Validation of Nuclear-Localized AR-V7 on Circulating Tumor Cells (CTC) as a Treatment-Selection Biomarker for Managing Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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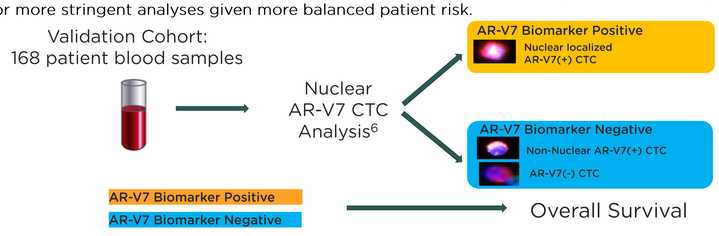
Background

- After 1st line failure of an androgen receptor signaling inhibitor (ARSi: abiraterone, enzalutamide) most patients are given a trial of another ARSi[1]
- Overall response rates are lower but a proportion do respond, who can not be predicted based on the response to the first drug administered.[2-5]
- Needed are biomarkers to predict who is better served (most likely to benefit) from a taxane or an ARSi, at the individual level in the 2nd+ line of mCRPC
- In a previous study[6] we observed superior overall survival (OS) with taxane use vs. ARSi in mCRPC patients positive for nuclear-localized AR-V7 protein in CTCs
- We sought to prospectively evaluate this relationship in an independent, blinded, multi-center cross-sectional cohort

Methods

- 168 patient samples were collected from mCRPC patients prior to initiation of ARSi or taxanes at three clinical sites: Memorial Sloan-Kettering (USA), Institute of Cancer Research (UK) and London Health Sciences (Canada).
- All samples were tested with the Epic Sciences CTC test for AR-V7 nuclear protein (see below), and treatment choice was at discretion of the attending physician without knowledge of AR-V7 test result
- A risk score was developed utilizing our previous cohort[6] in order to adjust for possible therapy selection bias by the treating physician. The relationship between overall survival, biomarker result (positive vs. negative), and therapy administered (ARSi vs. taxane) was analyzed both in the entire cohort, and within a subset of the cohort with requisite samples from all four groups for more stringent analyses given more balanced patient risk.



Patient Demographics

Patient Characteristics	Training Cohort	Validation Cohort			
Unique Patients	105	142			
Death Events	91 (87%)	85 (60%)			
Clinical Site	MSK: 105 (100%)	ICR: 25 (18%); LHS: 5 (3%); MSK: 112 (79%)			
Primary tx: Prostatectomy	50 (48%)	55 (39%)			
Primary tx: Radiation	17 (16%)	24 (17%)			
Primary tx: Brachytherapy	6 (6%)	6 (4%)			
Primary tx: None	32 (30%)	56 (39%)			
Sample Characteristics	**Training Total**	**Validation Total**	**Pre-ARSi**	**Pre-Taxane**	**p-value**
Total Samples	123	165	83	82	
2nd Line	50 (41%)	63 (38%)	44 (53%)	19 (23%)	
3rd Line	31 (25%)	52 (32%)	23 (28%)	29 (35%)	< 0.001
4th+ Line	42 (34%)	50 (30%)	16 (19%)	34 (42%)	
Median Survival (months)			17.2	13.2	0.14
Pretherapy Clinical Measures Available to Physician: Median (range)					
Age (years)	69 (48 – 91)	70 (40 - 91)	70 (40 - 91)	70 (48 – 85)	0.27
Albumin (g/dL)	4.2 (3.1 – 4.9)	4.1 (2.4 – 4.7)	4.1 (2.4 – 4.7)	4.1 (2.9 – 4.6)	0.25
Hemoglobin (g/dL)	11.7 (7.0 – 15.0)	11.8 (7.1 – 15.1)	11.9 (7.1 – 15.1)	11.5 (8.0 – 14.8)	0.20
Presence of Liver and/or Lung Metasteses	19 (15%)	41 (25%)	17 (20%)	24 (29%)	0.17
LDH (U/L)	237 (123 – 1004)	228 (101 – 2115)	203 (101 – 2115)	244.5 (147 – 1487)	0.06
PSA (ng/mL)	59.4 (0.009 – 3728.2)	65.2 (0.05 – 16275.1)	27.4 (0.05 – 1412)	112.3 (0.06 – 16275.1)	< 0.001
Alkaline Phosphatase (U/L)	123 (42 – 1816)	111 (43 – 1055)	91 (44 – 1040)	124 (43 – 1055)	0.05
Pretherapy Clinical Measures Unavailable to Physician					
AR-V7 Positivity	31 (25%)	37 (22%)	15 (18%)	22 (27%)	

Abbreviations: tx, therapy; LDH, lactate dehydrogenase; PSA: prostate-specific antigen

References

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4. Rathkopf DE, Antonarakis ES, Shore ND, et al. Safety and Antitumor Activity of Apalutamide (ARN-509) in Metastatic Castration-Resistant Prostate Cancer with and without Prior Abiraterone Acetate and Prednisone. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Jul 15 2017;23(14):3544-3551.
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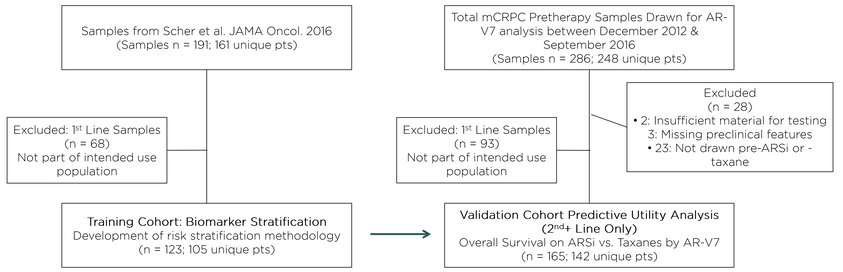
6. Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. *JAMA Oncol.* Nov 1 2016;2(11):1441-1449.

Validation Cohort Design

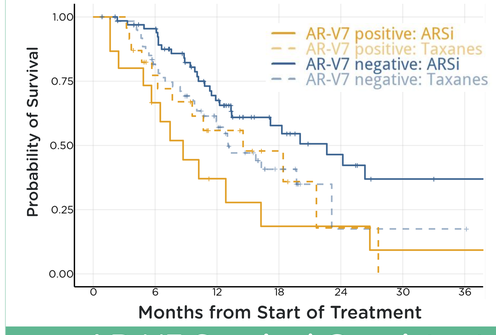
Distribution of Patient Samples in the Training Cohort and Validation Cohort



To account for cross-sectional (non-randomized) nature of data and potential treatment selection bias, 2nd+ line samples from Scher et al. JAMA Oncol. 2016 were analyzed as the training cohort, from which the risk stratification methodology was developed and applied to the validation cohort.

AR-V7 Predicts Therapy-Specific OS

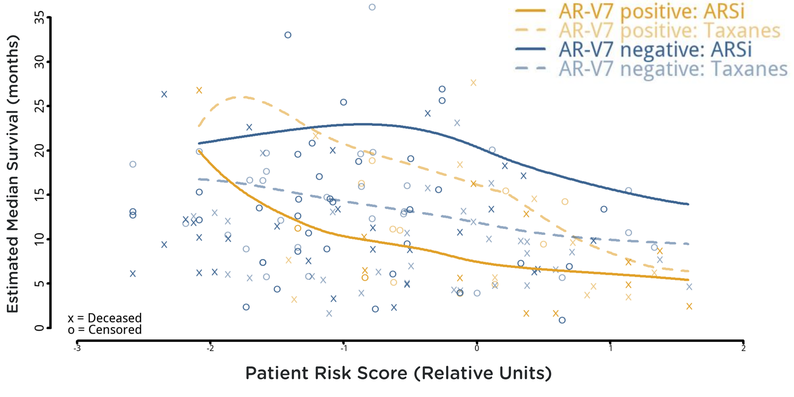
OS of mCRPC pts by AR-V7 Status & Therapy Type



Status	Drug	n	Median OS
AR-V7 +	ARSi	15	8.7 (5.6 – n/a)
	Taxanes	23	14.5 (7.7 – n/a)
AR-V7 -	ARSi	69	22.6 (13.4 – n/a)
	Taxanes	61	13.1 (10.7 – n/a)

AR-V7 Survival Consistent Across Patient Risk

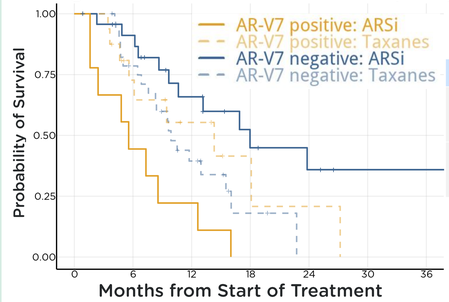
OS by Baseline Risk, AR-V7 and Therapy Class



Smoothed median estimates of OS as a function of patient risk and the four treatment-biomarker groups is shown. Censored and deceased patients are indicated by "o" and "x".

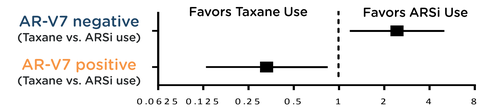
Risk Adjusted: AR-V7 Predicts Therapy-Specific OS

High Risk Patients: OS of mCRPC pts by AR-V7 Status & Therapy



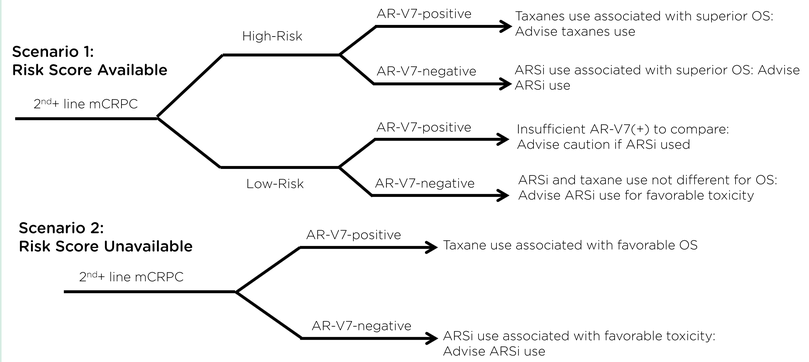
Status	Drug	n	Median OS
AR-V7 +	ARSi	9	5.6 (2.4 – n/a)
	Taxanes	16	14.3 (6.2 – n/a)
AR-V7 -	ARSi	24	18.0 (10.7 – n/a)
	Taxanes	29	9.9 (8.3 – n/a)

High Risk Group: Treatment-Specific Hazards of Death (Overall Survival)



There were sufficient samples of all four groups within the high risk range for more direct comparison of survival times and relative risk of death by biomarker result and therapy used. Forest plot of hazard ratios derived from Cox model incorporating patient risk is shown.

Clinical Decision Algorithm for Nuclear AR-V7 Test



Discussion

1. The study results validate the clinical utility of the Epic Sciences nuclear-localized AR-V7 assay, for the context of use as a predictive biomarker to inform the choice between ARS inhibitors or taxanes for mCRPC patients in need of a treatment change in the second line or greater setting
2. Patients who tested negative for nuclear AR-V7 had better OS on ARS inhibitors than taxanes.
3. Patients who tested positive for nuclear AR-V7 had a demonstrated survival advantage when treated with taxanes
4. In the context of second line or greater mCRPC when the decision between an ARS inhibitor vs. a taxane is being considered, the utilization of the Epic Sciences nuclear-localized AR-V7 test has demonstrated clinical utility as a predictive assay for overall survival

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