

BREAST | YEAR IN CANCER | REVIEW™

An Unmet Need in HR-Positive Endocrine-Resistant Breast Cancer



2021 Year in Review - Triple-Negative Breast Cancer

HR-positive, *HER2*-negative breast cancer is the most common type of breast cancer.¹ The mainstay of first-line treatment is endocrine therapy, but endocrine resistance is common.¹ For patients with HR-positive breast cancer, 3 types of antiestrogen therapies are currently available.¹ Endocrine therapy is still the most effective treatment for HR-positive early-stage breast cancer prophylaxis, both primary and secondary.¹ Selected estrogen receptor modulators such as tamoxifen; aromatase inhibitors (AIs) such as anastrozole, letrozole, and exemestane; and selective estrogen receptor degraders such as fulvestrant are all currently accessible endocrine therapies.¹ Tamoxifen or AIs are the standard endocrine therapies for early-stage breast cancer.¹ Endocrine therapy is the most common first-line treatment for HR-positive metastatic breast cancer patients.¹ Breast cancer that exhibits endocrine resistance has the potential to metastasize and cause death.²

Antiestrogen resistance, on the other hand, is a key roadblock to long-term illness control and avoiding chemotherapy.¹ Several novel targeted medicines, including CDK4/6 inhibitors, mTOR/PIK3 inhibitors, and histone deacetylase inhibitors, have shown higher performance in combination with antiestrogen therapy over the past decade, with the potential to overcome endocrine resistance.¹

The adjuvant CDK4/6 inhibitor abemaciclib in combination with an AI has shown efficacy in high-risk disease in preliminary data. However, no targeted monotherapy is approved for endocrine-resistant HR-positive breast cancer, meaning patients with endocrine resistance only have chemotherapy as a real option.¹ Clinically, there are 2 types of endocrine therapy resistance: primary, inherent resistance, in which estrogen receptor–positive tumors never respond effectively to endocrine treatment, and secondary, acquired resistance, which develops after an initial response.³ Intrinsic resistance mechanisms may overlap in certain ways, but they are still poorly understood.³

Endocrine therapy is the primary treatment for most women with advanced HR-positive breast cancer.¹ Recent research has linked the use of CDK4/6 inhibitors, mTOR inhibitors, and PI3K inhibitors in combination with hormone therapy to improved outcomes and a delay in chemotherapy initiation.

For HR-positive breast cancer, several new agents are being investigated.¹ To improve HR-positive breast cancer results, the future of overcoming resistance to focused therapy, new therapies, and predictive indicators is critical.¹ Treatment with antiestrogens has been linked to improved overall survival in patients with both early and advanced HR-positive breast cancer.¹

For patients with HR-positive advanced breast cancer, the current standard treatment is a combination of an AI or fulvestrant plus a CDK4/6 inhibitor.¹ An alternate endocrine treatment in combination with another targeted medication is a beneficial choice as the disease progresses.¹ The best sequence of multiple targeted drugs is unknown, and pathways of resistance to currently available therapies must be identified.¹ The therapy landscape for HR-positive breast cancer is rapidly developing, thanks to a greater knowledge of physiological processes and the discovery of novel biomarkers.¹

The role of immunotherapy in hormone-positive breast cancer is not as important as it is in triple-negative and HER2-positive cancers.⁴ Hormone-positive breast cancer has a diverse set of genes and phenotypes.⁴ As a result, greater research into combining immunotherapy and conventional therapy (chemotherapy, radiotherapy, and hormone therapy) based on more detailed gene expression or tumor microenvironment alteration is warranted.⁴ Breast cancer is molecularly complex; the more we learn about the variety of molecular and genetic characteristics associated with breast cancer, the more precise treatment decisions we may make.⁴

References

1. Andrahennadi S, Sami A, Manna M, et al. Current landscape of targeted therapy in hormone receptor-positive and HER2-negative breast cancer. *Curr Oncol.* 2021;28:1803-1822.
2. Lin Y, Lin J, Liu YE, et al. Nafamostat mesylate overcomes endocrine resistance of breast cancer through epigenetic regulation of CDK4 and CDK6 expression. *Transl Oncol.* 2022;15:101302.
3. Grote I, Bartels S, Kandt L, et al. TP53 mutations are associated with primary endocrine resistance in luminal early breast cancer. *Cancer Med.* 2021;10:8581-8594.
4. Chien T. A review of the endocrine resistance in hormone-positive breast cancer. *Am J Cancer Res.* 2021;11:3813-3831.

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By Matteo Lambertini, MD, PhD; Erica Stringer-Reasor, MD, Director; Sara M. Toloney, MD, MPH



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The Academy of Oncology Nurse & Patient Navigators (AONN+) and Eli Lilly and Company Medical Affairs are pleased to present a live webinar designed to facilitate conversations with patients regarding adherence to breast cancer treatments. Attendees will have an opportunity to participate in a live Q&A following the presentation.

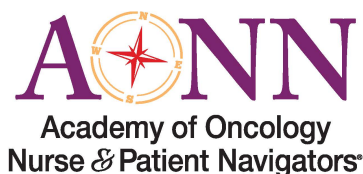
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