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Targeting PTEN: Why It Matters

### Announcer:

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### Dr. Taplin:

This is CE on ReachMD, and I'm Dr. Mary-Ellen Taplin. Joining me today is Dr. Scott Tagawa.

Dr. Tagawa, what does the emerging evidence tell us about targeting PTEN in hormone-sensitive prostate cancer?

### Dr. Tagawa:

So thank you very much for the question. We're learning much more about a number of different genomic alterations within prostate cancer, and a subset of them that we've known about for a while are important.

So if we look at the tumor suppressor genes, we know that there's a prognostic implication from a number of them across different stages of disease. PTEN is one of the tumor suppressor genes.

We also separately know that the pathway that's probably the most important in prostate cancer, really through the end in virtually all patients, is the AR pathway. But we know that tumors can be smart, and there's ways to kind of get around that. One of the ways around hitting the AR receptor pathway particularly hard is to bypass that with the PI3-kinase pathway. PI3-kinase is very difficult to inhibit safely in solid tumors because solid tumors are beyond just the delta pathway, and there's toxicity.

But there are other ways to get there, whether that is mTOR or the AKT pathway. And what we learned several years ago was that one AKT inhibitor, for what was called CRPC at the time, did have a progression-free survival advantage when added to abiraterone.

But now what we've done is to test that in the initial setting, the metastatic hormone-sensitive setting, specifically looking at patients with PTEN loss by immunohistochemistry. And we verified that that is a prognostic factor, but there may be a difference in outcome when we add an AKT inhibitor.

So, very specifically, what was done is approximately 6,000 patients were diagnosed with these disease states were tested, and about 1,000 of them were positive for at least a 90% loss by immunohistochemistry. And then they were treated with ADT plus abiraterone and prednisone, with the AKT inhibitor capivasertib or not, with the primary endpoint of radiographic progression-free survival. And those data were presented and subsequently published in *Annals of Oncology* as a positive trial. So those patients that had at least 90% PTEN loss had an advantage in terms of radiographic progression-free survival.

There was, of course, toxicity, as we'd expect with 3 drugs versus 2. We more or less expect more toxicity with that approach. Hyperglycemia is an on-pathway type of adverse event, but also GI toxicity and more fatigue, as we've come to know with AKT inhibition.

As kind of expected, the degree of PTEN loss showed a difference in the therapeutic index. So when we looked at 99% or 100% loss, the difference between the control and the investigation arm was bigger, mostly because of the poor prognosis. So the effect of the AKT inhibitor was more or less the same at 90% or greater loss, but as we had greater loss, looking at 99% and 100%, the control arm did worse, so maybe a differential effect. This remains an investigational approach in terms of prostate cancer.

So just kind of take a step back. Testing is very important, because we would not identify any of this, at least to be able to counsel patients in terms of the prognostic effect. But now we potentially have the molecular selected approach of AKT inhibition, which has science driving it. So I think it's very important for us to know about both the testing as well as the potential for the therapeutic intervention.

**Dr. Taplin:**

Thank you very much, Dr. Tagawa. That was very comprehensive.

So it's very exciting data. I know it's under review at the FDA. There was an ODAC panel held and more to come. But very important driver of prostate cancer growth and now a drug, capivasertib, that can potentially block that growth. And we have the opportunity to do tumor testing, look at the degree of PTEN loss, and then apply a treatment for those patients, with careful review of possible toxicity related to these treatments.

So very exciting, love that we're making progress in prostate cancer with patient- and tumor-directed therapy. Thanks for listening.

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