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Potential for Early Intervention in 1L HR+/HER2- Advanced Breast Cancer

Announcer:
You're listening to ReachMD. This medical industry feature titled "Potential for Early Intervention in 1L HR+/HER2- Advanced Breast Cancer" is sponsored by AstraZeneca.

Dr Wander:
Intervening at the earliest emergence of *ESR1* mutations during first-line endocrine treatment might address the endocrine resistance mechanism proactively, before the cancer becomes harder to treat.

It could be like taking your car to the mechanic when the 'check engine' light comes on, before any serious damage occurs. Or fixing a leaky faucet before it causes a flood in your house.

Hi, I'm Doctor Seth Wander. I'd like to share my perspectives as a medical oncologist.

Let's review the evidence that supports early intervention:

- Patient experiences on aromatase inhibitors,
- Efficacy declining from the first- to second-line treatment setting,
- Quality of life—declining from the first- to second-line setting and having no difference between regimens in the second-line setting,
- The interplay of quality of life and survival outcomes,
- Attrition rates, and

Links between *ESR1* mutations, clinical progression, tumor complexity, and efficacy outcomes.

The first line of evidence supporting early intervention involves patient experiences on aromatase inhibitors. The standard first-line treatment for hormone receptor-positive, HER2-negative advanced breast cancer is a regimen that includes an aromatase inhibitor and a CDK4/6 inhibitor. Although effective, this combination *does* have some limitations. Patients taking an AI may have mixed experiences regarding adverse reactions, tolerability, and quality of life.

For example, AI-induced musculoskeletal syndrome is well documented, causing symptoms such as arthralgia, myalgia, arthritis, and stiffness, and potentially leading to discontinuation of aromatase inhibitors. Therefore, hope remains that innovation of endocrine therapy combinations might be an effective strategy to improve patient outcomes and experiences before their first clinical progression.

Another line of evidence is efficacy declining from the first- to the second-line setting. The combination of an AI plus a CDK4/6 inhibitor may yield 25 to 28 months of median progression-free survival in the first-line setting, but disease progression is inevitable and treatment efficacy outcomes decline in the second-line setting. After 6 months of treatment with a first-line regimen, about 85 percent of women have cancer that is progression-free.

But in the second-line setting with FDA-approved monotherapies, only about 42 percent of women have cancer that still responds to treatment at 6 months. This steep decline in the second-line setting highlights the importance of maximizing time on treatment before the first clinical progression. Next up is quality of life declining from the first- to second-line treatment setting and having no difference between regimens in the second-line.

With the standard first-line regimen, there is generally an adequate quality of life for patients, but like efficacy, quality of life may also

worsen after patients move to second-line therapy. Such deterioration can involve increased depression, as well as declines in functional and physical well-being.

And in the second-line setting, 2 clinical trials using validated assessment methods showed that oral SERD monotherapy did not provide a clinically meaningful difference in quality of life or delay deterioration when compared with the control arm. Therefore, extending the duration and benefit of first-line treatment while delaying resistance is crucial for the well-being of patients.

Another line of evidence is the interplay between quality of life and survival outcomes. Surprisingly, measures for quality of life might capture more than just how patients feel during routine daily activities. In a systematic review and meta-analysis of more than 44,000 patients with solid tumors, higher scores in global health status and quality of life were associated with improved overall survival. These quality-of-life measures also offered independent prognostic information for overall survival across cancer types.

Next, let's discuss attrition rates. One approach to maximizing treatment outcomes might be to use the most effective treatments as early as possible. About 1 in 5 women never make it to second-line therapy. And women who develop visceral crisis or have rapidly progressing disease may only have chemotherapy as their next treatment option instead of endocrine therapy.

Based on medical records from 199 women with HER2-negative metastatic disease across 3 cancer centers in the US, 20% did not receive second-line treatment due to death, disease progression, adverse reactions, or even financial reasons. Likewise, two studies of more than 3,400 women with hormone receptor-positive, HER2-negative metastatic disease in Europe showed similar attrition rates, with seventeen to eighteen percent who didn't receive second-line treatment. To fully understand the current clinical situation with attrition rates and to aid in clinical decision-making about sequencing therapies, larger multicenter studies need to be completed across the US.

Finally, there are links between *ESR1* mutations, clinical progression, tumor complexity, and efficacy outcomes. Because aromatase inhibitors have no direct effect on the estrogen receptor, *ESR1* mutations may emerge that make the estrogen receptor active, even in the absence of estrogen. This is a well characterized and widely accepted resistance mechanism.

As the exposure to aromatase inhibitors increases, the rate of *ESR1* mutations also increases in the metastatic setting. To illustrate this, the rate of *ESR1* mutations is about 5% at diagnosis of advanced breast cancer and may increase to as much as 50% after progression on an AI regimen in the first-line metastatic setting. This increasing rate of *ESR1* mutations signals that the cancer is at risk of progression.

For example, a study of 104 women with hormone receptor-positive metastatic breast cancer showed about a 3-fold increase in the risk of disease progression within 6 months of detecting an *ESR1* mutation.

In addition, the emergence of *ESR1* mutations is associated with increased genetic complexity, including a high rate of polyclonal *ESR1* mutations and potentially other mutations. And most importantly, patients with *ESR1* mutations have shorter progression-free survival and overall survival than those without *ESR1* mutations detected during first-line treatment, as shown by these real-world results when the subgroup with *ESR1* mutations is compared to the subgroup without *ESR1* mutations detected.

These increases in tumor and mutational burden over time may be responsible for some of the limitations of current second-line therapies. This leads us to a potential approach to early intervention. A potential way to address that 'check engine' light, or fix that leaky faucet. To help patients have the best chance of extending the benefit of first-line AI plus CDK4/6 inhibitor regimens, it may be critical to detect emerging endocrine resistance as early as possible. One approach would be to integrate ctDNA monitoring for *ESR1* mutations with routine blood work. The hope is that an approach like this may lead to personalized treatments with improved patient outcomes. The right intervention for the right patient, at the right time.

For hormone receptor-positive, HER2-negative advanced breast cancer, proactive intervention could occur at the earliest emergence of *ESR1* mutations during first-line endocrine treatment, which may help address this mechanism of endocrine resistance, before the cancer becomes harder to treat.

Announcer:
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