Overall survival (OS) implications for patients with mCRPC through coverage and adoption of nuclear AR-V7 testing by healthcare systems

J Hornberger  
*Genomic Health*

R P. Graf  
*Epic Sciences Inc.*

M Hulling  
*Memorial Sloan-Kettering Cancer center*

G Attard  
*University of London - Institute of Cancer Research*

A Allan  
*Western University*

*See next page for additional authors*

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Overall survival (OS) implications for patients with mCRPC through coverage and adoption of nuclear AR-V7 testing by healthcare systems

J. Hornberger1, R.P. Graf2, M. Hulling3, G. Attard4, A. Allan5, R. Dittamore2, H.I. Scher5
1Clinical Economics and Outcomes Research, Genomic Health, Redwood City, CA, USA
2Translational Research, Epic Sciences, Inc., San Diego, CA, USA
3Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
4Medical Oncology, The Institute of Cancer Research and The Royal Marsden, London, UK
5Oncology and Anatomy and Cell Biology, Western University, London, ON, Canada

Background: Nuclear-localized AR-V7 testing of circulating tumor cells (CTCs) has been validated as a predictive biomarker of chemotherapy response and ARSi non-response in 2nd- and 3rd-line therapy for metastatic castration-resistant prostate cancer (mCRPC). A validation study showed that AR-V7(+/-) pts have improved OS with taxane chemotherapy, and AR-V7(-) pts have improved OS with ARSi. We assessed the effect of AR-V7 testing on OS when generalized to non-trial clinical settings, as found in third-party US healthcare systems.

Methods: The causal effect of treatment and nuclear AR-V7 status on OS was estimated from risk-adjusted hazard rates of the MSK, ICR, LHS validation study. Therapeutic strategies assessed were: (1) taxanes only, (2) ARSi only, (3) current US utilization rate of ARSi, and (4) nuclear AR-V7-guided treatment. Quality of life adjustments were extracted from meta-analysis of large cohort studies. We applied US utilization rate of consecutive ARSi administration (abiraterone after enzalutamide, or enzalutamide after abiraterone) and compared to switching with taxane-based chemotherapy (docetaxel after abiraterone, or docetaxel after enzalutamide).

Results: The following table shows OS, adjusted and unadjusted for quality of life, and treatment by strategy. The net effects on OS were robust to variation on the clinical effects, and on systems covariates, e.g., demographic, patient, and payer case-mix.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>% ARSi</th>
<th>OS (months)</th>
<th>Net OS gain (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only use taxanes</td>
<td>0%</td>
<td>19.2 / 12.2</td>
<td>-3.7 / -2.0</td>
</tr>
<tr>
<td>Only use ARSi’s</td>
<td>100%</td>
<td>25.4 / 15.6</td>
<td>2.5 / 1.4</td>
</tr>
<tr>
<td>Current use of ARSi (US)</td>
<td>60%</td>
<td>22.9 / 14.2</td>
<td>REF</td>
</tr>
<tr>
<td>AR-V7 guided treatment</td>
<td>77%</td>
<td>27.3 / 16.7</td>
<td>4.4 / 2.5</td>
</tr>
</tbody>
</table>

Conclusions: Health outcome modeling of the validation data support that current use and access to 2nd ARSi therapy can improve OS of patients over strict use of taxane chemotherapy (+3.7mo OS). 2nd- and 3rd-line nuclear-localized AR-V7-guided treatment for men with progressive mCRPC provides higher OS than non-guided, almost doubling the gain (+4.4mo OS) observed with current US utilization rate of ARSi and taxanes only. Cost effectiveness analyses of the adoption/coverage of nuclear AR-V7 testing in healthcare systems is ongoing.

Legal entity responsible for the study: MSKCC.

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Enzalutamide (ENZA) is an oral androgen receptor inhibitor approved for the treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC). ENZA was featured in a recent study which aimed to explore the relationship between ENZA, NDE plasma concentration and progression-free survival (PFS) in castration-resistant prostate cancer (CRPC) patients.

**Methods:**

In 2016, a phase II study was initiated to evaluate the safety and efficacy of enzalutamide in CRPC patients. Primary inclusion criteria for this study were a serum PSA level of 2.0-20.0 ng/ml, no metastatic disease, and a normal creatinine clearance rate. Patients were randomized to receive enzalutamide 160 mg daily for 84 days (D) with/without PROSTVAC (recombinant poxvirus PSA vaccine), but no ADT. After an amendment, patients were eligible for a 2nd course of enzalutamide. Eligible patients had a PSA between 2.0-20.0 ng/ml, no metastatic disease, normal creatinine clearance rate, and a Karnofsky performance status of 70-100. The study included 36 evaluable patients, and the primary endpoint was progression-free survival (PFS) as defined by the Prostate Working Group criteria.

**Results:**

Median age for all patients (n = 36) was 77.5 years (IQR 67.2-82.7). Median follow-up was 10.6 months (ms) (IQR 5.1-21.3 ms). Median trough plasma concentration of ENZA was 33.8%; IQR 5,4-10,1), with a coefficient of variation (CV) of 43.9%. High trough plasma concentration of ENZA was associated with a shorter PFS (9 ms vs 22.6 ms respectively in the high and the low group) (Hazard Ratio (HR) 0.2; 95% CI 0.04-0.57; p = 0.001) as was a journal impact factor greater than 15 (p = 0.03).

**Conclusions:**

Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. Trough plasma concentrations of ENZA and NDE were measured at steady-state one month after treatment start, using liquid chromatography. 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