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Endpoints in Adjuvant Breast Cancer Trials: Implications for Clinical Practice

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Rugo:
This is CME on ReachMD, and I'm Dr. Hope Rugo. Today, I'm looking at the endpoints that are used in adjuvant breast cancer trials, focusing on the CDK4/6 inhibitor trials combined with endocrine therapy for patients with early-stage, hormone receptor-positive, HER2-negative breast cancer, and we'll discuss the implications of these endpoints for clinical practice.

So what endpoints do we usually think about in these early-stage breast cancer trials? The primary endpoint for these trials has been invasive, disease-free survival, so whether or not a patient has an invasive breast cancer event. Now, this could be a local recurrence, or a local-regional recurrence. It could be a new invasive cancer, or it could be a distant recurrence. So an important secondary endpoint after the primary, where the statistical power is created, is actually looking at distant disease-free survival. Some trials also look at distant relapse-free survival, but I think we're most familiar with and most confident with looking at distant disease-free survival.

Of course, trials then also look at a number of different secondary endpoints, which may be important to us as clinicians. So one important secondary endpoint is taking IDFS and looking at subsets. You have to be powered to be able to evaluate the impact of a new treatment in these subsets. For example, in early-stage breast cancer, we might look at the patients who had more positive nodes versus less positive nodes, so 4 or more positive nodes versus 1 to 3 positive nodes. In the NATALEE trial, where patients with high-risk, stage II, node-negative disease were included, you could look at the benefit in the node-negative patients, an analysis which has been done already and presented.

So there are a number of different subsets that can be looked at. One interesting subset that was evaluated in the monarchE trial was to look at Ki-67, or key-67. This was a specific cohort of the monarchE trial, representing just 9% of the population who were enrolled with positive nodes and Ki-67 with 1 to 3 positive nodes as the primary eligibility criteria. But the trial also looked at the intent-to-treat overall population at the Ki-67 endpoint, dividing it by 20% or greater versus less than 20%.

All of these secondary endpoints, when powered, can be very important for clinical practice and have potency in terms of guiding our treatment and guiding prognosis for our patients. For example, Ki-67-positive nodes, which we already knew, higher-stage disease, all of which impacted prognosis, did not impact the relative benefit of CDK4/6 inhibitors. In other words, the hazard ratios for benefit in terms of IDFS were relatively similar.

So additional secondary endpoints which are important include safety. And safety can be analyzed in 2 different important ways. One is provider assessment of safety that includes symptoms as well as laboratory findings, which, of course, are hardwired; you know if somebody's neutropenic or not. But the number of episodes of diarrhea may be very subjective for an individual patient and require careful recording, as an example. Another important endpoint in terms of safety is patient-reported outcomes, which evaluates quality of

life, and that's important as well. But patient-reported outcomes, which are increasingly important to us in terms of evaluating the patient's experience on a trial, are limited by the number of patients who fill out those forms. And patients who drop off early due to toxicity may not be included in the overall assessment of patient-reported outcomes, something that's being worked on continuously to improve the reporting of patient-reported outcomes at any one period of time.

So how do these endpoints correlate with real-world practice? The most important endpoint to me as a provider, other than safety and PROs, is distant disease-free survival. I want to know whether the treatment prevents distant events. I want to look at the number of events as well as the time till treatment starts, so the relative follow-up. And understanding the time frame for when a distant event can occur in a patient population and the impact of this treatment over time, it makes a big impact on how you use these drugs in clinical practice. Understanding safety helps us up front in educating our staff and our patients to optimize treatment adherence and tolerance over time.

So I hope that I've shared with you the critical nature of specific endpoints in understanding new treatments and how they apply to clinical practice in the real-world setting every day.

Thank you for listening.

Announcer:
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