Evaluation of the clinical utility of the nuclear-localized AR-V7 biomarker in CTCs in the context of physician intuition measured through physician therapy choice propensity and patient risk

Howard I. Scher[1*], Ryon P. Graf[2], Melanie Hulling[1], Emily Carbone[1], Ethan Barnett[1], Ryan Dittamore[2]

[1]Center for Mechanism Based Therapy, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York *Department of Medicine, Weill Cornell Medical College, New York, New York [2]Epic Sciences, San Diego, California

Epic Sciences

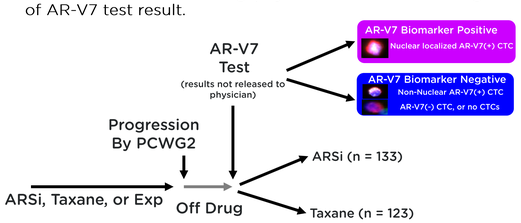
Memorial Sloan Kettering Cancer Center

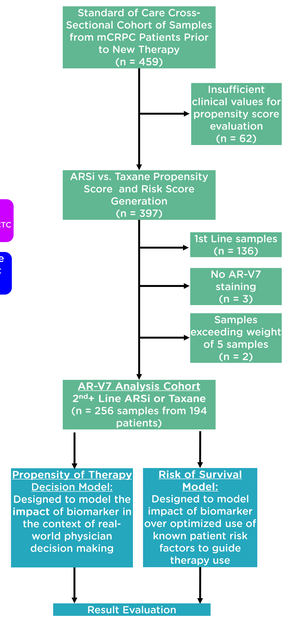
Background

- Clinical utility requires a demonstration that use of the biomarker result improves the outcome for a patient relative to the non use of the biomarker and relying only on information available in the context of routine management.
- We previously conducted two cross-sectional studies to evaluate the relationship between nuclear-localized AR-V7 status and patient outcome, and twice observed superior survival for mCRPC patients testing positive on taxanes vs. ARSi[1-2].
- The lack of standards to inform the use of an ARSi vs. taxane therapy in the 2nd line or greater therapy decisions defaults the choice to physician preference or intuition.
- Here, we sought to analyze the nuclear-localized AR-V7 biomarker in relationship to physician choice propensity (taxane vs. ARSi choice without AR-V7 knowledge) and patient risk (utilizing an optimized OS prognostic model) to determine if use of the nuclear-localized AR-V7 biomarker provides clinical utility in this context.

Methods and Patient Demographics

- 459 pre-therapy patient samples were collected from mCRPC patients in the clinical practice setting prior to initiation of ARSi or taxanes at Memorial Sloan-Kettering (USA) between December 2012 and September 2016. Of these, 397 contained sufficient information for propensity (physician choice) analyses, and 256 were within the intended use population of AR-V7 (see right).
- All samples were tested with the Epic Sciences CTC test for AR-V7 nuclear protein and treatment choice was at discretion of the attending physician without knowledge of AR-V7 test result.





Sample Characteristics	Total	Pre-ARSi	Pre-Taxane	p-val
Total Samples	225	133	123	
Unique Patients	194	125	111	
2nd line	100 (40%)	74 (55%)	26 (21%)	
3rd line	76 (29%)	34 (26%)	42 (34%)	< 0.001
4th+ line	80 (31%)	25 (19%)	55 (45%)	
Age (median)	69	70	69	0.19
Albumin (g/dL)	4.2	4.1	4.2	0.86
LDH (u/L)	235.5	212	248	< 0.001
PSA (ng/mL)	50.8	31.1	99.4	< 0.001
Hemoglobin (g/dL)	11.7	12	11.4	< 0.001
Alkaline Phosphatase	111	99	139	< 0.001
Liver Mets	29 (11%)	8 (6%)	21 (17%)	< 0.001
Bone Mets	227 (89%)	112 (84%)	115 (94%)	< 0.001
Lung Mets	29 (11%)	12 (9%)	17 (14%)	0.0602
Last Therapy was ARSi	169 (66%)	81 (61%)	88 (72%)	0.0065
AR-V7 positivity	58 (23%)	22 (17%)	36 (29%)	0.0011

The cohort was analyzed by two statistical methodologies:

- *Propensity of Therapy Decision Model:* A score indicating a physician's propensity to give Drug A vs. Drug B. The model simulates randomization through weighting patients to normalize for physician tx assignment habits. Specifically, we used a general linearized multiple regression model to develop weights for propensity score and R package 'MatchIt' to generate 0-1 propensity scale. Technique frequently used by epidemiologists and health economists to analyze real-world clinical data[3].
- *Risk Model:* Factors that influence a patient's underlying risk of an event (i.e. progression or death) independent of drug class or investigational biomarker. The model aims to understand the potential to both normalize for cohort imbalances, and evaluate the potential for an optimized evaluation using existing tools as a the predictive biomarker to compete with AR-V7. Technique is a consolidated Cox PH multivariable analysis where all factors other than AR-V7 and therapy are rolled into one Risk Score by combining the multivariable model coefficients. The model was trained from the same cohort as tested to optimize patient risk stratification in this cohort [4].

References

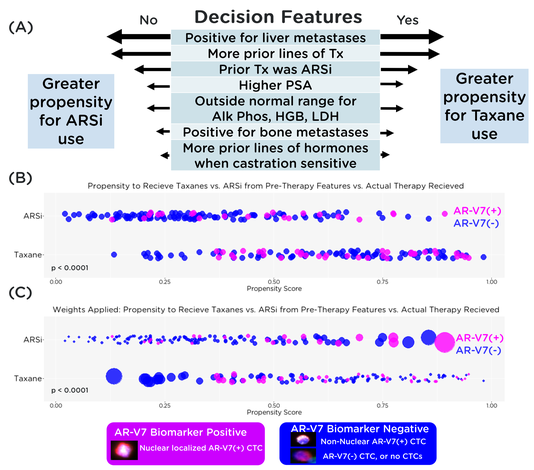
1. Scher HI, Lu D, Schreiber NA, Louw J, Graf RP, Vargas HA, et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. JAMA Oncol. 2016;2(11):1441-9.
2. Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncology. 2018.
3. Rubin DB. Causal Inference Using Potential Outcomes. Journal of the American Statistical Association. 2005;100(469):322-31.
4. Halabi S, Lin CY, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(7):671-7.

Physician Propensity to Use Taxane vs. ARSi

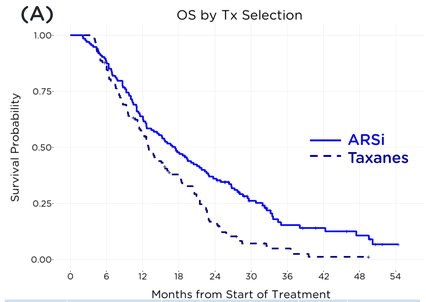
A) Model identifies the most important factors in the propensity to give an ARSi vs. Taxane in a real world setting at MSKCC. The size of the arrow indicates the relative weight for each feature derived from the model.

B) Propensity score of 0 = absolutely certain to get an ARSi, 1 = absolutely certain to get a taxane. Decision to given an ARSi vs. Taxane have large overlapping Propensity scores. Many AR-V7(+) patients were very confidently given an ARSi.

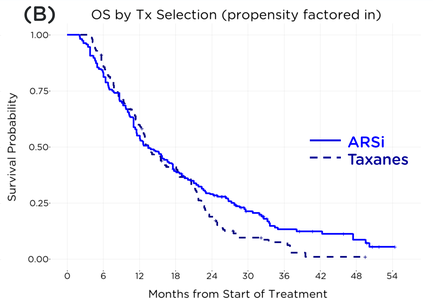
C) Individual patients are weighted based upon the number of patients with similar propensity scores who received the other drug type. Larger circle = more weight. The technique seeks to normalize for physician therapy choice biases in the standard of care setting.



In Context of Existing Drug Choice Propensities, AR-V7 Provides Significant Impact on Overall Survival



AR-V7	Tx Assigned	n	Median OS	HR	p-value
All	ARSi	133	17.4 mo	0.61	0.00026
All	Taxanes	123	13.0 mo		

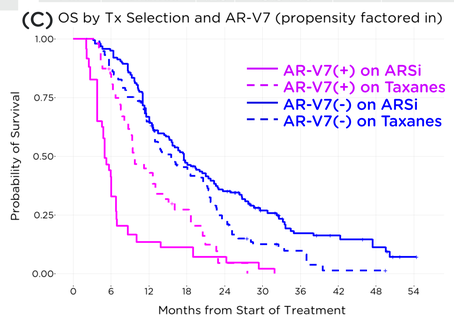


AR-V7	Tx Assigned	n	Median OS	HR	p-value
All	ARSi	133	13.4 mo	0.81	0.12
All	Taxanes	123	13.5 mo		

A) Cohort without adjustment for physician therapy choice propensity: Patients who were assigned an ARSi lived longer than those assigned a taxane.

B) When physician choice propensity is factored in, there is not a detectable difference in survival between patients who received an ARSi or taxane when AR-V7 is not considered.

C) ARSi and Taxane arms in (B) split up by AR-V7 status (positive or negative): The results show AR-V7(+) patient outcome correlated with better OS on taxanes and AR-V7(-) outcome correlated with better OS on ARSi.



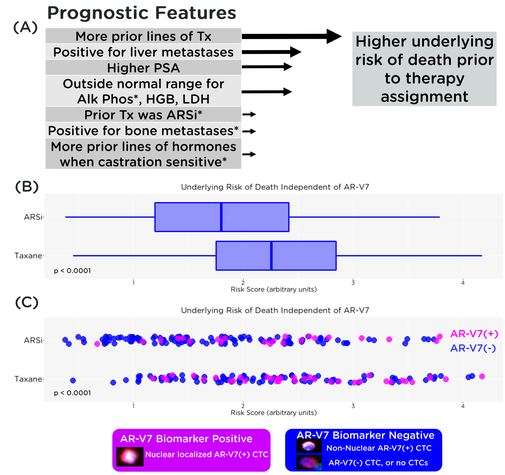
AR-V7	Tx Assigned	n	Median OS	HR	p-value
Positive	ARSi	22	5.0 mo	1.93	0.0175
Positive	Taxanes	36	9.8 mo		
Negative	ARSi	111	17.6 mo	0.69	0.0185
Negative	Taxanes	87	15.6 mo		

Optimized Patient Risk Assessment

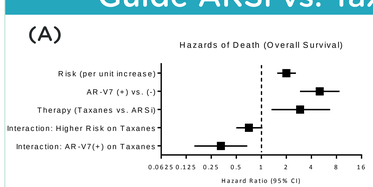
A) Prognostic factors associated with worse overall survival and their relative weight derived from the model.* Features that were significant for therapy choice propensity but not for overall survival.

B) Relationship between risk of death and tx choice (ARSi vs. Taxane). Patients receiving taxanes had higher Risk scores relative to ARSi (median 2.33 vs. 1.86, p < 0.0001), equating to a 25% higher risk of death on average, independent of AR-V7.

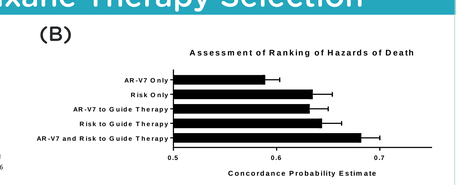
C) Association of AR-V7 status with Risk score obtained from prognostic factors. Patients can be AR-V7(+) independent of other factors indicating higher risk of death.



AR-V7 is Superior to Optimized Risk Assessment to Guide ARSi vs. Taxane Therapy Selection



	HR (95% CI)	p-value
Risk (per unit increase)	2.00 (1.55 – 2.59)	< 0.0001
AR-V7 Status (+ vs. -)	5.03 (1.92 - 8.67)	< 0.0001
Overall: Taxane vs. ARSi use	2.94 (1.28 – 6.74)	0.0109
Greater Risk on Taxanes vs. ARSi	0.710 (0.491 – 1.03)	0.0673
AR-V7(+) on Taxanes vs. ARSi	0.327 (0.158 - 0.679)	0.00269



Model	Covariates	CPE	SE
A) AR-V7 Only	AR-V7 (positive or negative)	0.589	0.014
B) Risk Only	Risk (continuous)	0.635	0.019
C) AR-V7 to guide Tx	AR-V7, Tx, and Tx Interaction	0.632	0.018
D) Risk to guide Tx	Risk, Tx, and Tx Interaction	0.644	0.019
E) AR-V7 and Risk to guide Tx	AR-V7, Risk, and Tx Interactions w/ both	0.682	0.018

A) Patient risk prior to therapy choice was incorporated into a multivariable model with therapy chosen, AR-V7 status, and interaction terms with Risk and therapy choice as well as interaction with AR-V7 and therapy choice. AR-V7(+) have great therapy interaction with Taxanes than Patient Risk

B) The additive value of using AR-V7 or patient risk prior to therapy to guide therapy choices is shown via CPE. With perfect knowledge of patient risk features within the cohort, AR-V7 contributes to prediction of patient risk.

Discussion

1. At a tertiary care center, factors most influencing the decision to administer an ARSi or taxane are the presence of liver metastases, the number of prior lines of therapy, and whether the prior therapy was an ARSi. In general, physicians tend to put patients with more advanced disease on taxanes
2. When physician choice propensity was accounted for, there was no discernable survival difference between ARSi and taxanes in the 2nd+ line of therapy mCRPC.
3. Even patients who were confidently assigned an ARSi (propensity < 0.5) or those with low risk features could test AR-V7 positive.
4. Patients who were AR-V7 positive had superior survival on taxanes.
5. Patients who were AR-V7 negative had marginally better survival on ARSi
6. Use of AR-V7 can optimize therapy guidance over risk assessment alone

Funding

Equal distributions of funds from NIH/NCI P50-CA92629 SPORE in Prostate Cancer, NIH/NCI Cancer Center Support Grant P30-CA008748, NIH grant R01-CA207220, Department of Defense Prostate Cancer Research Program (PC121111 and PC131984), Prostate Cancer Foundation Challenge Award, and David H. Koch Fund for Prostate Cancer Research were used to support the design and conduct of the study at Memorial Sloan Kettering Cancer Center.