Castration-resistant prostate cancer (CRPC) remains a lethal disease, despite marked improvements in outcomes over the past decade with incorporation of novel androgen-receptor signaling inhibitors (ARSi), taxane-based chemotherapies, sipuleucel-T and radium-223 (1). However, treatment sequencing is still based on subjective clinical parameters and physician experience, which remains a major challenge. Moreover, despite the identification of several prognostic markers, prospectively validated biomarkers used for treatment selection (that may guide oncologists in choosing the right treatment option for their patients at the right time) are still lacking.

Since the initial clinical observation in 2014 (2), several studies have interrogated whether the presence of the constitutively active androgen-receptor splice variant 7 (AR-V7) in tumor cells confers a primary or an acquired resistance to novel ARSi or other therapies, and whether it could be used as a treatment selection tool in clinical practice. In particular, the greatest clinical relevance of such a biomarker would be if the marker could discriminate between the use of an ARSi therapy versus a taxane chemotherapy. These studies have included different methods of evaluating the presence of AR-V7 in circulating tumor cells (CTCs); the two most accepted assays are the Johns Hopkins mRNA-based assay using the AdnaTest platform (2-4) and the EPIC Sciences protein-based assay developed in collaboration with Memorial Sloan Kettering Cancer Center (5). In aggregate, the published data including a recent meta-analysis (6), consistently demonstrate that the benefit of ARSi occurs predominantly in AR-V7 negative (−) CRPC patients while most AR-V7 positive (+) CRPC patients do not respond well or durably to abiraterone or enzalutamide. On the other hand, AR-V7 status appears to not correlate with efficacy of taxane-based chemotherapy, and the detection of AR-V7 does not preclude favorable responses to docetaxel or cabazitaxel (3,5,7).

The paper recently published by Scher et al. (8) in JAMA Oncology, reports on a multi-center validation of the EPIC Sciences AR-V7 test, an assay that requires not only immunofluorescence-based detection of the AR-V7 protein in patients’ CTCs, but also requires nuclear localization of the AR-V7 signal for a positive call. Thus, the detection of a cytoplasmic-only AR-V7 protein would not be denoted as an AR-V7(+) test by this definition. This observational study included 142 samples from patients with progressive metastatic CRPC prior to initiation of second-line CRPC treatment with either an ARSi (70 samples) or a taxane agent (72 samples). Overall, 34 of the 142 samples (23.9%) were AR-V7(+) and the results demonstrated that there was a higher overall survival (OS) rate for AR-V7(−) patients who had been treated with ARSi, when compared to the taxane-based chemotherapy group (19.8 vs. 12.8 months, P=0.05). Opposite results were observed for AR-V7(+) subjects, with a numerically greater OS seen in the chemotherapy-treated patients (14.3 vs. 7.3 months, P=0.25), a difference that was not statistically significant. These results provided further evidence supporting the clinical utility of AR-V7 determination prior to treatment selection for metastatic CRPC patients. A reasonable interpretation based on these
data is that metastatic CRPC patients with AR-V7(−) CTCs may fare better with an ARSi agent, while those with AR-V7(+) CTCs may fare better with a taxane drug. Nevertheless, the major limitation of this study (and of all published data thus far), is that these are non-randomized and observational studies, which can inevitably lead to patient selection bias and might have interfered with the results. Ideally, prior to definitive incorporation of AR-V7 testing as a predictive biomarker for treatment selection in CRPC, these results must be validated in a prospective trial. Towards this end, the initial results of the first prospective biomarker trial with the primary goal of validating AR-V7 as a predictive marker for achieving benefit with ARSi have been recently reported at the 2018 American Society of Clinical Oncology (ASCO) annual meeting (9). This study, called the PROPHECY trial (“Multicenter prospective trial of circulating tumor cell AR-V7 detection in men with CRPC receiving abiraterone or enzalutamide”) included 118 men with progressive, high-risk chemotherapynaive metastatic CRPC, who first received abiraterone or enzalutamide (by physician’s choice) until disease progression, followed by taxane chemotherapy. Blood was collected at baseline, upon disease progression on ARSi therapy, and then again at the time of progression on taxane chemotherapy (only the results of the first phase have been presented). Patients were sampled for several circulating biomarkers, including CTC-based AR-V7 determination, using three different assays: the Johns Hopkins AdnaTest assay, the EPIC Sciences assay, and a third CTC assay developed by Weill Cornell, which used a multiplex digital-droplet PCR (ddPCR) method for interrogating multiple AR splice variants at once (data from this third AR-V7 assay have not yet been disclosed).

The primary endpoint of the PROPHECY study was the association of baseline (i.e., pre-treatment) AR-V7 status with radiographic/clinical progression-free survival (rPFS). Importantly, PSA changes were not used to determine rPFS, and both the central labs and the clinical sites were blinded to the clinical outcomes data and AR-V7 data, respectively.

In this cohort of high-risk CRPC patients who were treated with abiraterone (N=56), enzalutamide (N=59) or both (N=3), the overall median rPFS and OS were 5.8 and 20.3 months, respectively. The prevalence of baseline AR-V7 positivity was 24% using the Johns Hopkins assay and 11% using the EPIC Sciences assay, with higher prevalence in patients with detectable CTCs (by CellSearch), and high LDH and alkaline phosphatase levels. In this study, both of the CTC AR-V7 assays met their primary biomarker objective: patients who were AR-V7(+) demonstrated an inferior rPFS and OS to abiraterone/ezalutamide compared to AR-V7(−) men. For the Johns Hopkins assay, median rPFS and OS were 3.1 vs. 6.9 months and 10.8 vs. 27.2 months for AR-V7(+) and AR-V7(−) subjects, respectively. For the EPIC Sciences assay, median rPFS and OS were 3.1 vs. 6.1 months and 8.4 vs. 20.3 months for AR-V7(+) and AR-V7(−) subsets, respectively. Very importantly, the AR-V7 status, using both assays, was independently associated with a worse rPFS and OS in a carefully conducted multivariable analysis, that was adjusted for multiple clinical parameters, as well as CellSearch CTC counts, retaining its prognostic value after these adjustments. Notably, this is the first time that AR-V7 has demonstrated its prognostic power after adjustment for CTC enumeration, suggesting that its detection is not purely related to tumor burden.

In terms of prostate-specific antigen (PSA) declines with abiraterone/ezalutamide treatment, almost all patients who achieved a PSA decline of >50% were AR-V7(−), and only 3/28 patients (11%) with AR-V7(−) CTCs using the Johns Hopkins assay had a PSA decline of >50%, while none (0/11) of the AR-V7(+) patients by the EPIC Sciences assay had a PSA response. Importantly, this study also demonstrated that AR-V7(+) CTCs can become detectable upon disease progression in men treated with abiraterone/enzalutamide who were AR-V7(−) at baseline, suggesting that the acquisition of AR-V7(+) CTCs may represent an important mechanism of resistance. Therefore, it is unlikely that further treatment with ARSi in this setting (sequential therapy with abiraterone after enzalutamide, or vice versa) would lead to response or clinical benefit. One other interesting finding in the PROPHECY study was the higher phenotypic heterogeneity of CTCs that was observed in AR-V7(+) versus AR-V7(−) cases (63% vs. 14%, respectively). CTC phenotypic heterogeneity has previously been correlated with lack of response to ARSi drugs, (10) and may reflect a subset of clinically aggressive CRPC with AR-low or AR-negative CTCs. Since the PROPHECY study is still active, results of the sequential treatments with taxanes and other biomarker analyses are ongoing so we can better understand the role of these possible biomarkers. It will also allow us to study the potential AR-V7 conversions (positive to negative) with taxane-based chemotherapy that have been described in prior small retrospective studies (11).

Are we ready to implement AR-V7 information to guide treatment choice for metastatic CRPC patients? We believe that the answer is yes, especially now that
AR-V7 status has been prospectively validated in the PROPHECY trial, which has added important data to the growing body of evidence that AR-V7(+) patients may have a very limited benefit from ARSi agents, such as abiraterone or enzalutamide. What is still lacking is a randomized biomarker trial that would assign patients into “biomarker-informed” and “biomarker-agnostic” groups. In the biomarker-informed randomization arm, AR-V7 status would be determined and reported, with AR-V7(+) patients being assigned to chemotherapy and AR-V7(−) patients being assigned to ARSi therapy. In the biomarker-agnostic randomization arm, the AR-V7 biomarker would be collected but not reported, and physicians/patients would be allowed to determine their choice of therapy (ARSi vs taxane) based on other considerations. The goal of such a study would be to prove that outcomes (e.g., rPFS or OS) were better in patients assigned to the biomarker-informed arm compared to those randomized to the biomarker-agnostic arm. Unfortunately, such a study is unlikely to be conducted, at least not in the United States.

Another way to indirectly assess the value of AR-V7 testing is to study its clinical utility using a self-reported physician questionnaire. Since both the Johns Hopkins and the EPIC Sciences assays are broadly available for ordering in the United States, many clinicians are now able to use these tests in a real-world scenario. To this end, a recent study evaluating the clinical utility of AR-V7 testing (using the Johns Hopkins central lab) suggested that AR-V7 results were useful to oncologists for their clinical decisions more than half the time, and a greater frequency of PSA responses was observed with the subsequent therapy when the AR-V7 test results were used (as opposed to not being used) to direct the choice of next systemic therapy (12). One potential reason for this was that AR-V7(+) patients were often offered investigational therapies [e.g., immunotherapy (13)] which may have produced a favorable effect. This clinical utility study was clearly biased by the fact that physicians ordering the AR-V7 test were interested in receiving the result, and thus may have been more likely to report that the test influenced their clinical management.

In the near future, we believe that AR-V7 (as well as other molecular markers) will be used for guiding treatment decisions at each specific time point in the course of disease for patients with metastatic CRPC. It is likely that many biomarkers under investigation will be integrated into routine clinical practice (14), including an assessment of AR mutations and amplification, CTC heterogeneity, and presence of DNA repair gene alterations, especially those mediating homologous-recombination repair and mismatch repair, microsatellite instability, and potentially others. Moreover, a better understanding of the disease biology of individual patients at a particular moment in time, will help clinicians to make better decisions regarding treatment sequencing and drug combination strategies. The overarching goal is to increase the value of the available therapies by selecting active and safe drugs, avoiding ineffective or toxic therapies, and ultimately leading to significant improvements in the survival and quality of life for our patients.

Acknowledgements
None.

Footnote
Conflicts of Interest: ES Antonarakis has served as a paid consultant/advisor for Janssen, Astellas, Sanofi, Dendreon, Merck, Essa, and Medivation; has received research funding to his institution from Janssen, Johnson & Johnson, Medivation, Sanofi, Dendreon, Bristol Myers Squibb, Genentech, Novartis, Bayer and Tokai; and is a co-inventor of an AR-V7 biomarker technology that has been licensed to Qiagen. DA Bastos has served as a paid consultant/advisor for Janssen, Astellas, Sanofi, Merck, and Roche; and has received research funding to his institution from Janssen.

References
5. Scher HI, Lu D, Schreiber NA, et al. Association of AR-


doi: 10.21037/pcm.2018.09.01

Cite this article as: Bastos DA, Antonarakis ES. AR-V7 and treatment selection in advanced prostate cancer: are we there yet? Precis Cancer Med 2018;1:13.