

Blood-based biomarker may identify prostate cancers that will be resistant to Enzalutamide

8 April 2014

Men with metastatic, castration-resistant prostate cancer who started treatment with the drug enzalutamide (Xtandi) and had a molecule called AR-V7 present in circulating tumor cells (CTCs) obtained prior to treatment had a worse response to enzalutamide compared with those who had no detectable AR-V7, according to results presented here at the AACR Annual Meeting 2014, April 5-9.

"Enzalutamide has been hailed as a miracle drug for many [patients](#) with advanced [prostate cancer](#), but a significant proportion of patients do not receive any clinical benefit from this agent," said Emmanuel Antonarakis, M.D., an assistant professor of oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore. "Our data show that AR-V7 seems to predict resistance to enzalutamide in virtually all cases. These findings are clinically relevant and could save patients time and money because oncologists could identify those men that are unlikely to respond to enzalutamide before they receive it and direct them to alternative therapies."

Hormones, such as testosterone, are the main drivers of prostate cancer. They work by binding to a protein called the androgen receptor (AR), which then attaches to certain regions of the genetic material (the DNA) of the prostate cancer cell, fueling its growth and division. The AR-V7 protein is a shortened form of the AR protein. It is missing the part of AR that testosterone binds, which is the same part that enzalutamide binds, but it can still attach to DNA and fuel cell growth and division, even when testosterone is not bound to it.

"Even though we understand that AR-V7 is constitutively active in the absence of hormones, it has previously not been clear whether it can drive resistance to drugs like enzalutamide, which block hormones binding AR, because preclinical studies

in animal models and human prostate cancer cell lines have produced mixed results," said Antonarakis. "Clinical data are urgently needed to document the presence and impact of AR-V7 in men with castration-resistant prostate cancer, and our data are among the first to link AR-V7 to enzalutamide resistance in humans."

Antonarakis and colleagues prospectively enrolled to their study 31 patients with metastatic, castration-resistant prostate cancer who were about to begin enzalutamide treatment. Blood samples were obtained from each patient prior to starting treatment with enzalutamide, at the time of the patient's maximum response to treatment, and at the time of disease progression. CTCs were isolated from [blood samples](#) and analyzed for the presence of AR-V7 mRNA, an intermediate between the AR gene and the AR-V7 protein.

The researchers found that 12 of the 31 patients had AR-V7 mRNA detectable in CTCs obtained prior to the start of enzalutamide treatment. These AR-V7-positive patients had worse responses to enzalutamide compared with patients who had no AR-V7 mRNA detected in CTCs. Levels of prostate-specific antigen (PSA), a measure of prostate cancer disease activity, failed to drop in the blood of all 12 AR-V7-positive patients, whereas PSA levels dropped by 50 percent or more in 10 of the 19 AR-V7-negative patients.

AR-V7-positive patients also had their disease progress sooner (as assessed by bone scan or computed tomography) compared with those who were AR-V7-negative: Time to radiographic progression was 2.1 months compared with 6.1 months.

"This is a fairly small study, and AR-V7 analysis was performed in a research laboratory," said

Antonarakis. "Before we can conduct the large-scale prospective trials needed to verify our results, we need to have the test that we used to detect AR-V7 mRNA in CTCs certified in a Clinical Laboratory Improvement Amendments (CLIA) setting to ensure the necessary quality control. We are currently in the process of doing this and we hope that things will run smoothly so we can continue to move forward.

"We are also conducting a small study to see whether AR-V7 might predict resistance to another AR-targeted therapy, abiraterone [Zytiga]," added Antonarakis. "We hope to be able to present the results from that study later this year."

Provided by American Association for Cancer Research

APA citation: Blood-based biomarker may identify prostate cancers that will be resistant to Enzalutamide (2014, April 8) retrieved 9 July 2022 from <https://medicalxpress.com/news/2014-04-blood-based-biomarker-prostate-cancers-resistant.html>

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