Transcript Details

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The Unmet Need in 1L HR+/HER2− Advanced Breast Cancer

Announcer:
You're listening to ReachMD. This medical industry feature titled "The Unmet Need in First-Line HR-Positive, HER2-Negative Advanced Breast Cancer" is sponsored by AstraZeneca.

Narrator:
Step by step, over the past 50 years, endocrine therapies have improved patient outcomes in HR-positive, HER2-negative advanced breast cancer.

It all started in 1977, when the Food and Drug Administration approved tamoxifen to treat metastatic breast cancer in the first-line setting for postmenopausal women. It was not until the 1990s that aromatase inhibitor monotherapy established a new benchmark of about 10 months without disease progression. The SERD fulvestrant was then investigated in the early 2010s as a monotherapy, setting a new standard of 16 months of progression-free survival. Soon after, the combination of a CDK4/6 inhibitor and an aromatase inhibitor raised PFS to about 25 months.

This upward trajectory raises a compelling question: can the next generation of endocrine therapies continue to push boundaries and slow disease progression?

This is crucial for advanced HR-positive, HER2-negative breast cancer. After first-line treatment with an endocrine therapy plus a CDK4/6 inhibitor, progression-free survival typically decreases with the next line of therapy. And health-related quality of life may also deteriorate with the next line of therapy, potentially including worsened rates of depression, anxiety, or physical and functional well-being. This suggests that each patient should receive the treatment regimen that provides the strongest benefit in the first-line setting.

So, how do these endocrine therapies work? First, let's review the standards of care. Aromatase inhibitors block the production of estrogen by inhibiting the enzyme aromatase, which converts androgens to estrogens.

SERMs, like tamoxifen, are selective estrogen receptor modulators. They competitively bind to the estrogen receptor and inhibit ER-related transcription in the breast, while allowing that activity in other tissues like bone and endometrium.

SERDs are selective estrogen receptor degraders. They competitively bind to the ER too, but in addition to blocking ER signaling, they also target the ER for degradation by the proteasome.

Although fulvestrant was the first-approved SERD, it has limitations. It must be injected intramuscularly every month and is less effective against certain mutant forms of the ER. To overcome these limitations, next-generation SERDs are being developed to still target the ER for degradation but also be orally available and potentially more effective than fulvestrant.

Some next-generation SERDs are called complete ER antagonists due to their ability to inhibit the ER in all tissues, while others only act as ER antagonists at high doses.

Also on the horizon are PROTACs, which bind to the ER and contain a domain that can mark the ER for degradation.

Ultimately, the hope is clear that one or more of these investigational endocrine therapies will one day help delay progression and improve outcomes in HR-positive advanced breast cancer.

Announcer:
This program was sponsored by AstraZeneca. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can be part of the knowledge.

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