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Released: 12/30/2024
Valid until: 12/30/2025
Time needed to complete: 1h 32m

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Adjuvant Treatments for HR+/HER2- EBC: The Role of CDK4/6 and PARP Inhibitors

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Dr. Mayer:
Hello. I'm Erica Mayer from Dana-Farber Cancer Institute in Boston, and welcome to CME on ReachMD. Today, I'm going to review current guidelines for adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer. So let's get started.

Despite all the improvements that we've had in systemic therapy over the decades, there remains a persistent risk of disease recurrence for patients with hormone receptor-positive, HER2-negative disease, particularly those with higher-risk disease determined by positive lymph nodes or other biologic features. Luckily, we've had some great improvements in therapies over the past few years, including the introduction of CDK4/6 inhibitors as well as PARP inhibitors in the adjuvant setting, which have improved outcomes for patients. Both of these types of strategies are included in NCCN Guidelines for both premenopausal and postmenopausal patients.

Let's first talk about CDK4/6 inhibitors. So there have been multiple trials, 4 large randomized trials, looking at CDK4/6 inhibitors, 2 of the trials being positive, looking at abemaciclib and ribociclib. Let's start with abema. Abemaciclib was studied in the phase 3 monarchE study in which patients who had high-risk node-positive disease, defined as having 4 or more involved axillary lymph nodes or 1 to 3 involved axillary lymph nodes with an additional high-risk feature, such as being grade 3, having a tumor size of 5 cm or more, or high Ki-67, were randomized to receive adjuvant endocrine therapy alone or with the addition of 2 years of abemaciclib. Results from the study have now been presented with 5-year follow-up and demonstrate a significant improvement in invasive disease-free survival for patients who received abemaciclib.

What's so interesting is that the benefit has grown year by year. At the most recent data cut, it was about 7.8% benefit with a significant hazard ratio. Based on this data, this has led to the FDA approval of adjuvant abemaciclib for high-risk node-positive patients, initially in 2021, updated in 2023, and this has now become a standard of care for us.

More recently, we've seen data from the NATALEE study, which has looked at adjuvant ribociclib. There are some important differences between these studies. First of all, the study uses ribo, not abema. The ribo is given for 3 years instead of 2 years. Additionally, the dose of ribociclib used is different than the dose used in the metastatic setting.

In the metastatic setting, we give 600 mg a day. In the NATALEE study it was lower, 400 mg a day, in an effort to reduce side effects. Finally, the NATALEE study included not only the high-risk node-positive patients, but also high-risk node-negative patients. This included node-negative with grade 3 or node-negative grade 2, and an additional high-risk feature including a high genomic score, such as oncotype, or an elevated Ki-67.

So it's important to note that the NATALEE eligibility included a broader group of patients than who enrolled in monarchE. Essentially with the absence of stage 1 patients and lower-risk T2 N0, almost everyone else could have been eligible for NATALEE. Results from

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this study have now been presented and have similarly demonstrated an improvement in invasive disease-free survival, not only while the patients were taking the drug, but now in follow-up, when all the patients have completed the drug, there is a growing benefit in terms of IDFS, which is statistically significant. This benefit is seen in stage II and stage III patients and also has been seen in the node-negative patients as well. And this has led most recently, just this September 2024, for FDA approval of ribociclib in the adjuvant setting.

These drugs have different side effect profiles. Abemaciclib is more likely to cause diarrhea, fatigue, some cytopenias, whereas ribociclib is more likely to cause neutropenia, LFT abnormalities, and we have to monitor QT prolongation. Importantly, the toxicities seen with ribociclib were improved using a lower dose, although LFT abnormalities continue to be an issue, about 10% of people with grade 3 LFT abnormalities.

Moving on. For patients who have BRCA1/2 gene mutation, there's also the option to use olaparib, and this is approved not only in the metastatic setting but also in the early-stage setting for patients BRCA1/2 mutations.

Results from OLYMPIA have demonstrated a sustained benefit, not only in terms of invasive disease-free survival, but also overall survival. It's very challenging and difficult to have drugs show overall survival benefits in the adjuvant setting, so this is really notable.

So in conclusion, adjuvant CDK4/6 inhibitors are available for patients with higher-risk hormone receptor-positive, HER2-negative breast cancer. We have abema for high-risk node positive. We have ribo for high-risk node positive as well as higher-risk node negative.

The data for abemaciclib is more mature than that seen for ribociclib, although the ribociclib data is improving over time. The side effect profile between these 2 drugs is different, and this requires a conversation between providers and patients to decide which is the best agent for them. And I'll point out for our patients with BRCA1/2 gene mutations, we have adjuvant olaparib available as well for patients with high-risk disease.

Thank you for your attention. I hope this discussion will be helpful for your practice.

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