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[www.reachmd.com](http://www.reachmd.com)

[info@reachmd.com](mailto:info@reachmd.com)

(866) 423-7849

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## ADT Intensification in Biochemically Recurrent Prostate Cancer: When to Act

### 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.

Let's explore how to approach treatment intensification in prostate cancer patients who've had local therapy and now have a PSA or biochemical relapse.

Scott, can you tell us about the results of the PRESTO and the EMBARK trial and how to apply those results for our patients with biochemical relapse?

### Dr. Tagawa:

Sure, I'm happy to discuss this scenario, which unfortunately is common, ie, that when someone has a treatment, typically surgery or radiation with or without hormone therapy, with a goal of cure, not everyone is cured. And depending on the risk factors, 1/4 to 1/3 worldwide might have not be cured, ie, PSA goes up. I think the first principle is to remember that some of those patients can be cured. We have salvage local therapy, salvage designed to salvage the cure. And what I tell patients, simply, it's kind of what they didn't have first. So if they started with surgery, most often we employ radiation, sometimes with hormone therapy. And then if they had radiation, then surgery, or nowadays some sort of ablative therapy, or some specialized form of radiation. But I do think that is quite important, that there is a shot at cure, and this is one of the reasons that we monitor patients closely.

This setting has been quite large, in part because not everyone was cured, and we also had less sensitive imaging modalities than we have now. But what we learned from a bunch of initially negative trials—is that PSA is quite prognostic in this situation. So the higher the PSA is, and especially the faster it is rising, typically measured by a PSA doubling time—so a shorter PSA doubling time—is quite prognostic and is associated with a shorter time to metastatic disease and death.

So that's when we're thinking about a patient that has a PSA that's going up, some are very low, going very slowly, and observation may be appropriate. But for those who it's going up quickly, we now have studies that intensify the hormonal therapy. So we have something that is better than ADT. I'd say there's 2 trials that are out there, as mentioned by Mary-Ellen, PRESTO and EMBARK.

I'm going to focus on EMBARK really first because that's the bigger trial, which was a group of patients that we just mentioned, rising PSA. If they're eligible for local salvage therapy, they could get that. But then it was rising again, PSA doubling time less than 9 months,

and negative CT and bone scan, no PSMA PETs in that particular study.

And they're randomized to 1 of 3 arms: ADT alone, ADT plus enzalutamide, or enzalutamide alone. Actually, the ADT alone one had a placebo control. And the primary endpoint was metastasis-free survival by traditional imaging, CT and bone scan, so a pretty hard endpoint. There was an induction period. If they got to an undetectable PSA at around 9 months, or rounding off because that's what I tell patients, there was a pause, and then once PSA went back up, they restarted. That time was supposed to be continuous from that time point.

And the bottom line is that the main intervention, ADT plus enzalutamide, beat ADT alone in terms of metastasis-free survival and subsequently overall survival.

Now, the other arm that was enzalutamide alone was compared directly to ADT, ADT plus placebo, and also hit the endpoint of an improvement in metastasis-free survival.

So now we have a couple of options using ARPIs in this particular setting, and I think very impressive to have an overall survival benefit this early.

PRESTO, just kind of briefly, was an analogous study that also had 3 arms. It was slightly different. This was through the Alliance Foundation. One difference, it was a year of therapy and then stopped. The other difference it was ADT alone, ADT plus abiraterone plus apalutamide, or ADT and apalutamide. And the intensified arms were superior in terms of the main PSA endpoints. The triplet arm was only minimally better—and not really so much better—but had more toxicity. So what we consider the positive arm is the ADT plus ARPI, just like in EMBARK.

So I think we have a couple of options here.

Just kind of quickly, we now have PSMA PET. Many times we see lesions that throws them in possibly into a metastatic setting, or we could imply this here. The main point is that sometimes people are implying the EMBARK regimen and also adding metastasis-directed therapy. It's not part of the study, but extrapolating from other studies, it is part of people's practice to kind of give that 9 months plus metastasis-directed therapy and hope that either there's some cures or at least a lot longer time off therapy.

**Dr. Taplin:**

Thank you very much, Dr. Tagawa. I'd like to summarize by saying patients who have a PSA relapse after local therapy are a heterogeneous group of patients, and one of the key biomarkers to look at is the PSA doubling time. And if a patient has a long PSA doubling time, often they can be observed. In those patients with a shorter PSA doubling time, in the EMBARK trial and the PRESTO trial that was defined as a PSA doubling time of less than 9 months, should be considered for treatment intensification with not only ADT but the addition of an androgen receptor pathway inhibitor such as the enzalutamide in EMBARK or apalutamide as in the PRESTO trial.

So this concludes our episode. Thank you for listening, and we hope to see you again.

**Announcer:**

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