Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/frontlines-prostate-cancer/mcrpc-care-predicting-outcomes-with-a-novel-cell-free-dna-sequencing-assay/32210/

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

mCRPC Care: Predicting Outcomes with a Novel Cell-Free DNA Sequencing Assay

Announcer:
Welcome to *On the Frontlines of Prostate Cancer* on ReachMD. On this episode, we'll hear from Dr. Scott Dehm, who's a Professor and Apogee Enterprises Chair in Cancer Research in the Department of Laboratory Medicine and Pathology at the University of Minnesota's Masonic Cancer Center. He'll be discussing a new test that can detect circulating tumor DNA in patients with metastatic castration-resistant prostate cancer. Let's hear from Dr. Dehm now.

Dr. Dehm:
The objective of the study was to take advantage of biobanked plasma that was collected as part of a phase III clinical trial of advanced metastatic castration-resistant prostate cancer patients who were treated in a phase III clinical trial that was randomized to treatment with the drugs enzalutamide or enzalutamide plus abiraterone acetate plus prednisone. And the hypothesis that we had was that detection of circulating tumor DNA in the plasma cell-free DNA of these patients would be associated with worse prognosis and inferior outcomes. So the methods that we used for this study was to take that biobanked plasma that was available and extract the cell-free DNA in that plasma fraction and then use a targeted DNA sequencing assay that we developed, which we named AR-ctDETECT. And we're going to use this targeted cell-free DNA sequencing assay with that plasma cell-free DNA to detect alterations that are occurring in the tumor cells but can be detected in the circulating DNA.

The challenge that we had with this study initially was that we had low levels of plasma and low levels of cell-free DNA, and so we needed to tune this assay to some of the very high-intensity signals that are present in the plasma in these patients. And so what we observed is that a gene called the androgen receptor was frequently altered in our data—and this is well known and has been established in DNA sequencing assays from prostate cancer tissues—but what we found is that we could leverage this very high signal to detect the circulating tumor DNA above a threshold of noise. And so one of the objectives of our study was to ask whether we could leverage information from frequently altered genes like the antigen receptor and look at the diversity of alterations in this gene—mainly gained in the gene body and in the upstream cancer mutations in the gene—as well as genetic structural rearrangements in the gene to detect that circulating tumor DNA.

So using these signals, we were able to identify what we thought was circulating tumor DNA in the cell-free DNA fraction. And I think one of the unique aspects of this study is that it was a blinded study where all the DNA sequencing and data analysis was performed in my lab and with my colleagues at the University of Minnesota. And then once we had locked down our definitions of circulating tumor DNA and the types of alterations that would characterize the circulating tumor DNA, we sent those definitions to our biostatistician collaborator, Dr. Susan Halabi, who then, in a blinded fashion on her side, took the samples that we had classified as being positive and the samples that we had classified as being negative to test our ultimate hypothesis as to whether the detection of circulating tumor DNA was associated with inferior outcomes. And it turned out that it was, so in that regard, it was a successful outcome.

In the plasma cell-free DNA from 776 patients, we identified that approximately 60 percent of those patients were positive for circulating tumor DNA, and we derived two definitions of a circulating tumor DNA positivity in this data set. The first definition was using a traditional strategy of defining a cutoff for alterations that were genome wide detecting aneuploidy in the tumor DNA, and those samples turned out to be associated with the worst prognosis in our cohort. We took a novel approach of identifying a second cohort of patients who we deemed to be circulating tumor DNA positive by virtue of having detectable alterations in genes like the antigen receptor but also in two additional genes, MIC and MIC-N. And this group represented an intermediate group that also had poor prognosis when compared to the patients that we had identified as being circulating tumor DNA negative. So the main outcome is that the patients who

were deemed to be ctDNA positive had a higher risk of demonstrating progression in the trial and had a shorter survival in the trial.

Announcer:
That was Dr. Scott Dehm discussing a recent study on detecting circulating tumor DNA in patients with metastatic castration-resistant prostate cancer. To access this and other episodes in our series, visit *On the Frontlines of Prostate Cancer* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!