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Beyond Fulvestrant: Oral SERDs Redefining ER Targeting

Dr. Jhaveri:

This is CE on ReachMD, and I'm Dr. Komal Jhaveri, a breast medical oncologist from Memorial Sloan Kettering Cancer Center in New York. Today, I'll review clinical data on single-agent oral SERDs, or serum estrogen receptor degraders, in the treatment of HR-positive, HER2-negative metastatic breast cancer.

So certainly, it's been an exciting time to now have newer novel endocrine agents, specifically oral SERDs, that are now FDA-approved and available for our patients in clinic, especially for ESR1 mutant tumors. So let's review the data for the very first SERD that got approved in January of 2023, which was elacestrant. And this was based on the pivotal phase 3 EMERALD trial that led to its approval.

Now, EMERALD was a trial that evaluated patients with hormone receptor-positive, HER2 negative metastatic breast cancer who've had no more than 2 lines of endocrine therapy in the metastatic setting, no more than 1 line of chemotherapy, and then were enrolled and randomized to receiving either elacestrant or physician choice endocrine therapy.

There were dual primary endpoints that were designed for this EMERALD study, which was looking at PFS in all patients and also looking at PFS in ESR1-mutant tumors.

We did see a statistically significant improvement in progression-free survival favoring elacestrant in all patients. We also saw that the benefit was deeper and better in the ESR1-mutant tumors. A higher proportion were progression free at landmark analyses of 6 months and 12 months, favoring elacestrant in the EMERALD trial, again, with a deeper and better benefit in ESR1-mutant tumors.

So when the FDA reviewed the data and they looked at the exploratory analysis in those patients who did not harbor an ESR1 mutation, where the benefit was even smaller and the hazard ratio even higher, the approval was therefore given only for elacestrant use in ESR1-mutant tumors in clinic.

The medication is actually very well tolerated with very low-grade toxicities. The most common toxicity that we face actually in clinic is nausea and some fatigue.

However, it is important to note that the nausea does not necessarily have a lot of grade 3 side effects.

One other thing to remind ourselves when we think about monitoring is looking at the lipid profile. There were some instances of hypercholesterolemia, and so the package insert does remind us to monitor lipid levels before we start patients and periodically while on therapy.

Now, let's move on to talk about the second drug with single-agent activity, which is imlunestrant, based on the EMBER-3 trial that just received approval on September 25th, 2025. Now, EMBER-3 enrolled patients that had progressed either on an aromatase inhibitor with or without CDK4/6 inhibitor in the adjuvant setting or first-line metastatic setting. And the trial actually had 3 arms. Patients were randomized either to imlunestrant alone at 400 mg orally daily, compared to physician choice, fulvestrant or exemestane-based therapy. And a third arm was eventually added shortly after the trial had begun enrollment, so within 6 months, to study imlunestrant plus abemaciclib.

The primary endpoints were 3, looking at monotherapy comparisons for progression-free survival between imlunestrant and physician choice therapy in all patients and in ESR1-mutant patients, which was the second primary endpoint. And if either of the 2 were positive, only then the combination of imlunestrant/abemaciclib would be compared to imlunestrant alone.

So let's focus on the single-agent data, again, similar to what we learned in EMERALD. We saw a statistically significant and clinically meaningful improvement with imlunestrant compared to physician's choice therapy in ESR1-mutant tumors. Improvement from 3.8 months in the control arm to 5.5 months. There was no statistical significant improvement in PFS in all patients, and hence the approval for monotherapy is limited in ESR1-mutant tumors.

With respect to safety on imlunestrant, again, very well tolerated. In fact, grade 3 or higher toxicities were 17% in the imlunestrant arm and 21% in the physician choice endocrine therapy arm. And with imlunestrant, the toxicities that we see are diarrhea, nausea, fatigue, which were predominantly grade 1 and mostly single episodes. Discontinuation rates, again, were very low at 4%, which was very reassuring.

And last but not the least, we also heard data at the ASCO annual meeting for vepdegestrant, a PROTAC, or proteolysis-targeting chimera, in the metastatic setting from the phase 3 registration of VERITAC-2 study, comparing this PROTAC to fulvestrant.

But the improvement, again, was specifically limited to the ESR1-mutant tumors with vepdegestrant in the VERITAC-2 trial, improvement from 2.1 months in the control arm to 5 months with vepdegestrant. So a similar story, but good exciting times where we can at least offer oral options and better efficacious options to our patients with ESR1-mutant tumors. Certainly need to do a little bit more work about trying to make this durability of benefit better, and hopefully that can be achieved with combination-based regimens.

So that wraps up this session. I hope this brief overview is really useful to your practice, and thank you for listening.