Measurement Science of the Androgen Receptor Splice Variant-7 (AR-V7) Protein in Primary and Castration Resistant Prostate Cancer (CRPC) Tissue.

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Background: Liquid biopsies demonstrated that the constitutively active androgen receptor splice variant-7 (AR-V7) associates with reduced response to and overall survival (OS) from endocrine therapies in castration resistant prostate cancer (CRPC). However, these studies provide little information pertaining to AR-V7 expression in prostate cancer (PC) tissue.

Methods: Following generation and validation of a novel AR-V7 antibody (RevMAb Biosciences) for immunohistochemistry (IHC), AR-V7 protein expression was determined for 358 primary PC samples and 293 metastatic CRPC biopsies. Associations with disease progression, full length AR (AR-FL) expression, response to therapy, gene expression, and AdnaTest™ circulating tumor cell (CTC) status and CTC AR-V7 mRNA expression were also investigated.

Results: We demonstrated that AR-V7 protein is rarely expressed (<1% of 358 cases) in primary PC but is frequently detected (75% of 40 cases) following primary androgen deprivation therapy alone (H-score 40; interquartile range 1.25-92.5), with a further significant (p=0.020) increase in expression following abiraterone acetate or enzalutamide therapy (90; 20-150). In CRPC, AR-V7 expression is predominantly nuclear (94% of 144 cases) and correlates with AR-FL expression (p=<0.001) and AR copy number (p=0.026). However, many patients with high AR copy number and AR-FL expression do not express AR-V7, suggesting alternative splicing remains crucial for AR-V7 generation. AR-V7 expression is heterogeneous in different metastases from the same patient (p<0.001) although AR-V7 expression is homogeneous within single metastases (p=0.997). In addition, AR-V7 expression correlates with a unique 59-gene signature in CRPC, including HOXB13, a critical co-regulator of AR-V7 function. Moreover, AR-V7 negative disease associates with better PSA response (100% vs 54%; p=0.03) and OS (74.3 vs 25.2mo, HR 0.23 [0.07-0.79], p=0.02) from endocrine therapies (pre-chemotherapy). Finally, we compared AR-V7 mRNA expression in CTCs of peripheral blood with paired AR-V7 protein expression in tissue biopsies of CRPC metastases. CTC+/AR-V7+ blood samples had significantly (p=0.004) higher AR-V7 protein expression (100; 62.5-147.5) in paired tissue biopsy compared to CTC+/AR-V7- blood samples (15; 0.0-112.5). In addition, AR-V7 protein expression is frequently detected (63% of 16 samples) in tissue of patients with CTC- blood samples.

Conclusion: AR-V7 protein is not expressed until the cancer is castration resistant and is common after primary androgen deprivation therapy alone suggesting it may drive the initial phase of castration resistance. In addition, levels of AR-V7 protein vary between metastases, and although AR-V7 associates with response to AR targeting therapies, this suggests that multiple mechanism of resistance exist in the same patient. This study provides impetus to develop therapies that abrogate AR-V7 signaling to improve our understanding of AR-V7 biology and to confirm its clinical significance. If successfully developed, such agents may be best explored earlier in the course of disease and in combination with other therapies to provide clinical benefit for those patients with lethal CRPC.

Conflict of Interest: AS, JCW, MBKL, WY, DNR, DD, IF, LP, CA, PR, MK, JF, ZA, GF, BE, PF, SS, CB, GS, RR, AN, SC and JSdB are employees of The Institute of Cancer Research, which has a commercial interest in abiraterone. JL is an inventor of a relevant technology that has been licensed to A&G, Tokai, and Qiagen. JSdB has served as a consultant/advisory member for Astellas Pharma, AstraZeneca, Bayer, Genmab, Genentech, GlaxoSmithKline, Janssen, Medivation, Orion Pharma, Pfizer and Sanofi. IC, CS, JWR, TU, CM, PSN, SPB, LDT and SRP have no competing interests.

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