated intracellular transcription factors; hence, it is considered for its gene regulatory capabilities. Depending on the type of signaling pathway stimulation, the steroid hormone receptors may have either or both positive and negative gene regulation activities to repress or trigger cellular processes such as proliferation, migration, and apoptosis (Shah et al., 2013; Bonotto et al., 2014; Gerratana et al., 2015; Ahn et al., 2016; Pietri et al., 2016).

A. Gene Profile of the AR in BC Subtypes

The AR is a frequently occurring theragnostic BC marker expressed in 70% to 90% of all types of breast malignancies and is even more abundant than ER or PR (Niemeier et al., 2010; Collins et al., 2011). The AR can be detected in two different subpopulations of mammary epithelial cells: invasive metaplastic apocrine carcinomas and luminal epithelial cells. However, the expression of the AR has markedly varied between these two subpopulations (Rahim and O'Regan, 2017). Molecular apocrine BC is a BC subtype that is very similar to the LAR subtype; hence, both are associated with a uniform expression in the metaplastic ER−/PR- apocrine cells. These cells are the most common cell population of the breast tissue (especially the fibrocystic ones).

In contrast, the luminal epithelial cells typically lack apocrine differentiation. The AR expression is not uniform; only 5% to 30% of this type of mammary epithelial cell content may contain AR. In these cells, the AR is often coexpressed with ER and PR (Rahim and O'Regan, 2017). It should be noted that the tumor originated from two different subpopulations of mammary epithelial cells, causing two distinct neoplasms with different morphology and molecular signatures, even if they are identical in the expression of AR. This fact describes the different efficacy of the AR-based targeted therapies in these two subpopulations with two other AR-related regulatory mechanisms and expression levels. Therefore, the therapeutic response against AR-based targeted therapies is more dependent on the histologic origin of the BC tumors (either molecular apocrine tumors or luminal epithelial abnormalities) (Bratthauer et al., 2002; Safarpour et al., 2014).

B. Structural and Functional Attributes of the Androgen Receptor

The AR is a nuclear receptor with a dynamic nucleocytoplasmic localization that acts as an intermediate for the cellular responses to the androgenic hormones (Nguyen et al., 2009). Like any other nuclear receptor, the AR is primarily a DNA-binding transcription factor—that is, in the nucleus and can directly interact with DNA, mediating a range of DNA-binding-dependent signaling pathways (Gao, 2010). In physiologic conditions and the absence of the androgens, the free form of AR, which is transcriptionally inactive, is localized to the cytoplasm. However, upon binding an androgen molecule, it was translocated into the nucleus, where it can induce the expression of a specific set of AR-related genes. On the other hand, the cytoplasmic concentration of free AR is under control; hence, cytoplasmic depletion of the AR acts as a signal that modulates the export of the nuclear AR from the nucleolus to the cytoplasm (Nguyen et al., 2009).

The AR gene is located on chromosome X (locus: Xq11–12) (Fig. 2). This gene encodes eight exons, translated into a full-length protein of 920 amino acids and a molecular weight of 110 kDa. The AR full-length protein consists of four distinct functional and/or structural domains, including (i) N-terminal domain (NTD); (ii) DNA binding domain (DBD), also known as the central domain; (iii) a hinge region; and (iv) ligand-binding domain (LBD) (Anestis et al., 2015) (Fig. 3). The N-C terminals interaction was a crucial requirement for AR activity. This interaction activates some of the binding domains for different ligands and is known as AR self-transactivation (Monaghan and McEwan, 2016).

The AR's primary functions serve as a DNA-binding transcription factor mediated by the AR-NTD (amino acids 1–559). The AR-NTD is a sizeable regulatory domain composed of several more specific functional subdomains that do not adopt a well-defined independent 3D structure; therefore, they are not structurally well-separated. A number of the AR-NTD functional subdomains serve as binding sites for transcription factors, while others bind to the transcription cofactors. These subdomains actively regulate the expression of the genes involved in initiating the upstream signaling pathways linked to the AR (Reid et al., 2003; Anestis et al., 2015). The AR-NTD is critical for AR transactivation. Most AR transactivation function is mediated by the AR-NTD's activation function subdomain-1 (also known as AR-AF-1)

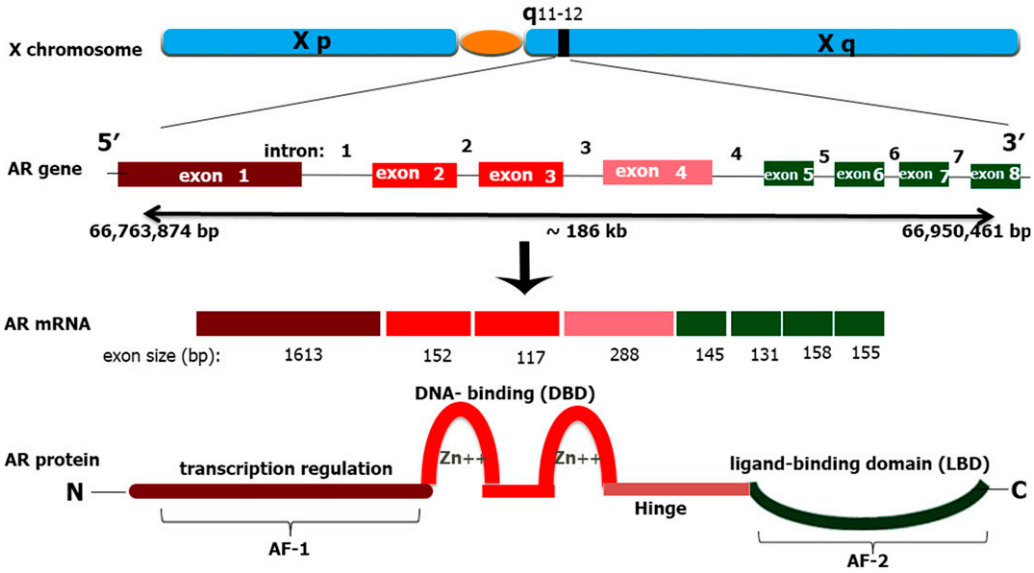

Fig. 2. Schematic representation of AR gene and AR protein. Top, the AR gene is found on the Xq11–12 chromosome. Middle, eight exons (exons 1–8) are separated by seven introns in the AR protein. The lower part of the figure shows the communication between the exon and AR protein domains: exon 1 coding for N-terminal region (AR-NTD); exons 2 and 3 coding for DNA binding domain (AR-DBD); the 5′ area of exon 4 encoded for a hinge domain, which contains the nuclear localization signal; and the 3′ region of exons 4–8 coding for the AR-LBD.

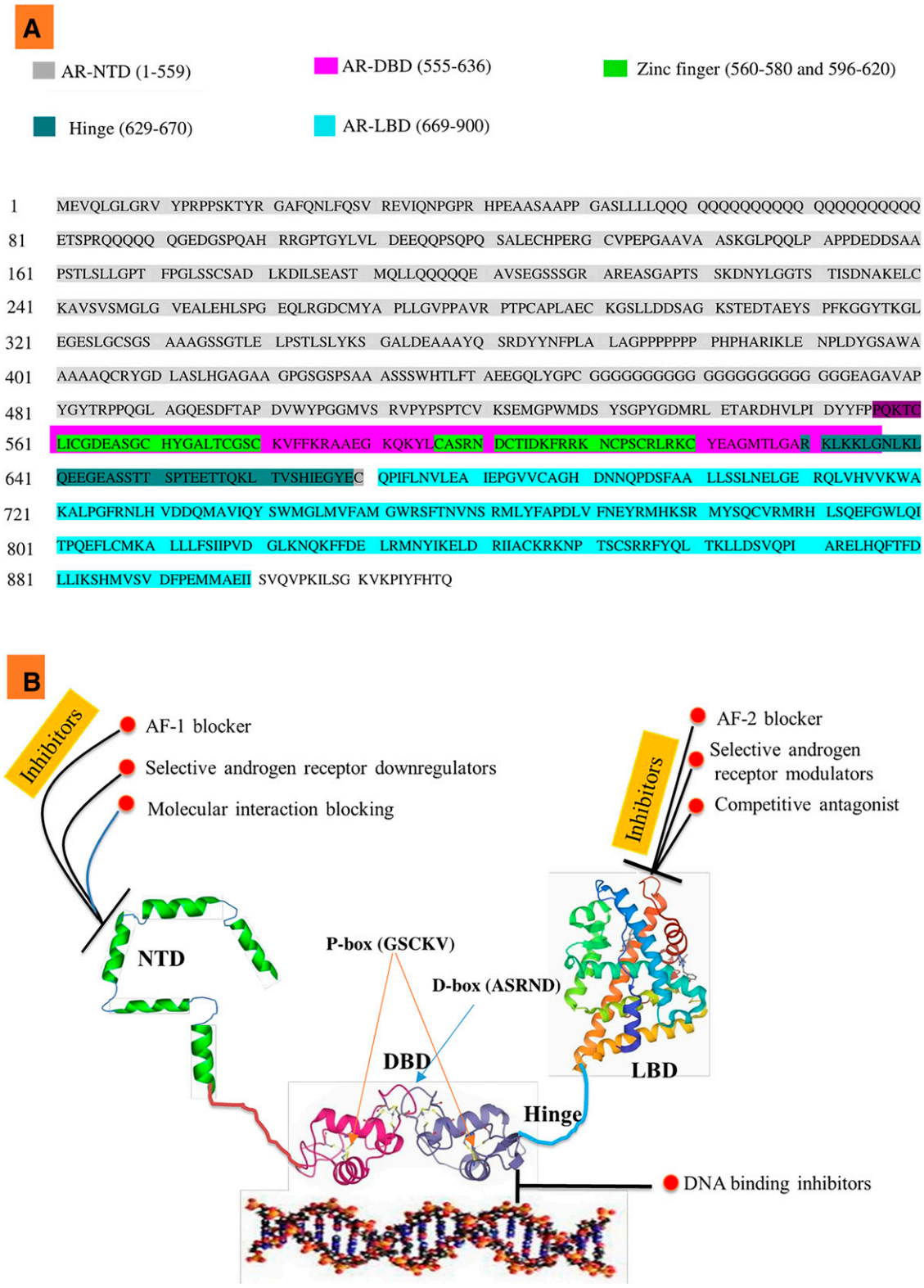

Fig. 3. Amino acid sequence (A), and 3D structure and its inhibitors (B) of AR. Abbreviations: AF-1, AF-2, DBD, LBD, and NTD.

(Zhao et al., 2002). The AR-AF-1 is composed of two main transactivator units (TAUs; TAU-1 and TAU-5. TAU-1 (amino acids 141–338) functions as a ligand-dependent transactivator, while TAU-5 (amino acids 380–529) acts as a ligand-independent transactivator. Another distinguishable part of the AR-NTD is its flexible five–amino acid motif (aminoacids 23–27,) which is necessary for the AR's N-C terminals interaction. This flexible motif

is also known as the FxxLF motif (Monaghan and McEwan, 2016). Considering the determinative crucial role of the AR-NTD in the AR activities, it is not surprising that mutations located in this region are responsible for most of the AR-related pathogenesis (Gottlieb et al., 2012; Mohler et al., 2012; Chandrasekar et al., 2015; Meakin and Clifton, 2019). For example, in 2012, Gottlieb et al. (2012) found that about 30% of AR receptor mutations linked with prostate cancer (PC) are mapped to the AR-NTD.

The central AR-DBD (amino acids 555–636) is a structurally well-defined region between the AR-NTD and the AR-hinge. Similar to other DBDs, the AR-DBD is responsible for DNA recognition. The AR-DBD is a highly conserved segment of the AR and is composed of two zinc-finger structural motifs (amino acids 560–580 and 596–620). Each motif consists of an α-helix (D-box and P-box) primarily composed of hydrophobic amino acids (see Fig. 3). The D-box (amino acids 560–580 and 596–620) is required for AR dimerization, while the P-box (amino acid residues 577–581) is essential for recognizing the DNA-binding elements in the transcription factor motifs, enhancer regions, and promotors of the downstream-regulated genes linked to the AR (Monaghan and McEwan, 2016; Radaeva et al., 2021). Evidence indicated that central roles in the AR-NTD are involved in modulating AR-DBD functions; this revealed an intradomain functional dependency in the AR (Brodie and McEwan, 2005). Like AR-NTD, mutations in the AR-DBD were also accompanied by several diseases and abnormalities, such as complete androgen insensitivity syndrome (Chauhan et al., 2018).

The AR-hinge region (amino acids 629–670) is a flexible segment between the AR-DBD and AR-CTD. This segment plays a vital role in the translocalization of the AR molecule from the cytoplasm into the nucleus, and vice versa. The AR-hinge region function is modulated by post-translationally modifications on the AR-RKLKKL motif, whose sequences are located from amino acids 629–644. The AR-hinge region was responsible for the integration of the signals that are from different pathways. Mutations occurring in the AR-hinge region were also accompanied by several abnormalities, such as castrate-resistant disease (Haelens et al., 2007; Clinckemalie et al., 2012; Monaghan and McEwan, 2016).

The multifunctional AR-CTD (amino acids 673–918) is crucial for interaction and recognizing the androgenic hormones; it is known as the AR's main LBD. The AR-LBD is the main target of androgen and antiandrogen therapies and is of great interest to clinical pharmacologists. AR-LBD (amino acids 669–900) has a well-defined 3D structure composed of 12 α-helixes and 4 β-sheets. In parallel with the AR-AF-1, which is located in the AR-NTD, the AR-CTD also contains an activation function segment known as AR-CTD's activation function subdomain-2 (also known as AR-AF-2). This region located on the surface area of the AR-CTD 3D structure actively promoted the AR's N-C terminals crosstalk. The binding function-3 was the other main surface pocket of the AR-CTD. It is believed that the AR-binding function-3 segment is involved in the allosteric regulation of the AF-2 function via its binding affinity for several agonists and antagonists. The most central subdomain of the AR-LBD is its hormone-binding pocket. The AR-hormone-binding pocket comprises hydrophobic residues that can anchor specific ligands by a strong network of hydrophobic interactions and hydrogen bonds (Li et al., 2006; Estébanez-Perpiñá et al., 2007; Anestis et al., 2015; Caiazza et al., 2016; Monaghan and McEwan, 2016). Like the other AR domains, mutations in the AR-CTD can also lead to various diseases and abnormalities, including many types of cancers. Some AR-CTD mutations may also lead to resistance against anti-androgens therapies (Monaghan and McEwan, 2016).

Researchers have shown that many AR-related mutations and abnormalities were involved in the pathogenesis and progression of TNBC. Many TN cell lines (e.g., HCC3153, HCC1937, HCC1395, SUM149PT, SUM1315M02, MDA-MB-436) have been used for ex vivo evaluation of the AR-related abnormalities. For example, Moore et al. used the AR^+ TNBC (MDA-MB-453 cell line) to show that androgens modulate essential biologic mechanisms, such as cell proliferation (Moore et al., 2012; Nguyen et al., 2009). The function of androgens in tumor formation and proliferation has also been demonstrated with research on other cell lines. In both the MFM223 and SUM185PE cell lines, a significant decrease in colony formation in culture was reported when AR was interrupted by (siRNA) (Lehmann et al., 2011).

Research using the MDA-MB-453 cell line indicates that AR signaling may play a role in the development of ER-negative BC cells that have a molecular apocrine phenotype. MDA-MB-453 demonstrates a molecular apocrine differentiation expressed as a mutated type of AR that occurs following Q865H mutation. This mutant has a diminished sensitivity to 5-alpha- small interfering RNA dihydrotestosterone (DHT) and does not react to AR antagonists or nonandrogenic ligands (Moore et al., 2012). These findings all indicate that androgens in TNBC cell lines can excite proliferation.

IV. A Glimpse to Androgen Receptor in Prostate Cancer

As with BC, AR is an excellent target for treating prostate cancerous cells. PC is one of the most prevalent cancers in the male population (Ban et al., 2021). The incidence rate and mortality risk of PC are strongly age-dependent and are more pronounced in older populations

(Rawla et al., 2019). There is a continuous effort to introduce and develop safer and more efficient therapeutics against PC. Considering the crucial role of AR in the initiation and progression of PC, it has been in the spotlight of drug design and development programs over the past years. Many therapeutic agents for AR-directed targeting are currently under clinical trial or emerging into the market (Lokeshwar et al., 2021; Mohler et al., 2021; Saranyutanon et al., 2019).

The AR-directed therapies are classified into three main categories: androgen ablation therapies, androgen deprivation therapies, and AR-targeting therapies (Kim and Ryan, 2012). Our focus in this study is on androgen precursor-targeting therapies. Most of the AR antagonists (or anti-androgens) were directly bound to the LBD and inhibited the biologic activity of androgens. Another strategy was the inhibition of androgen secretion; this was partly achieved by prostatectomy, which reduces testosterone levels by 95%. However, androgen hormones will still produce via the adrenal glands (Helsen et al., 2014), which points to the growing demand for the development of AR-directed therapies.

Steroidal and nonsteroidal anti-androgens are the two most potent anti-androgens inhibitors. Steroidal anti-androgens can bind to AR due to their structural similarity to androgens (Ahmed et al., 2014). Several steroidal anti-androgens, such as cyproterone acetate, dienogest, megestrol acetate, and chlormadinone acetate, are used to inhibit AR in patients. Currently, several steroidal anti-androgens, such as cyproterone acetate, dienogest, megestrol acetate, and chlormadinone acetate, are available to inhibit AR in patients. Cyproterone acetate is a member of steroidal anti-androgens that was widely used to treat PC. However, many of these steroidal anti-androgens are no longer recommended due to their insufficient efficacy and unacceptable side effects (Narayanan, 2020). Compared with steroidal anti-androgens, nonsteroidal androgens were accompanied by fewer adverse side reactions. Among nonsteroidal anti-androgens, flutamide, bicalutamide, and nilutamide are first-generation nonsteroidal anti-androgens, while enzalutamide (Enza) and apalutamide are the potent second-generation therapeutics (Table 3).

V. The Androgen Receptor Signaling Pathway in Triple-Negative Breast Cancer

Unlike ER and PR, AR was expressed in most BC subtypes. At present, we know that AR is expressed in about 53% to 80% of all subtypes of the breast's cancerous cells. It was estimated that AR was expressed in about 50% of the triple-negative tumor cells. The AR elevated expression levels in BC tumor cells are higher than ER or PR (Gucalp and Traina, 2016; Mina et al., 2017). Compared with ER and PR, functions, dynamics, and regulation of AR in BC have not been widely studied. In recent years, we learned much about the critical roles of AR in the pathogenesis and progression of various subtypes of BC; now, many more studies have focused on the functions and regulation of AR in BC (McNamara et al., 2013). Nevertheless, more information is needed to describe a robust correlation between AR expression levels and the BC theranostics, especially regarding the bulk of contradictory evidence on the biologic functions of androgens in TNBC (Safarpour et al., 2014).

On the other hand, there are positive and promising findings on the robustness of the AR targeting strategies in treating TNBC patients. Besides, several AR targeting agents are in the early stage of clinical trials (Anestis et al., 2015). The mechanisms by which AR signaling pathways affect breast carcinogenesis and its response to hormone therapies are not fully understood and need further investigation. We reviewed and discussed the recent findings on the efficacy of AR inhibition in treating TNBC. Much more attention was paid to the clinical data on the anti-androgen therapies among AR^+ TNBC.

VI. Androgen Receptor Targeting in Triple-Negative Breast Cancer

The lack of known molecular targets in TNBC makes it ineffective against typical endocrine and HER2 inhibitor drugs. The development of next-generation anti-androgen drugs to treat PC has sparked an interest in scientists in using AR inhibitors as a new treatment of TNBC, which can improve prognosis and limit off-target effects (Barton et al., 2015). In 1980, the first clinical trials of AR in BC were performed. In advanced BC, flutamide was used as an oral anti-androgen with unknown estrogen, progesterone, and HER2 status. At that time, scientists did not demonstrate any significant behavior related to AR targeting during their research (Rampurwala et al., 2016; Gucalp and Traina, 2017). In recent years, several clinical trials have shown the activity of anti-androgen therapy in the treatment of AR^+ TNBC (Table 4).

A. Monotherapy Approaches

Given the potential role of AR in TNBC, many attempts have been made to design innovative therapeutic agents to inhibit its signaling pathways. Currently, several clinical trials are being conducted on various experimental monotherapy anti-androgens (Table 4).

1. Bicalutamide. The first registered clinical trial for targeting ARs was against advanced BC in the 1980s. After that, several investigations were conducted that were aimed at controlling AR pathways (Perrault et al., 1988; Zhao and He, 1988). For example, Gucalp et al. (2013) achieved significant success for anti-androgen therapy in BC patients. They revealed that bicalutamide dramatically inhibited cancer cells. In addition, the Translational Breast Cancer

TABLE 3
Current clinical trials targeting the AR-signaling pathway in prostate cancer

Agent	Clinicaltrials.gov Identifier	Phase	Mechanism of Action	Objectives	Ref
Hydroxyflutamide	NCT02341404	II	Antiandrogen	Characterize and quantify the histopathological changes in the surgical specimens	(Gupta et al., 2017)
Enzalutamide	NCT01927627	II	Antiandrogen	Evaluating the clinical activity and safety of Enza in men with high-risk PC	(Ornstein et al., 2016)
Apalutamide (ARN-509)	NCT02770391	II	Antiandrogen	Determine if neo-adjuvant leuprolide and ARN-509 have different effects on DHT levels in benign prostate tissue. Evaluate the differential effect of neoadjuvant leuprolide and ARN-509 on other androgens	(Al-Salama, 2018; Smith et al., 2016)
Bicalutamide	NCT00846976	III	Antiandrogen	Check the health of patients receiving a 200 mg daily dose of CASODEX.	(Laufer et al., 1999; Osguthorpe and Hagler, 2011)
Flutamide	NCT00006214	II	Antiandrogen	Determine the ability of flutamide to reduce the incidence of PC in patients with high-grade prostatic intraepithelial neoplasia	(Eisenberger et al., 1998)
Darolutamide	NCT04157088	III	Antiandrogen	Compare the effects of the drug darolutamide and drug Enza on physical function, including balance and daily activity, in patients with castration-resistant PC	(Fizazi et al., 2019)
Galeterone	NCT01709734	II	Antiandrogen	Two-part trial to evaluate the safety and efficacy of galeterone in CRPC patients	(Bastos and Antonarakis, 2016)
Nilutamide	NCT00918385	II	Antiandrogen	Determine the clinical impact of using a patient-specific genomic expression signature of AR activity to determine therapy for patients with CRPC.	(Dole and Holdsworth, 1997)

Research Consortium clinical study reported a similarly successful experience to androgen inhibition in metastatic BC. This phase II multicenter study assessed the regular oral bicalutamide efficacy in both locally advanced (AR+, ER−/PR−) and metastatic BC (Gucalp et al., 2012). The Food and Drug Administration approved bicalutamide as a nonsteroidal, pure AR antagonist anti-androgen for PC treatment (Ismail et al., 2020). To treat advanced cases of PC, bicalutamide is used along with an analog of luteinizing hormone-releasing hormone. It is competitively bonded to AR to induce the accumulation of the inactivated AR and improve AR degradation (Park et al., 2011) (Fig. 4). Besides PC, many studies showed that AR inhibition with bicalutamide significantly diminishes proliferation and migration invasion and increases apoptosis in LAR and non-LAR TNBC subtypes, mesenchymal-like, mesenchymal stem-like, and basal-like 2 (Barton et al., 2015; Zhu et al., 2016).

2. Enzalutamide. Enza, a second-generation AR antagonist, was supposed to suppress AR's nuclear translocation, its DNA binding, and co-activator mobilization (Fig. 4). After receiving docetaxel, a multicenter placebo-controlled randomized clinical trial showed improved survival of patients with castration-resistant PC (CRPC). Enza was Food and Drug Administration approved for patients with metastatic CRPC who had received docetaxel. It was demonstrated that the median progression-free survival (PFS) of Enza is longer than bicalutamide (Bernales et al., 2012; Cochrane et al., 2012).

Therapeutic outcomes of Enza have been examined in PR^-/ER^- BC preclinical models. Treatment with Enza in the AR^+, ER^- MDA-MB-453 cell line, and the xenograft models led to increased apoptosis, reduced AR localization, and tumor growth inhibition. A similar effect has been shown in dihydrotestosterone-induced models of tumor growth (Bernales et al., 2012; Cochrane et al., 2012). Enza influences the AR signaling pathway at several different levels. Enza's AR affinity is remarkably higher than bicalutamide (Cochrane et al., 2014). Fatigue, nausea, and vomiting were the most frequent adverse reactions associated with Enza medication (Traina et al., 2013; Elias et al., 2016).

3. Abiraterone Acetate. Abiraterone acetate is an androgen-directed therapy under evaluation to treat patients with AR^+ BC. It is a specific, potent and irreversible inhibitor of CYP17A1, the enzyme involved in the gonadal and adrenal glucocorticoids' biosynthesis; thus, it reduces both estrogen and androgen expression. Currently, this inhibitor is under clinical evaluation (phase II) in monotherapy form (NCT00755885; NCT01842321) and combined with AR antagonists (NCT01884285; NCT02580448) (Bonnefoi et al., 2016;

TABLE 4
Recently completed and recruiting clinical trials targeting androgen, CDK4/6, and PI3K signaling in TNBC

Agent	Clinicaltrials.gov Identifier	Phase	Mechanism of Action	Study Arm(s)	Recruitment Status	Trial Design (total n patients)	Year (start–estimated study completion date)	Responsible Party	Listed Location Countries	Reference(s)
	NCT03055312	III	AR inhibitor	Bicalutamide vs. TPC (taxotere and xeloda, GT or gemcitabine and carboplatin)	Recruiting	18–70 years, female (262)	December 2016–December 2020	Zhong-yu Yuan, Sun Yat-sen University	China	Hwang et al. (2019)
Bicalutamide	NCT00468715	II	AR inhibitor	Bicalutamide	Active, not recruiting	18–120 years, all (28)	May 2007–March 2021	Memorial Sloan-Kettering Cancer Center	United States	Gucalp et al. (2013)
	NCT02353988	II	AR inhibitor	Bicalutamide vs. physician's choice	Not yet recruiting	18–70 years, female (60)	January 2015–January 2017	Xiaoxiang Guan, Jinling Hospital, China	Not Provided	Gucalp et al. (2013)
	NCT01889238	II	AR inhibitor	Enza	Active, not recruiting	18+ years, female (118)	June 2013–April 2020	Pfizer	Canada, Italy, Spain, United Kingdom, United States	Traina et al. (2015)
Enza	NCT02750358	II	AR inhibitor	Enza	Active, not recruiting	18+ years, female (200)	April 2016–May 2021	Memorial Sloan-Kettering Cancer Cente	United States	Lyons et al. (2018)
	NCT02689427	IIB	AR inhibitor + antimicrotubule	Enza + paclitaxel	Recruiting	18+ years, all (37)	February 2016–September 2020	M.D. Anderson Cancer Center	United States	Gerratana et al. (2018)
Abiraterone acetate	NCT00755885	II	CYP17 inhibitor	Abiraterone acetate	Completed	18+, female (77)	September 2008–June 2016	Cancer Research UK	United Kingdom	Gerratana et al. (2018)
	NCT01842321	II	CYP17 inhibitor	Abiraterone acetate + prednisone	Active, not recruiting	18+ years, female (31)	April 2013–July 2015	UNICANCER	France	Bonnefoi et al. (2016)
Seviteronel	NCT02580448	II	CYP17 inhibitor	Seviteronel	Completed	18+ years, all (175)	October 2015–January 2019	Innocrin Pharmaceutical	United States	Bardia et al. (2018); Michmerhuizen et al. (2020)
	NCT02130700	II	CYP17 inhibitor	Seviteronel	Completed	18+ years, all (175)	April 2014–September 2017	Innocrin Pharmaceutical	United States	Michmerhuizen et al. (2020)
CDK4/6 + AR inhibition	NCT03090165	I/II	AR inhibitor + CDK 4/6 inhibitor	Bicalutamide + ribociclib	Active, not recruiting	18+ years, all (11)	March 2017–September 2022	Ruth O'Regan, M.D., Big Ten Cancer Research Consortium	United States	Wang et al. (2021)
	NCT02605486	I/II	AR inhibitor + CDK 4/6 inhibitor	Bicalutamide + palbociclib	Active, not recruiting	18+ years, female (46)	November 2015–November 2022	Memorial Sloan-Kettering Cancer Center	United States United States	Gucalp et al. (2016); Wang et al. (2021)
	NCT02457910	Ib/II	AR inhibitor + PI3K inhibitor	Enza + taselisib	Active, not recruiting	18+ years, all (30)	May 2015–May 7, 2020	Vandana Abramson, Vanderbilt-Ingram Cancer Center	United States	Lehmann et al. (2020)
AR inhibitor + PI3K inhibitor	NCT01884285	I	AR inhibitor + PI3K inhibitor+ mTOR inhibitor	AZD8186 + AZD2014+ abiraterone	Completed	18+ years, all (147)	June 2013–March 2019	AstraZeneca	Canada, Spain, United Kingdom, United States	Lebert et al. (2018)
	NCT03207529	I	AR inhibitor + PI3K inhibitor	Enza + alpelisib	Recruiting	18+ years, all (28)	June 2017–December 2020	M.D. Anderson Cancer Center	United States	Garrido-Castro et al. (2019)

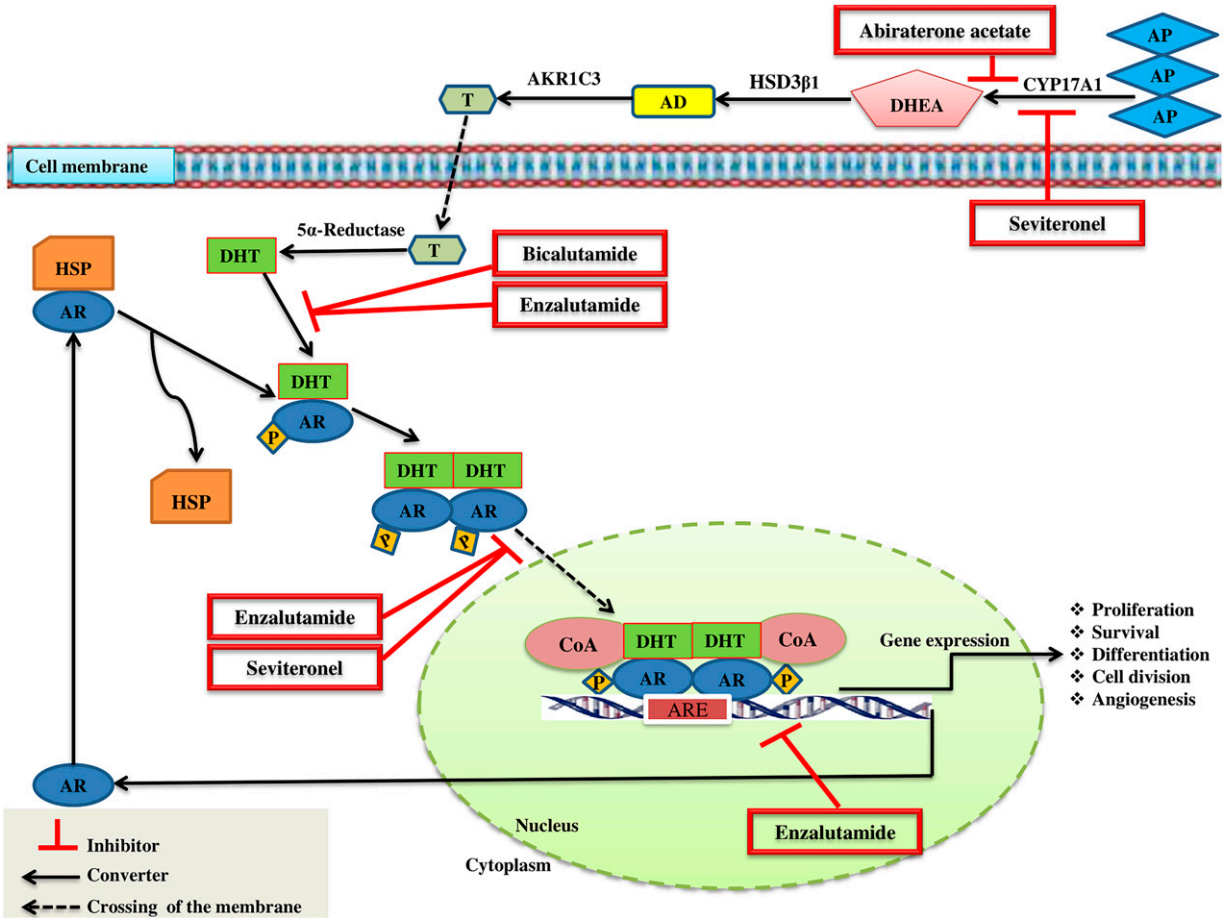

Fig. 4. Representation mechanisms of blockade of AR in TNBC subtype. The enzyme CYP17A1 is responsible for converting the androgen precursors to dehydroepiandrosterone, whereas HSD3β1 performs dehydroepiandrosterone conversion to androstenedione, aldo-keto reductase family 1 member C3 performs androstenedione conversion to T. Abiraterone acetate is an inhibitor of CYP17. Also, seviteronel (VT-464) is a CYP17A1 inhibitor. Seviteronel directly inhibits AR activity in the preclinical models. Following cytoplasm entrance, T was reduced to DHT using 5α-reductase. Heat shock proteins release AR, and it is activated through DHT binding. Enza and bicalutamide are AR antagonists binding to the AR ligand site, preventing ligands from binding to AR. Enza inhibits AR nucleus translocation and prevents AR-mediated transcription.

Gucalp and Traina, 2017) (Table 4). UNICANCER, a French cooperative team, performed a multicenter clinical trial (phase II) in women with inoperable locally advanced or metastatic AR$^+$ TNBC to define abiraterone acetate's efficacy and safety along with prednisone (Gucalp and Traina, 2016). This study has hopeful outcomes in inhibiting TNBC.

For women suffering from AR$^+$ TNBC, oral administration of abiraterone (1000 mg) was given daily, adding prednisone (5 mg) twice daily to prevent side effects associated with elevated mineralocorticoid levels (Gerratana et al., 2018). Given the action mechanism of abiraterone acetate as a CYP17 inhibitor, it is reasonable to study its potential advantage in patients with AR$^+$ TNBC since it is expected that the levels of androgens are reduced due to the steroid synthesis pathway upstream inhibition (Bonnefoi et al., 2016) (Fig. 4).

4. Seviteronel (VT-464). Seviteronel is a new androgen-directed agent for patients with PC. Also, it is under examination for treating patients with AR$^+$ TNBC. Seviteronel is an oral CYP17-L inhibitor, selective, as well as an AR antagonist reducing androgen production, and hence may be potentially beneficial for AR TNBC patients (Gucalp and Traina, 2016) (Fig. 4). Seviteronel showed an approximately 10-fold higher selectivity for inhibition of CYP17 lyase compared with CYP17 17-alpha hydroxylase. In addition to being a better selection for CYP17 lyase than abiraterone (Rafferty et al., 2014), it is a competitive antagonist to the mutations leading to resistance to Enza and abiraterone (Norris et al., 2017).

Seviteronel inhibited the progression of several BC subtypes, both in vivo and in vitro. Currently, seviteronel completed a phase II clinical trial examination for men suffering from advanced CRPC as well as women and men suffering from advanced ER$^+$ or TNBC (Table 4). The tolerability and safety of seviteronel was confirmed for women with AR and ER TNBC and men with CRPC from the phase II trial (NCT02580448 and NCT02130700) (Bardia et al., 2018; Gupta et al., 2018).

B. Combination Therapy

According to clinical and preclinical studies, AR stimulates HER2+ BC or TNBC growth. Some combination therapies are directly engaged in the cell cycle's progression (CDK4/6 inhibitors), whereas others (MEK, phosphoinositide 3-kinase, and Ras inhibitors) are involved in regulating the most critical intracellular circuits leading to drug escape survival, proliferation, and invasiveness. Thus, the optimal results can be achieved using combination therapies, including AR antagonists and the mentioned pathway inhibitor (Bianchini et al., 2016; Robles et al., 2016) (Table 4).

1. Combination of CDK4/6 and Androgen Receptor Inhibitors. Studies demonstrated that, compared with mesenchymal and basal-like subtypes, LAR TNBC cell lines show particular susceptibility to CDK4/6 inhibitors, similar to ER^+ MCF7 cell line (Asghar et al., 2017). As a CDK4/6 antagonist, palbociclib inhibits cell proliferation by stopping the cell cycle in the G1-phase (Fry et al., 2004). Preclinical evidence suggests that palbociclib's greatest activity is in the luminal profile tumors with elevated Rb protein and cyclin D1 (CCND1) expression and p16 reduced expression. Rb protein is intact in AR^+ TNBC, a potent target for palbociclib. It has been shown that palbociclib represses the cell growth in the MDA-MB-453 cell line (AR^+ TNBC) by decreasing Rb phosphorylation and preventing the thymidine incorporation into the DNA of RB^+ BC (Finn et al., 2009). A recent preclinical investigation has shown that abemaciclib, an inhibitor of the cell cycle CDK4/6, in combination with seviteronel, an agent that targets both androgen biosynthesis and AR activity, demonstrated synergy in an AR^+ TNBC model compared with each drug alone (Christenson et al., 2021).

A limited number of studies have been conducted using CDK 4/6 in patients with metastatic TNBC. DeMichele et al. (2015) evaluated the effect of palbociclib in 37 patients (phase II clinical trial) with RB1 wild-type metastatic BC, including four TNBC patients. Two clinical trials (NCT03090165 and NCT02605486) on AR^+ TNBC patients are currently underway, including the combination of palbociclib/bicalutamide and ribociclib/bicalutamide, respectively. The results of these studies refer to the remarkable inhibiting of CDK4/6 and AR in treated patients (Asghar et al., 2015; Rampurwala et al., 2016) (Table 4).

2. Combination of P13k and Androgen Receptor Inhibitors. Among the introduced targets against BC, phosphatidylinositol-3-kinase (PI3K), which is known as a potent inhibitor (Koboldt et al., 2012; Cuenca-López et al., 2014) and involved in Akt and mechanistic target of rapamycin (mTOR) pathways.

The rate of PIK3CA mutation among AR^+ BC is greater (approximately 40%) compared with the AR^- BC (4%) (Lehmann et al., 2014). PI3K inhibitors are promising to be effective for patients with TNBC. For example, alpelisib, a PI3K inhibitor, has been fruitful for patients with $HR^+/HER2^-$ BC, according to the SOLAR-1 trial (Norris et al., 2017).

A preclinical study combined AR inhibitors therapy with PI3K antagonists demonstrated a synergistic apoptotic effect on the AR^+ TNBC cell line (Cuenca-López et al., 2014). In addition, the combination of AR inhibitors with PI3K/mTOR antagonists showed synergistic action on the TNBC AR^+ models (Lehmann et al., 2014). Based on the phase I outcomes of clinical trials (NCT01884285 and NCT03207529), which were performed to evaluate the effectiveness of the combination of AR inhibitors with PI3K/mTOR antagonists in patients with metastatic TNBC and AR^+/PTEN low TNBC, respectively, it was determined that combination therapy significantly promoted the effectiveness of cancer therapy in BC.

C. Novel Androgen Receptor Inhibitors

LBD inhibitors, chaperone inhibitors, and selective AR modulators are the newly developed inhibitors against AR-related signaling pathways.

1. Ligand-Binding Domain Targeting Using Next-Generation Androgen Receptor Inhibitors. For patients carrying LBD mutants, it was expected that targeting other domains could be helpful. Apalutamide (ARN-509), as the next-generation AR antagonist (Clegg et al., 2012), irreversibly and selectively binds to AR's ligand-binding domain with high affinity, resulting in AR's conformational change inhibiting the receptor complex's translocation to the nucleus; as a result, DNA binding and the concentration of AR accessible to bind androgen response elements are reduced, eventually inhibiting AR-mediated transcription (Clegg et al., 2012; Smith et al., 2016; Isaacsson Velho et al., 2021). It was thought that the activity of apalutamide was slightly higher compared with Enza, and it caused fewer seizurogenic side effects compared with Enza (Smith et al., 2018). Compared with bicalutamide, apalutamide has a 7- to 10-fold greater affinity for directly binding the AR (Isaacsson Velho et al., 2021). Preclinical results for ARN-509 indicated antitumor effects in the MDA-MB-453 cell line as AR^+ TNBC, but the research has not progressed past the preclinical level (Clegg et al., 2012; Speers et al., 2017).

Darolutamide is another second-generation AR antagonist with a unique molecular structure that targets LBD (Yu et al., 2019). It exhibits more binding potency for wild-type AR compared with Enza. It inhibits translocation to the nucleus and does not exhibit an agonist effect in case of AR overexpression, thus preventing or limiting possible seizurogenic effects (Moilanen et al., 2013), It was established as ODM-201 by Orion Pharmaceuticals and further developed by Bayer (Fizazi et al., 2019).

Darolutamide inhibits AR variations such as W741L, T877A, H874Y, and F876L mutants competitively, binds to AR-LBD, and greatly reduces the development of enzalutamide-resistant PC cells in vivo (Yu et al., 2019). To date, no study has reported the use of this drug in BC. Darolutamide was recently approved in the United States for the treatment of males with nonmetastatic CRPC on the basis of favorable findings from the phase III ARAMIS study (Fizazi et al., 2019; Markham and Duggan, 2019).

2. Chaperone Inhibitors. AR's normal activity depends on the binding of the ligand and the interaction between the chaperone proteins and co-activators. In the absence of the ligand, the AR is found in the cytoplasm and is bound to the heat shock proteins (HSPs) as well as the rest of the inactive co-chaperones (Osguthorpe and Hagler, 2011). Molecular chaperones such as Hsp90 are engaged in protein folding, AR activation, transcription, and trafficking in the AR signaling pathway. Exposed Hsp90 inhibitors lead to AR degradation in TNBC cells (Agyeman et al., 2016).

Onalespib (AT13387) and ganetespib (STA-9090) are the inhibitors of Hsp90 and OGX-427. An inhibitor of Hsp27 was developed in both BC and PC (Proia et al., 2014; Spiegelberg et al., 2020). Hsp90 repression by onalespib leads to proteasomal degradation and inhibition of several signal transduction pathways, such as the full-length AR (AR-FL) pathway (Slovin et al., 2019). In PC cell lines, onalespib decreases AR-FL protein in a concentration and in a time-dependent manner, regardless of the AR-FL status (i.e., wild-type or mutant). Onalespib affects the splicing of at least 557 genes in PC cells, including AR, according to bioinformatic analysis of transcriptome-wide RNA sequencing data (Ferraldeschi et al., 2016). To date, no information has been reported on the use of onalespib alone in BC patients. However, the combination of this drug with paclitaxel is being investigated in TNBC (phase Ib clinical trial) (Wesolowski et al., 2019).

Ganetespib, as a next-generation Hsp90 inhibitor, is a triazolone molecule with improved anticancer efficacy and safety profile compared with first-generation Hsp90 inhibitors. The interaction between Hsp90 and co-chaperone p23, which is necessary for an effective chaperone function, is disrupted by ganetespib binding. Ganetespib inhibits the expression of HIF-1 target genes that contribute to the progression of TNBC (Wesolowski et al., 2019). Ganetespib induced the powerful and simultaneous disruption of the epidermal growth factor receptor, AKT, and mTOR signaling pathways in TNBC cell lines, resulting in low nanomolar cytotoxicity values in vitro and significant tumor growth reduction in xenograft models (Xiang et al., 2014). Ganetespibsignificantly decreases the size of MDA-MB-231(TNBC cell)-derived xenograft tumors, both alone and combined with several conventional chemotherapeutics (Proia et al., 2014). Also, ganetespib suppressed the growth of MDA-MB-231 and MCF-7 xenografts and, in the BT-474 model, led to tumor regression (Friedland et al., 2014).

3. Selective Androgen Receptor Modulators. Since their discovery in the late 20th century (Dalton et al., 1998), selective androgen receptor modulators (SARMs) have been considered potential androgen therapies. SARMs were expected to radically transform the field of androgen therapy because they have the satisfaction and ability to extend androgen therapy to patients with BC without virilizing adverse effects (Negro-Vilar, 1999; Narayanan et al., 2014). Compared with DMSO-treated tumors, SARMs suppress the proliferation of AR^+ TNBC and decrease tumor growth and weight by more than 90%. Through its effects on AR, SARM therapy prevents the intratumoral expression of genes and pathways that encourage the development of BC (Narayanan et al., 2014). SARMs include a class of underdeveloped drugs; contrary to the androgen synthesis inhibitors, they function as selective agonists of androgens and are promising as a possible treatment approach for BC. Enobosarm (GTx-024) is the most advanced drug in this category in clinical research; it exhibits an agonistic activity preventing BC progression in certain patients. Preclinical outcomes demonstrated GTx-024 antitumor activity in AR^+ stable expressions of MDA-MB-231 (TNBC) and MCF-7 (ER^+) cell lines subcutaneously implanted in the nude mice (Dalton et al., 2013).

SARMs are small molecule compounds produced by chemical engineering, selectively used for various degrees of antagonist and agonist effects on AR in the different body tissues. SARMs' entrance to the cytoplasm is similar to androgens, and they can bind to the AR. The SARM-AR complex functions as a transcriptional regulator when translocated to the nucleus. It recruits the co-regulatory proteins and co-factors to modulate the AR complex's transcriptional response (Solomon et al., 2019; Christiansen et al., 2020). Phase 1 clinical trial showed RAD140 a novel SARM, has an acceptable safety profile as well as preliminary indications of target engagement and anticancer efficacy in the treatment of AR^+/ER^+/HER2 metastatic BC (LoRusso et al., 2022). Thus, it appears SARMs' signaling ability via AR depends on the interaction between specific conformations, AR's functional domains, the method of interaction between those domains, and the cellular regulatory environment for targeting DNA expression. Since SARM-AR complexes show diverse conformations and particular AR expression patterns in tissues, transcriptional regulation, and co-regulatory protein levels, it can refer to tremendous diversity and capability of action.

VII. Genome Editing Against Androgen Receptor-Positive Cells: CRISPR/cas9 Enters the Scene

In recent years, many genome-editing approaches have introduced rational changes in the genome, and

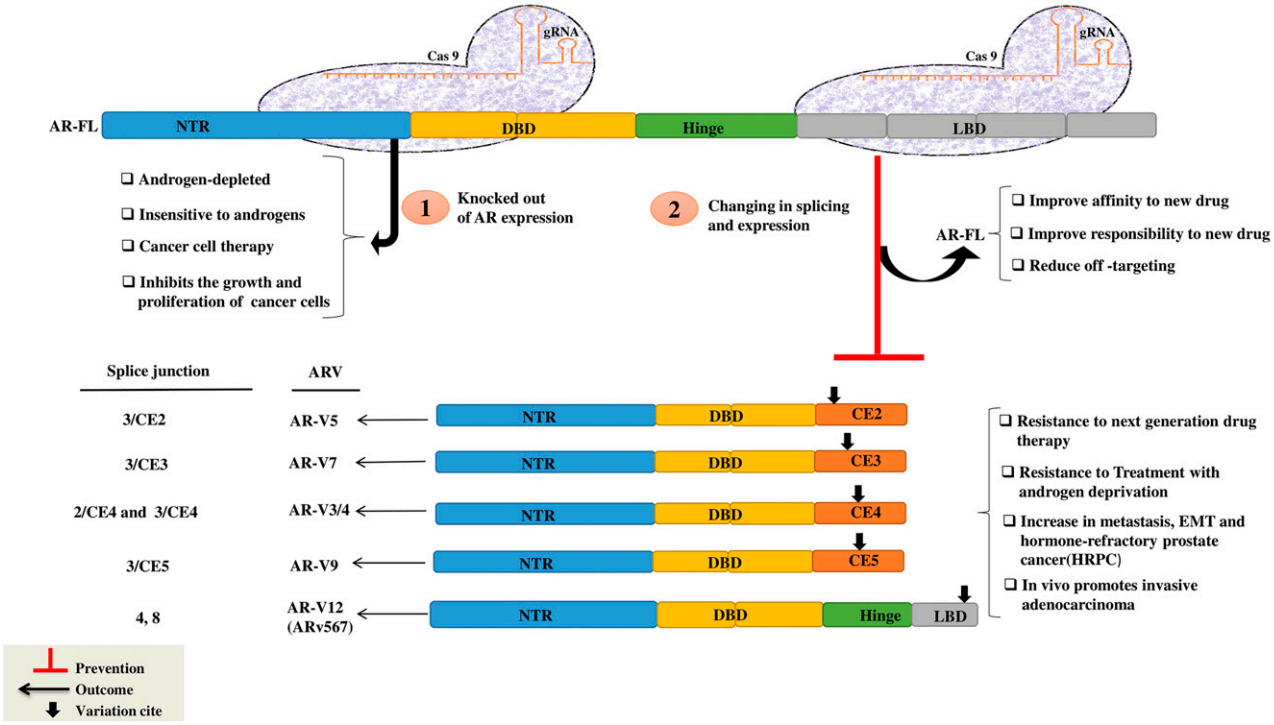

Fig. 5. Mechanism of CRISPR activity to target AT in BC and PC. AR gene expression can be changed in two ways using the CRISPR system. First, knocked out; expression of the AR gene is blocked in this manner. As a result, the cells are entirely depleted of AR, effective in inhibiting cancer cell growth and proliferation, and also show insensitivity to androgens. Second, changes in splicing and expression by editing the genome.

CRISPR (clustered regularly interspaced short palindromic repeats) is one of them. Compared with other genome editing techniques—namely, zinc-finger nucleases and transcription activator-like effector nuclease—the CRISPR/Cas9 method has more advantages in performance, repeatability, and accuracy. The CRISPR/Cas9 method has the potential to influence AR expression theoretically via two main pathways mediated by targeting the AR gene and mRNA modulation. At the DNA stage, the AR silencing gene could be achieved by being knocked out/in, and at the mRNA level, changes in splicing, expression, and polyadenylation can be considered (Fig. 5). When the CRISPR system knocks out the AR gene, the cells are deprived of AR and become insensitive to androgens. Studies showed that when AR is partially knocked out, the CRISPR system inhibits the growth and proliferation of LNCaP cancer cells (Wei et al., 2018). Given androgen receptor enhancer activity like the Cis-regulatory element, the CRISPR interference selectively inhibits annotated Cis-regulatory elements and quantifies the impact on AR-mediated gene expression (Huang et al., 2021). Another application of the CRISPR/CAS method could be regarded in Kounatido et al. (2019). They derived a valuable model for the study of receptor splice variants and introduced a stop codon into exon 5 of the AR locus by CRISPR/Cas9 -mediating knock-in that leads to the CRISPR-derived FL-AR knockout CWR22Rv1 cell line, which is called CWR22Rv1-AR-EK (Kounatidou et al., 2019).

Resistance to AR-targeted treatments is a severe concern in PC and BC. Changes that occur at the genome or mRNA level in the AR gene cause different variants of the gene (Fig. 5). For example, deletion of exons 5 to 7 in the AR-FL genome results in the AR-V12 (ARv567), which lacks the LBD domain at the protein level and thus resistance to next-generation drugs such as Enza, which binds to the LBD domain. Variations due to different splicing and polyadenylation at the mRNA level create AR-V7 and AR-V9 variants. These variants lack the second LBD at the protein level and are insensitive to next-generation drugs that bind to the domain. Expression of AR-V1, AR-V7, and AR-V12 increased in hormone-refractory PC and metastasis, which increasd resistance to Enza and androgen deprivation therapy and also induce an invasive adenocarcinoma and EMT in vivo (Ware et al., 2014; Radaeva et al., 2021). CRISPR can prevent exon deletion by targeting the desired sequence in the AR gene and modifying this sequence, as well as prevent the development of resistant variants by different splicing and polyhadilation at the mRNA level (Yong et al., 2017).

SF3B2 plays a crucial role in splicing AR-FL and creating AR-V7. Studies showed that different splicing due to overexpression of SF3B2 is one of the mechanisms of

PC progression and resistance to treatment. These studies proposed SF3B2 as a therapeutic target candidate for the treatment of cancer patients (Kawamura et al., 2019). CRISPR technology could be a good option for treating cancer patients by targeting SF3B2 and preventing the development of resistant androgen receptor variants. Another study examined the role of the heterogeneous nuclear ribonucleoprotein A1 as a splicing factor and found that the factor played an important role in increasing AR-V7 expression (Tietz and Dehm, 2020). By knocking down heterogeneous nuclear ribonucleoprotein A1 in cancerous cells and thereby reducing AR-V7 expression, these cells lost resistance to Enza. CRISPR/Cas9 proved successful in targeting AR in PC. It is predicted that the same method will also work in TNBC, although studies in this area are limited.

VIII. Overcoming Drug Resistance in Triple-Negative Breast Cancer by Nanotechnology

Despite many advances in well-known treatment protocols such as chemotherapy and radiation therapy (Mahmoudi Gomari et al., 2021), cancer therapy is still far from a favorable state. Nonspecific distribution, low drug concentrations at the tumor site, high toxicity, off-target activity, and drug resistance are the most common obstacles in the field of drug delivery against malignant cells. Therefore, developing efficient technologies for targeted therapy in cancer is a principal issue (Misra et al., 2010). In recent years, advances in nanotechnology have introduced new approaches for drug delivery against cancer cells (Jin et al., 2020). By designing diverse nanoparticles for targeted therapy, nanotechnology promises solutions to several current barriers against cancer. Nanoparticles are particles at the nanoscale (1–100 nm) composed of materials such as metals, polymers, and ceramics and have different morphologies depending on the fabrication method (Wang et al., 2008; Aghamiri et al., 2019; Rostami and Davarnejad, 2021). Nanoparticles have been considered in the treatment of BC, especially TNBC, due to their small size, high drug-loading capacity, high circulating half-life, low systemic toxicity, efficient permeability to tumor tissue, and controlled release (Thakur and Kutty, 2019).

Liposomes are well-known nanoparticles about 400 nanometers in size. A commercial form of liposome containing doxorubicin is currently available for BC therapy (Franco et al., 2018). Daei et al. (2014) designed a liposome that efficiently targets TNBC. This liposome was successfully implemented to deliver doxorubicin and sorafenib. In another study, Andey et al. (2015) designed a liposome attached to estrogen derivatives and showed anticancer activity in mice with TNBC xenograft tumors. In a similar study, Dreaden et al. (2012) showed that anti-androgen gold nanoparticles bound an androgen receptor with 5- to 11-fold greater affinity than free antiandrogens and per particle bound the androgen receptor with an affinity superior to endogenous androgens, allowing for further improved therapy effectiveness.

IX. Conclusions and Future Perspectives

Many experimental treatments are being developed to conquer mechanisms that cause resistance to AR antagonists in PC. The function of the AR and its pathways is not well known in TNBC. However, experimental studies found that inhibition of AR activity in patients with AR^+ TNBC can be considered an option in BC therapy protocols. Early androgen signaling inhibitors were first studied as regular androgen deprivation therapy for PC. Wong and Xie (2001) examined the correlation between androgen exposure and BC in rat models. They demonstrated androgens inducing histologic transformation reversed with the androgen-blocking agent flutamide. Many preclinical studies confirmed that AR could be a druggable therapeutic target for BC patients; in particular, the $ER^-/PR^-/AR^+$ subtype inhibition of the AR pathway may be helpful against TNBC (Ahn et al., 2016).

- Some of the most important reasons that AR inhibitor drugs have not been used as a targeted therapy for BC patients as much as in PC patients are listed as follows:
- As a result of a lack of information on the signaling pathway and the role of ARs in BC, no drugs have been developed to inhibit this receptor in the past. Nevertheless, in recent years, as our understanding of ARs and BC has grown, numerous drugs have been designed, and most are in the clinical trials stage.
- The standard ARs expression assay for PC is well known; however, in BC, there is no definitive method.
- After AR-directed therapy for PC, the predictive utility of ARs in tumor response has been clearly shown; however, its predictive function in the treatment of TNBC is still unknown.
- ARs antagonists are being studied in both preclinical and clinical study for treatment of TNBC; however, currently, no reliable biomarker has been found to predict treatment efficacy (Witzel et al., 2019; Sridhar et al., 2022).

Based on the reported data, it is proposed that the signaling cascades involved in AR^-–related pathways have fundamental roles in TNBC initiation and progression. For example, anti-AR, PI3K, and CDK4/6 exhibit high activity against the TNBC LAR subtype (Lehmann et al., 2011). Available evidence indicates that in AR^+ TNBC patients, the combinatorial targeting of the AR with CDK4/6 or PI3K pathways would be of clinical

benefit (Lehmann et al., 2014; Gucalp and Traina, 2016). The evaluation of combination therapy protocols such as anti-AR with CDK4/6, mTOR, P13k, and immune checkpoint inhibitors should be further examined to increase the effectiveness of the therapy. Targeting more than one signaling pathway involved in carcinogenesis seems to be promising, provided that suitable targets are chosen and the most effective and less toxic combinations of agents are employed.

CRISPR and nanotechnology raise hopes for targeting cancerous cells in TNBC patients as two newly emerging approaches. Targeting different regions of the AR gene using the CRISPR system is a potential gene-editing method to control expression. Studies revealed that knocking out the AR gene using the CRISPR method attenuates cancer cell growth and proliferation (Wei et al., 2018). Different AR splicing variants that confer resistance to new drugs can be overridden by editing the AR genome in TNBC cells using CRISPR technology if tumor-specific delivery can be achieved.

The efficiency of TNBC therapy can be considerably improved by nanotechnology. In addition to enhancing drug toxicity, targeted therapy, and timely drug release, nanoparticles may be used, as CRISPR promotes genome editing accurately in TNBC models. Many studies have been performed on AR suppressors by nanoparticles in PC (Lee et al., 2012, 2016; Yamamoto et al., 2015; Zhang et al., 2017) However, in the context of TNBC, there has been no evaluation of nanoparticles suppressing the AR gene. Therefore, the use of nanocarriers for suppression and targeted therapy of AR in TNBC is warranted for future studies.

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