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# Targeting the androgen receptor in triple-negative breast cancer

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ABSTRACT

Triple-negative breast cancer represents approximately 15%-20% of all newly diagnosed breast cancers, but it accounts for a disproportionate number of breast cancer-related deaths each year. Owing to the lack of estrogen, progesterone, and human epidermal growth factor receptor 2 expression, patients with triple-negative breast cancer do not benefit from generally well-tolerated and effective therapies targeting the estrogen and human epidermal growth factor receptor 2 signaling pathways and are faced with an increased risk of disease progression and poorer overall survival. The heterogeneity of triple-negative breast cancer has been increasingly recognized and this may lead to therapeutic opportunities because of newly defined oncogenic drivers and targets. A subset of triple-negative breast tumors expresses the androgen receptor (AR) and this may benefit from treatments that inhibit the AR-signaling pathway. The first proof-of-concept trial established activity of the AR antagonist, bicalutamide, in patients with advanced AR+ triple-negative breast cancer. Since that time, evidence further supports the activity of other next-generation AR-targeted agents such as enzalutamide. Not unlike in estrogen receptor-positive breast cancer, mechanisms of resistance are being investigated and rationale exists for thoughtful, well-designed combination regimens such as AR antagonism with CDK4/6 pathway inhibitors or PI3K inhibitors.

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Furthermore, novel agents developed for the treatment of prostate cancer, which reduce androgen production such as abiraterone acetate and seviteronel, are being tested as well. This review summarizes the underlying biology of AR signaling in breast cancer development and the available clinical trial data for the use of anti-androgen therapy in the treatment of AR+ triple-negative breast cancer.



## Introduction

Triple-negative breast cancer (TNBC), a relatively new term first published in 2005,[1] is used to describe a subset of breast cancers characterized by the absence of expression of the estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor (HER2) protein. TNBC represents approximately 15%-20 % of all newly diagnosed breast cancers, but accounts for a disproportionate number of breast cancer-related deaths each year making up 5% of all cancer deaths annually.[2,3] Owing to the lack of receptors, patients with TNBC do not benefit from generally well-tolerated and effective therapies targeting the ER and HER2 and often experience a more aggressive clinical course with increased risk of disease progression and poorer overall survival.[4] A subset of TNBC tumors express the androgen receptor (AR) and may benefit from treatments that inhibit the AR-signaling pathway. This review summarizes the underlying biology of AR signaling in breast cancer development and the available clinical trial data for the use of antiandrogen therapy in the treatment of AR+ TNBC.

## Structure and function of the androgen

AR is a member of the steroid-hormone family of receptors, which also includes the estrogen, progesterone, glucocorticoid, and mineralocorticoid receptors. Located on chromosome Xq11-12, physiologically AR-regulated signaling is responsible for male sexual differentiation and reproductive development. In adult males, androgens maintain libido, spermatogenesis, muscle mass and strength, bone mineral density, and erythropoiesis. The gene for AR encodes a 110 kDa polypeptide with 4 distinct functional regions: (1) an N-terminal region involved in transcriptional activation (ligand-independent activation function 1 (AF1) domain), (2) a DNA-binding domain composed of 2 zinc fingers that interacts with androgen response elements, (3) a ligand-binding domain (LBD) to which androgens and antiandrogens bind that includes an androgen-dependent activation function 2 domain at the C-terminus), and (4) a hinge region that connects the DNA-binding domain and LBD, and controls nuclear localization.

Unbound AR resides primarily in the cytoplasm, bound to chaperone proteins such as heat shock proteins that stabilize the receptor in a conformation that promotes ligand binding. In the presence of androgens (testosterone and dihydrotestosterone), the AR undergoes a series of conformational changes, dissociates from the heat shock proteins, and forms a homodimer that translocates to the nucleus. In the nucleus, the AR-complex binds to androgen response elements and recruits coregulatory activators leading to the activation of target gene transcription.[5-7]

Published data support that the androgen-signaling pathway has a role in breast cancer development. Notably, both growth stimulatory and inhibitory effects of androgens have been described in breast cancer cells lines.[8,9] Reconciling these seemingly paradoxical effects is complex. However, emerging data suggest that the function of the AR in breast cancer pathogenesis may be in part dependent on the underlying molecular phenotype of the tumor, the relative coexpression of other hormone receptors (HRs), and the hormonal environment. Historically androgens, such as fluoxymesterone, testolactone, and calusterone have been