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From Resistance to Response: Evolving Treatment Pathways in HR+ Breast Cancer

### Announcer:

You're listening to *Project Oncology* on ReachMD. On this episode, Dr. Seth Wander will share insights from his presentation at the San Antonio Breast Cancer Symposium on addressing treatment resistance in breast cancer. Dr. Wander is an Assistant Professor of Medicine at Harvard Medical School and the Director of Precision Medicine at the Termeer Center for Targeted Therapies at Mass General Brigham Cancer Institute. Let's hear from him now.

### Dr. Wander:

We've learned a lot about endocrine resistance and CDK4/6 inhibitor resistance over the last five to 10 years. CDK4/6 inhibitors entered clinical practice around 2015. We now have three FDA-approved agents, including palbociclib, ribociclib, and abemaciclib. And we've been using more of these agents. They typically are deployed in the first-line setting, but we have data for use in the second-line setting in combination with fulvestrant. And for ribociclib and abemaciclib, we now have data for use in the adjuvant setting for high-risk patients. And then finally, we have some more recent data for HER2-positive disease utilizing palbociclib in the maintenance setting for frontline hormone receptor-positive HER2-positive patients.

We've had a lot of interesting studies over the past five to 10 years, and just broadly speaking, these studies and translational efforts span a wide spectrum of tools. So, for example, we have studies from both clinical trials and institutional data sets where we have tumor biopsies that have been sequenced with various methodologies to look for genetic mechanisms of resistance. We have studies that have utilized laboratory models where cancer cells develop resistance to CDK4/6 inhibitors and can be characterized for different genomic or molecular changes. We have real-world data sets and all of the above. That's a 50,000-foot view on the kinds of tools that we're using.

The take-home message that I would highlight is the fact that there is no single dominant resistance driver to the anti-estrogen CDK4/6 inhibitors. Broadly speaking, many of the resistance alterations can be categorized into things that impact the cell cycle machinery, the division machinery of the cell, or alterations that impact oncogenic signal transduction—these growth and survival pathways. For example, there's evidence that disruption of the RB tumor suppressor, upregulation of CDK6, upregulation of cyclin E and CDK2, activation and upregulation of the Aurora kinase protein, and all of these things impact the machinery of cell division and allow the tumor cells to continue to divide even in the presence of CDK4/6 inhibitors. On the other side of things, we have activation of the AKT-PTEN mTOR pathway and activation of FGFR, HER2, RAS, and MAP kinase. All of these have also been shown to provoke resistance to anti-estrogen elements as well as to CDK4/6 inhibitors.

Antibody-drug conjugates are increasingly important for the use of metastatic cancer therapy. The way I think about describing them to patients is they're sort of in between hormonal targeted therapy and combination cytotoxic traditional chemotherapy. They do have real toxicities. They're IV drugs. Some of them can cause GI toxicity. Some of them can cause reduction in blood counts. Some of them can cause hair loss and fatigue. So these are not necessarily the easiest drugs to give, particularly when you contrast them with hormonal therapy or with, for example, some of the CDK4/6 inhibitors that have a lot less toxicity. So we have increasing amounts of data suggesting that earlier deployment of antibody-drug conjugates and hormone receptor-positive metastatic breast cancer can pay clinical dividends, but the guidelines and the way that those studies were done were really in patients that have exhausted endocrine-based therapy. So I typically would reserve the use of antibody drug conjugate agents until a time where I feel like I didn't have any other good endocrine or targeted therapies.

We're making good progress here, but these drugs are relatively more recent addition to our arsenal, and every time we get a new drug, it takes time to deploy the sequencing tools, the translational efforts in the laboratory to start to uncover some of these mechanisms.

**Announcer:**

That was Dr. Seth Wander discussing treatment resistance and evolving management strategies in breast cancer. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!