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Unmet Needs in Endocrine Therapy: Rethinking the HR+/HER2- mBC Treatment Roadmap

Dr. Jhaveri:
This is CE on ReachMD, and I'm Dr. Komal Jhaveri, a breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York. And today, I'll examine the unmet needs in endocrine therapy for treating hormone receptor-positive, HER2-negative metastatic breast cancer.

Now, let me start by saying that when we think about hormone receptor signaling, the estrogen receptor really consists of 3 domains: an activation function domain 1, a DNA-binding domain, and a ligand-binding domain, which is also called as AF-2, or activating function-2 domain. And this hormone receptor, or estrogen receptor, is complexed with HSP90 that maintains the receptor in an off state. Now, when estradiol binds to the ligand-binding domain, it triggers the release from the HSP90, causing receptor dimerization and DNA engagement. This DNA engagement then causes coordinated recruitment of cofactors and transcriptional machinery that drives gene expression changes. And certainly, estrogen receptor is the most important target when it comes to treatment of ER-positive breast cancer, with many approved strategies to reduce this estrogen.

And how do we do that? We can achieve that by using aromatase inhibitors, which inhibit the conversion of androgens to estrogen by inhibiting the aromatase enzyme. We can achieve that with serum estrogen receptor modulators, such as tamoxifen, which really works in a tissue-specific fashion. It works as an ER antagonist in the breast, and it works as an ER agonist in the uterus, causing decline in this ER transcriptional machinery or ER transcription downstream. And last but not the least, we have serum estrogen receptor degrader, or down-regulator, which not only inhibits the ER transcription but also degrades the actual estrogen receptor itself.

Now, while anti-estrogen therapies are very, very effective and have been very beneficial in clinic for our patients, unfortunately, resistance is inevitable. And there are several networking signaling pathways that can explain endocrine resistance, including the cyclin D pathway, the PI3K/AKT/mTOR pathway, and then mutations in the estrogen receptor itself, which is ESR1 mutation, which is what is the focus of today's discussion.

So what happens is there could be, under the selective pressure of aromatase inhibitors, ligand-independent yet estrogen-dependent pathway activation, and this is due to ESR1 mutations.

So this has really been a challenge that we've faced in clinic where we know that it's not other mechanisms or other stem cells that are causing endocrine resistance, but a new target is being created, yet the tumor is still ER-dependent and we need newer novel endocrine agents to overcome this new endocrine resistance issue, this new target, which is ESR1 mutation.

In addition to this endocrine resistance mechanisms, there are also limitations to our existing approved therapies, which are not necessarily limited to their toxicity profile, but they can also be challenged by their pharmacological liabilities. For instance, tamoxifen is thought to be a weak ER suppressor. And certainly, it has its own toxicities, including 1% risk of developing blood clots or uterine cancer.

Aromatase inhibitors certainly have their own toxicity profiles, and as we said under their selective pressure, are the emergence of these ESR1 mutations. And last but not the least, fulvestrant is challenged by lack of oral bioavailability. It is also dose-dependent when it

comes to its efficacy, but we cannot go higher than the 500-mg intramuscular dose. Its activity, after progression on a CDK4/6 inhibitor, is rather very modest in clinic. And even though it works against some ESR1 mutations, its activity is limited against the most common ESR1 mutation, which is the Y537S.

So all of these reasons is why we need this effort to identify newer next-generation of novel endocrine agents that can overcome the liability issues, which is pharmacologic. They can overcome the existing toxicity issues, which are not only an issue in metastatic but early-stage setting, but also overcome the endocrine resistance mechanisms, specifically ESR1 mutations.

Well, my time is up, and I hope you found this overview helpful, and thank you for listening.