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Platinum Priority – Prostate Cancer

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Role of Androgen Receptor Variants in Prostate Cancer: Report from the 2017 Mission Androgen Receptor Variants Meeting

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Abstract

Context: Although a number of studies have demonstrated the importance of constitutively active androgen receptor variants (AR-Vs) in prostate cancer, questions still remain about the precise role of AR-Vs in the progression of castration-resistant prostate cancer (CRPC).
Objective: Key stakeholders and opinion leaders in prostate cancer convened on May 11, 2017 in Boston to establish the current state of the field of AR-Vs.
Evidence acquisition: The meeting "Mission Androgen Receptor Variants" was the second of its kind sponsored by the Prostate Cancer Foundation (PCF). This invitation-only event was attended by international leaders in the field and representatives from sponsoring organizations (PCF and industry sponsors). Eighteen faculty members gave short presentations, which were followed by in-depth discussions. Discussions focused on three thematic topics: (1) potential of AR-Vs as biomarkers of therapeutic resistance; (2) role of AR-Vs as functionally active CRPC progression drivers; and (3) utility of AR-Vs as therapeutic targets in CRPC.
Evidence synthesis: The three meeting organizers synthesized this meeting report, which is intended to summarize major data discussed at the meeting and identify key questions as well as strategies for addressing these questions. There was a critical consensus that further study of the AR-Vs is an important research focus in CRPC. Contrasting views and emphasis, each supported by data, were presented at the meeting, discussed among the participants, and synthesized in this report.
Conclusions: This article highlights the state of knowledge and outlines the most pressing questions that need to be addressed to advance the AR-V field.
Patient summary: Although further investigation is needed to delineate the role of androgen receptor (AR) variants in metastatic castration-resistant prostate cancer, advances in measurement science have enabled development of blood-based tests for treatment selection. Detection of AR variants (eg, AR-V7) identified a patient population with poor outcomes to existing AR-targeting therapies, highlighting the need for novel therapeutic agents currently under development.

1. Introduction

As prostate cancer is an androgen-dependent disease, the androgen receptor (AR) is the primary molecular target for systemic prostate cancer therapy. Despite initial robust responses to first-line androgen deprivation therapies (ADTs), nearly all patients with advanced prostate cancer progress to lethal castration-resistant prostate cancer (CRPC). Importantly, in CRPC, the AR continues to be the primary molecular driver, as evidenced by efficacy of novel hormonal therapies, abiraterone and enzalutamide, in CRPC patients [1–4]. While effective, therapies targeting AR are not curative, due to intrinsic and acquired resistance to first-line ADTs and novel hormonal therapies. Molecular mechanisms of resistance are largely driven by AR aberrations including AR protein overexpression, AR gene amplification, AR gene mutations, and AR variants (AR-Vs) [5].

AR-Vs are truncated AR proteins lacking the AR ligand-binding domain (AR-LBD) [6]. While AR-Vs have frequently been detected in CRPC, their expression and functional role in benign prostate tissues and primary prostate cancers is not readily apparent. Structural rearrangements in the AR gene and alternative AR mRNA splicing are at least two mechanisms for expression of AR-Vs in CRPC [6]. Multiple AR-Vs arising from AR gene rearrangements and/or alternative splicing have been characterized. To date, AR splice variant-7 (AR-V7) has been studied in greatest detail owing to its relative abundance and frequency of detection in CRPC [7,8], as well as its potential clinical utility as a marker for treatment selection in men with metastatic CRPC (mCRPC) [9]. However, in-depth studies have also been conducted on other AR-Vs, including AR-V1, AR-V3, AR-V7, AR-V9, and ARv567es [10–12]. Structural differences of these AR-Vs are illustrated in Figure 1. Since AR-Vs contain the AR DNA-binding domain (DBD) and the AR transcriptional activation domain, they are capable of transcriptional regulation, in spite of the loss of the AR-LBD. Further, since the AR-Vs lack the AR-LBD, they are not regulated by either first-line or novel hormonal therapies currently used in the clinic. At the Mission Androgen Receptor Variants (MARS) 2 meeting, our efforts were streamlined to evaluate the role of AR-Vs as biomarkers, molecular drivers, and therapeutic targets. The authors identified key consensus, discussion points, and critical future work needed to advance the field.

2. Evidence acquisition

The MARS meeting was the second of its kind sponsored by the Prostate Cancer Foundation (PCF). This invitation-only event was attended by international leaders in the field and representatives from sponsoring organizations (PCF and industry sponsors). Eighteen faculty members gave short presentations, which were followed by in-depth discussions. Discussions focused on three thematic topics: (1) potential of AR-Vs as biomarkers of therapeutic resistance;

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