The Role of AR-V7 in the Management of Metastatic Castration-Resistant Prostate Cancer

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Important milestones in the treatment of prostate cancer

- **1941**: Use of androgen deprivation therapy
- **1947**: First radical prostatectomy for the treatment of prostate cancer
- **2004**: Docetaxel approved for treatment of metastatic prostate cancer
- **2010**: Provenge (immunotherapy) approved by FDA
- **The targeted therapy era (ARSi)**:
  - **4/2011**: Initial approval of abiraterone (ZYTIGA®)
  - **8/2012**: Enzalutamide approved (XTANDI®)
  - **2/2018**: Apalutamide approved (Erlead™)
How do these targeted therapies work? And what is AR-V7??

• Prostate cells (and most tumor cells) need androgen to grow and function.

• *Androgen Receptor Signaling Inhibitors* (ARSis) work either by targeting and inhibiting the androgen binding receptors in tumor cells or by preventing creation of androgen.

• **These drugs slow tumor growth.**

• AR-V7 is a variant of the normal androgen receptor and can allow prostate tumor cells to remain active and growing even *without* androgen.
  
  • It seems to develop as a resistance mechanism when men are exposed to ARSi therapy.
Why is it important to know AR-V7 status and who should be tested?

• The presence or AR-V7 in the nucleus of circulating tumor cells can tell us about prognosis and predict which treatment is better – ARSi or chemotherapy.
• AR-V7 is measured in a blood sample.

• Who should be tested?
  1. Men with metastatic castration-resistant prostate cancer
  2. Men who have taken an ARSi in the past
  3. Men who are trying to determine their next treatment (chemotherapy or another ARSi)
Why is it important to have taken an ARSi in the past?

<table>
<thead>
<tr>
<th>Line of Treatment in mCRPC setting</th>
<th>First (n=67)</th>
<th>Second (n=50)</th>
<th>Third or greater (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples with AR-V7-positive CTCs n (%)</td>
<td>2 (3%)</td>
<td>9 (18%)</td>
<td>23 (31%)</td>
</tr>
</tbody>
</table>

AR-V7–androgen receptor splice variant 7; CTC–circulating tumor cells

Men with AR-V7 nuclear-positive disease do worse on ARSi therapy…

Overall survival: pre-AR signaling inhibitor samples

- AR-V7 negative, n = 112
- AR-V7 positive, n = 16

HR = 11.45 (95% CI: 5.67-23.82)

P < .001

Median survival: 4.6 mo vs not reached

Scher et al, JAMA Oncology, November 2016
…but do better with chemotherapy
Men with AR-V7 nuclear-positive disease do not respond to ARSi therapy


AR−androgen receptor; AR-V7−androgen receptor splice variant 7; PSA−prostate-specific antigen
What should we remember?

• ARSi drugs have made a great impact on survival and quality of life for men with metastatic castration-resistant prostate cancer.

• If an ARSi seems to be losing its beneficial effect, another therapy may be required to maintain control of disease.
  • This could be another ARSi or chemotherapy.

• Knowing the nuclear AR-V7 status at this point is important to determine the best course of therapy and prolong survival.

• ZERO patients with nuclear AR-V7-positive disease respond to ARSi therapy but may get significant benefit from chemotherapy.
Patient Report

AR-V7 Nucleus Detect Report

[RESULT]

Medical Record/Patient #: 1234567-01
Specimen Source/ID: Blood/SP_16_0123456
Date of Collection: 20-Jun-2016
Specimen Received: 23-Jun-2016

Client: XXXX
Study #: XXXX

Results

Nuclear AR-V7

Positive: One or more nuclear localized AR-V7 positive CTCs identified

Clinical Interpretation

In large clinical studies, patients with a positive test result were:

- Not likely to respond to or benefit from abiraterone or enzalutamide
- Substantially more likely to live longer when treated with a taxane chemotherapy.

Intended Use

The AR-V7 Nucleus Detect test is intended for use in patients with metastatic castration-resistant prostate cancer (mCRPC) who are considering androgen receptor signalling inhibitors (e.g., abiraterone, enzalutamide). The test identifies the presence of AR-V7 protein in the nucleus of circulating tumor cells (CTCs) in blood samples from mCRPC patients to inform clinical decision-making.
Why Nuclear AR-V7

Ryan Dittamore
Chief of Medical Innovation
Epic Sciences, Inc.
Who is Epic Sciences? Where is my blood sample going?

**Goal:** To make **predictive, personalized and precise** tests designed around **clinical decisions** to improve patient survival.

- San Diego, CA
- 40,000 sq ft facility
- CAP accredited /CLIA registered lab

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2008
founded

75
employees

**Partnerships**
- Academic: 35
- Biopharma: 48
- Commercial:
- Consortium:

**Clinical Research**
- 175+ clinical trials
- 35,000+ patient blood samples
In 2012, I visited Dr. Howard Scher at MSKCC in NY.

Dr. Scher posed a question to me:

*Can we develop a blood test that can help guide therapy decisions between AR signaling therapies (Abiraterone & Enzalutamide) vs. taxane chemotherapy?*

Why is this question important?

Prior therapy history, therapy response didn’t predict which drug would work best. In short, there was no way for him to predict which drug to give a patient.
Our Goal:

Could a single, simple tube of blood and Epic’s technology inform treatment decisions and extend lives?

As good as Abiraterone or Enzalutamide?
Query the cell – find 1 in 50 million with deep, advanced analysis

Epic’s no cell left behind™ technology was founded with computer vision and machine learning. We look at 6 million cells per patient to find rare circulating tumor cells.
Disruptive platform for finding patterns of cells that matter

Tagging proteins in cells with fluorescence to analyze morphology and functional status
Over the last 6 years we have accumulated the largest biobank of mCRPC patient blood samples. Specifically to ensure we can answer the question
The biology of metastatic prostate cancer drugs – I

Androgen receptor (AR), full length protein

Testosterone hormone

Cancer cell growth
Androgen receptor (AR), full length protein

Testosterone

No binding, AR can’t get to the nucleus

Don’t need binding, drugs can’t bind
AR-V7 can go to the nucleus and be active
Truncated androgen receptor protein (AR-V7)

• AR-V7 is in the cytoplasm.
  • Functionally **INACTIVE**.
  • No resistance to Enzalutamide (Xtandi) or Abiraterone (Zytiga).

• AR-V7 is in the nucleus.
  • Functionally **ACTIVE**.
  • **RESISTANT** to Enzalutamide (Xtandi) or Abiraterone (Zytiga).
AR-V7 – Nuclear Localization Matters!

= AR-V7 negative; may benefit from another ARSi

= AR-V7 positive; chemotherapy may be the better option
AR-V7 Nucleus Detect Test is superior to AR-V7 mRNA tests

Nuclear-specific AR-V7 Protein Localization is Necessary to Guide Treatment Selection in Metastatic Castration-resistant Prostate Cancer


AR-V7 can be nuclear or cytoplasmic

Nuclear AR-V7 is only PREDICTIVE Test

Outcome difference between:
Nuclear and Any AR-V7

ARSi OS

Taxane OS
What about other studies?
• Patients who had already received a systemic therapy (Abiraterone, Enzalutamide, Docetaxel) were received from:
  – MSKCC (New York)
  – ICR (Sutton, UK)
  – LHS (London, Canada)

• Physicians were blinded of nuclear AR-V7 status; Epic Sciences was blinded of patient outcomes

• 84 patients had received Abiraterone or Enzalutamide

• 84 patients had received taxane chemotherapy

**Patient Overall Survival was the endpoint!!!
Nuclear AR-V7 Overall Survival Results

Patient Median Overall Survival:

**Positive**
- ARSi = 8.6 months
- Taxane = 14.3 months

**Negative**
- ARSi = 22.3 months
- Taxane = 12.9 months

Either result has the ability to add ~1.7X life expectancy
Medicare Reimbursement is expected very soon!

Launched February 2018

~4-5 months

Expected Medicare Reimbursement
~ July 2018
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