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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Future of Oral SERDs: Combination Strategies

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 be breaking down clinical data on combination regimens involving oral SERDs in the treatment of HR-positive, HER2-negative metastatic breast cancer.

So while we have approval for imlunestrant and elacestrant for ESR1-mutant tumors as monotherapy, I think what we have come to realize, based on all the data from various randomized studies, is that 40% across the board still have early progression on monotherapy and about 60% still have less than 6 months of benefit, indicating a need for combination-based regimen. And this is why we think majority of our patients will derive benefit from this combination-based regimen and it's exciting to see data sets now with combination data.

So let's talk about first the combination data from the EMBER-3 trial from the third arm, arm C, that looked at imlunestrant plus abemaciclib. And here we see for the very first time a statistically significant and a clinically meaningful improvement in the order of 9.4 months compared to 5.5 months with imlunestrant alone. Hazard ratio of 0.57.

Not only that, in the 65% of the patients with prior CDK4/6 inhibitor, again, the benefit was maintained at a median PFS of 9.1 months. So we're used to seeing PFSs of around 6 months in the second-line space, so this was exciting to see a PFS of 9 months with this combination. The benefit was also seen in a key subgroup of PI3K mutant tumors, where the median PFS for the combination of imlunestrant and abemaciclib was 7.6 months.

More importantly, while the benefit with monotherapy and the approval is limited in ESR1-mutant tumors, subgroup analysis in EMBER-3 showed that the benefit for the combination was seen regardless of ESR1 mutation status. In fact, the median PFS for the combination was 11.1 months for ESR1-mutant tumors and 9.1 months in those without ESR1 mutations.

The combination was very well tolerated. No new surprises. I think that the toxicity was mostly what we know about the individual drugs, diarrhea being the most common with abemaciclib, which was the most common toxicity with this combination. There were no drug-drug PK interactions and no additional diarrhea because imlunestrant added. Because of that, the discontinuation rates for the combination were low at 6%, which was very reassuring as well.

Now, beyond EMBER-3, we also saw data for SERENA-6 with camizestrant and CDK4/6 inhibitor. Now, camizestrant and CDK4/6i in SERENA-6 was a very unique study because it looked at intervention at the time of molecular progression. So these patients were all treated in the first-line metastatic setting with an AI, CDK4/6i with serial monitoring of ESR1 mutations. Once an ESR1 mutation was detected, and if there was no radiological progression, patients were randomized to continuing the same AI, CDKi as we would have done in standard of care, vs switching the AI to camizestrant, but still continuing the same CDK4/6 inhibitor. But a primary endpoint of PFS.

And in SERENA-6, which is now published, we saw a statistically significant improvement in PFS from 9 months in the control arm to 16 months with the switch to camizestrant for molecular progression. What we don't really have yet is the overall survival data.

So the phase 3 evERA trial was an interesting trial and the first readout of a combination of giredestrant with everolimus. With giredestrant being another oral SERD, compared to physician choice endocrine therapy and everolimus. So patients could have been treated with exemestane- or fulvestrant-based backbones in the physician choice therapy arm.

No prior chemotherapy was allowed. No more than 2 lines of endocrine therapy were allowed. Majority of the patients were treated in the second-line metastatic setting, which is about 3/4 of the patient population. And there were dual primary endpoints looking at investigator assessed PFS in all patients and in ESR1-mutant tumors.

And what we learned was that the trial was statistically significant and clinically meaningful for all patients and in ESR1-mutant tumors. The median progression-free survival with giredestrant plus everolimus in ESR1-mutant tumors was 9.9 months compared to 5.45 months with a hazard ratio of 0.38. In all patients, again, it was statistically significant, with median PFS of giredestrant/everolimus of 8.7 months compared to 5.49 months, again with the hazard ratio of 0.56. However, in the exploratory analysis of ESR1 non-molecularly detected patients, there was no statistical significance, and the hazard ratio was 0.84.

Well, this was brief, but I'm glad that I had the opportunity to share these exciting data, and thank you all for listening in.