Targeting the Androgen Receptor in Castration Resistant Prostate Cancer

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IPCU
January 2017
Disclosures

– Consultant: Myriad, CUSP, Tolmar, Integra Cloud, Cellay

– Speakers Bureau: Dendreon, Astellas, Bayer, Janssen, Sanofi, Medivation, Amgen
ARS 1

Which of the following is not a complication of ADT?

a. Neurocognitive dysfunction
b. Cardiovascular dysfunction
c. Insulin resistance
d. Osteoporosis
e. None of the above. They are all complications of ADT
ARS 2

• The N terminus of the androgen receptor binds the androgen ligand (T/DHT)?
  a. True
  b. False
STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA
OF THE PROSTATE GLAND

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AND

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CHICAGO

The thesis of this work may be briefly summarized. In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount or inactivated. In this paper evidence is presented that significant improvement often occurs in the clinical condition of patients with far advanced cancer of the prostate after they have been subjected to castration. Conversely, the symptoms are aggravated when androgens are injected. We believe that this work provides a new concept of prostatic carcinoma.

The evidence that prostatic carcinoma is often composed of an adult type of epithelium derives from a study of such tissue with respect to the phosphatase which manifests optimum activity at \( p_H \) 5. An important advance in the technic of investigation of the prostate gland was made by Kutscher and Wolbergs,\(^1\) who found that this enzyme is present in large amounts in adult human and monkey prostate glands; indeed, this phosphatase is present in prostate tissue in larger amounts than any phosphatase in any other tissue. Gutman and Gutman\(^2\) found that the enzyme is present in small amounts in infancy and childhood and is increased during puberty to the high values found in the adult. These

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From the Department of Surgery, University of Chicago.

Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

This investigation was supported by a grant from the Committee for Research in Problems of Sex of the National Research Council.


209
Androgens are produced at 3 sites:
- Testes
- Adrenal gland
- Prostate tumor cells
Historical Landmarks: 1st Effective Treatment, 1st Marker, 2 Nobel Prizes

- **1867**: First perineal prostatectomy performed
- **1904**: First RP
- **1920s**: RT for PC using radium
- **1938**: Acid Phos. 1940 - Huggins - endocrine control Advent of orchietomy and estrogen treatment (Awarded Nobel Prize for this discovery)
- **1940**: 1st Marker
- **1948**: 1970s Steroidal and non-steroidal AAs available
- **1950s**: Steroidal and non-steroidal AAs available
- **1960s and 70s**: Synthetic estrogens developed
- **1960s**: RT established as important treatment for PC
- **1970s**: Long-acting synthetic LHRH agonists
- **1980s**: Long-acting synthetic LHRH agonists
- **1980**: First GnRH blocker (abarelix) launched
- **1995**: Cryosurgery accepted as a treatment option for recurrent cancer after RT
- **2000**: Docetaxel in combination with prednisone approved
- **2003**: First GnRH blocker (abarelix) launched
- **2008**: Degarelix approved in US
- **2009**: ARSI Developed

**The future**
New androgen receptor-targeted drugs. AA vaccines, biomarkers, genetic research

**ARSI** = Androgen Receptor Signaling Inhibitor; **AA** = antiandrogen; **LHRH** = luteinizing hormone releasing hormone.

Figure courtesy of Dr. E. David Crawford
Androgen deprivation therapy (ADT)
  - Estrogens (DES)
  - Surgical castration (bilateral orchiectomy)
  - LHRH/GnRH analogs (agonists/antagonists)

Antiandrogens

Combined androgen blockade (CAB)

17,20 Lyase Inhibitors
Complications of ADT

1. Hot Flashes
2. Anemia
3. Sexual dysfunction
4. Cognitive dysfunction
5. **OSTEOPOROSIS**
6. Metabolic Syndrome
   - obesity
   - Insulin resistance
   - Dyslipidemia
   - Hypertension

Gaztanaga and Cook, JNCCN. 2012;10.
**NCCN Guidelines Version 3.2016**

**Prostate Cancer**

**SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER**

- CRPC, studies positive for metastases
  - Maintain castrate levels of serum testosterone (<50 ng/dL)
  - Consider bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
  - Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1 (category 1) *(See PROS-G)*
  - Palliative RT for painful bony metastases
  - Best supportive care

**Visceral metastases**

- No
  - Abiraterone<sup>1</sup><sup>cc</sup> with prednisone (category 1)
  - Docetaxel<sup>1</sup><sup>dd</sup> with prednisone (category 1)
  - Enzalutamide<sup>1</sup> (category 1)
  - Radium-223 for symptomatic bone metastases (category 1)<sup>ee</sup>
  - Clinical trial
  - Secondary hormone therapy
    - Antiandrogen
    - Antiandrogen withdrawal
    - Ketoconazole ± hydrocortisone
    - Corticosteroid
    - DES or other estrogen<sup>aa</sup>

- Yes
  - Docetaxel<sup>1</sup><sup>dd</sup> with prednisone (category 1)
  - Enzalutamide<sup>1</sup> (category 1)
  - Abiraterone<sup>1</sup><sup>cc</sup> with prednisone
  - Alternative chemotherapy
    - (mitoxantrone with prednisone)<sup>yx</sup><sup>cc</sup>
  - Clinical trial
  - Secondary hormone therapy
    - Antiandrogen
    - Antiandrogen withdrawal
    - Ketoconazole ± hydrocortisone
    - Corticosteroid
    - DES or other estrogen<sup>aa</sup>

**Progression** after:
- Abiraterone
- Enzalutamide
- Docetaxel
  - See Subsequent Therapy for M1 CRPC: No Visceral Metastases (PROS-12)
  - or
  - See Subsequent Therapy for M1 CRPC: Visceral Metastases (PROS-13)

**Progression** after all other therapies

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<sup>1</sup>See Principles of Imaging (PROS-B).
<sup>2</sup>See Principles of Androgen Deprivation Therapy (PROS-F).
<sup>3</sup>Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET. See Principles of Imaging (PROS-B).
<sup>4</sup>See Principles of Immunotherapy and Chemotherapy (PROS-G).
<sup>aa</sup>DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
<sup>bb</sup>Sipuleucel-T has not been studied in patients with visceral metastases.

<sup>cc</sup>For patients who are not candidates for docetaxel-based regimens.
<sup>dd</sup>Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.
<sup>ee</sup>Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
Key phase III clinical trials since 2004

- **Androgen receptor signaling**
  - Abiraterone acetate
  - Enzalutamide
  - Orteronel (TAK-700)

- **Metastasis / invasion inhibitors**
  - OGX-011 (1st line)
  - OGX-011 (2nd line)

- **TKI inhibitors**
  - Sunitinib
  - Dasatinib
  - Cabozantinib

- **Endothelin receptor inhibitors**
  - Atrasentan
  - Zibotentan

- **Angiogenesis inhibitors**
  - Bevacizumab
  - Lenalidomide
  - Aflibercept
  - Tasquinimod

- **Microtubule inhibitors**
  - Cabazitaxel

- **Radiotherapy**
  - Radium 223

- **Immunotherapy**
  - Sipuleucel T
  - Ipilimumab
  - Prostvac
Key phase III clinical trials since 2004

- **Androgen receptor signaling**
  - Abiraterone acetate
  - Enzalutamide
  - Orteronel (TAK-700)
- **Metastasis / invasion inhibitors**
  - OGX-011 (1st line)
  - OGX-011 (2nd line)
- **TKI inhibitors**
  - Sunitinib
  - Dasatinib
  - Cabozantinib
- **Endothelin receptor inhibitors**
  - Atrasentan x2
  - Zibotentan x3
- **Angiogenesis inhibitors**
  - Bevacizumab
  - Lenalidomide
  - Aflibercept
  - Tasquinimod
- **Microtubule inhibitors**
  - Cabazitaxel
- **Radiotherapy**
  - Radium 223
- **Immunotherapy**
  - Sipuleucel T
  - Ipilimumab
  - Prostvac

Note: OGX-011 and Prostvac status uncertain.
## Summary of clinical trial outcome

<table>
<thead>
<tr>
<th>Patient setting</th>
<th>Control</th>
<th>Increase in median, months</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel/P</strong>¹</td>
<td>First-line Mitoxantrone/P</td>
<td>2.9</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Cabazitaxel/P</strong>²</td>
<td>Post-docetaxel Mitoxantrone/P</td>
<td>2.4</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Abiraterone/P</strong>³</td>
<td>Post-docetaxel Placebo/P</td>
<td>4.6</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Abiraterone/P</strong>⁴</td>
<td>Chemo-naïve Placebo/P</td>
<td>5.2</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong>⁵</td>
<td>Post-docetaxel Placebo</td>
<td>4.8</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong>⁶</td>
<td>Chemo-naïve Placebo</td>
<td>2.2</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Radium-223</strong>⁷</td>
<td>Bone metastases, Pre- and post docetaxel Placebo</td>
<td>3.6</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*OS did not reach the prespecified efficacy boundary (p=0.0035)


These studies are different (in type, population, inclusion/exclusion criteria, design and method, primary objectives) and therefore a comparison cannot be made.
Molecular Components of the AR

- The AR is composed of 3 major functional domains:
  - **N-terminal domain (NTD)**
    Responsible for the majority of transcription activity
  - **DNA-binding domain (DBD)**
    Contains 2 zinc finger motifs that facilitate DNA binding
  - **Ligand-binding domain (LBD)**
    Mediates ligand binding

The Development of mCRPC Involves Alterations in AR-Signaling

Androgen Signaling

Pathways to Castration Resistance

Aggressive forms of CRPC, such as neuroendocrine, and small-cell carcinomas often lack AR expression.
Target 1: Gonadal/Circulating T

LHRH
Leuprolide
Goserelin
Degarelix
…others…
Estrogens

TESTOSTERONE

SHBG

GTX758 (ERa agonist)

SHBG

Free T

Modified from Peter Nelson, MD
Target 2: Adrenal/Intracrine Ligands

Modified from Peter Nelson, MD
Target 3: AR Degradation

HSP90 Antagonists
- 17AAG
- STA9090
- AT13387
- Others...

Selective AR downregulators or degraders*
- Curcumin
- TOK001
- AZD3514
- ASC-J9
- PPD
- Antisense

*many others with low potency

Modified from Peter Nelson, MD
Target 4: Androgen Receptor Blockade

Target: Androgen Receptor Blockade

- Translocation block
- Unproductive transcription
- Enhanced degradation

Competitive Antagonists:
- Flutamide
- Bicalutamide
- Nilutamide
- Enzalutamide
- ARN509
- TOK001

Modified from Peter Nelson, MD
Target 5: Prevent AR Nuclear Translocation

Microtubule Inhibitors
- Enzalutamide
- Paclitaxel
- Docetaxel
- Cabazitaxel

Modified from: Peter Nelson, MD
Target 6: Interfere With AR ‘Enablers’

Signaling Pathways
- Her2/3
- IGF1R
- CDKs
- others

Modified from: Peter Nelson, MD
Target 7: Block AR–DNA/Co-Activator Interaction

Androgen-response Elements (ARE)

Target Gene Expression

Coactivators

Important as they may target ARsv

Non-Competitive Antagonists*

EPI-001
‘D2’
Pyrivinium
Harmol HCL
Others

*N-C interactions
Nuclear translocations
AR AF2-LXXLL Interactions
Co-factor inhibition

Modified from Peter Nelson, MD
Target 8: AR Downstream ‘Effectors’

- **PI3K-Pathway Inhibitors**
- **ETS-family Inhibitors**
- **Proliferation**
- **Survival**
- **Metabolism**

Modified from Peter Nelson, MD
Advancing Precision Medicine for Prostate Cancer Through Genomics
Samir Khoury

ABSTRACT
Prostate cancer is the most common type of cancer in men and the second leading cause of cancer death in men in the United States. The recent surge of high-throughput sequencing of cancer genomes has supported an expanding classification of prostate cancer. Translation of these basic science studies into clinically valuable biomarkers for diagnosis and prognosis and biomarkers that are predictive for therapy is critical to the development of precision medicine in prostate cancer. We review potential applications aimed at improving screening specificity in prostate cancer and differentiating aggressive versus indolent prostate cancers. Furthermore, we review predictive biomarker candidates involving ETS gene rearrangements, PTEN inactivation, and androgen receptor signaling. These and other putative biomarkers may signal aberrant oncogenic pathway activation and provide a rationale for matching patients with molecularly targeted therapies in clinical trials. Lastly, we advocate innovations for clinical trial design to incorporate tumor biopsy and molecular characterization to develop biomarkers and understand mechanisms of resistance.

INTRODUCTION
Prostate cancer is the most common non-skin cancer and the second leading cause of cancer death in men in the United States. Although there has been significant progress in the treatment of prostate cancer, with the approval of three new therapies for metastatic prostate cancer this year, several challenges persist such as a means to match patients with targeted therapies and the implementation of rational combination therapies. The Institute of Medicine recently critiqued the cooperative clinical trial groups in oncology and recommended innovative trial design through the incorporation of predictive biomarker stratification for patient selection. A molecular classification of cancer has the potential benefits of improving response, minimizing the time and adverse effects of treating patients with ineffective therapies, and reducing the sample size needed to show efficacy. High-throughput sequencing technologies have accelerated the molecular characterization of prostate cancer and positioned opportunities for development of precision medicine for therapeutic decision making in this disease. Here we examine the current data on molecular alterations in prostate cancer, the progress in translating these findings into the clinic, and the challenges that lay ahead for translational genomics in prostate cancer.

ETS GENE FUSIONS AND URINE TESTING
Gene fusions in prostate cancer were first described in 2005 using a bioinformatics approach that detected outlier transcript expression of genes with microarrays. The most common chromosomal rearrangements involve the 5 untranslated region of the androgen-regulated gene TMPRSS2 and
### Table 1. Clinically Relevant Genomic Alterations in Prostate Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration Type</th>
<th>Frequency (%)</th>
<th>Potential Treatment Hypotheses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETS transcription factors</strong></td>
<td>Rearrangement</td>
<td>50(^7)</td>
<td>Indirect targeting of ETS gene fusions through PARP or DNAPK inhibitors(^8)</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>Mutation</td>
<td>50(^9,10)</td>
<td>Androgen synthesis inhibitors, next-generation androgen receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>50(^9,10)</td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Loss</td>
<td>50(^9)</td>
<td>PI3K pathway inhibitors(^11)</td>
</tr>
<tr>
<td><strong>RB1</strong></td>
<td>Loss</td>
<td>25 to 60(^9)</td>
<td>Role in disease progression and castrate resistance(^12) with potential for targeting</td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>Amplification</td>
<td>10(^10)</td>
<td>PI3K pathway inhibitors(^11)</td>
</tr>
<tr>
<td></td>
<td>Mutation</td>
<td>5(^10)</td>
<td></td>
</tr>
<tr>
<td><strong>MYC</strong></td>
<td>Amplification</td>
<td>9(^9)</td>
<td>Potential for targeting(^13) Neuroendocrine prostate cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40(^10)</td>
<td></td>
</tr>
<tr>
<td><strong>AURKA</strong></td>
<td>Amplification</td>
<td>5(^10)</td>
<td>Aurora kinase inhibitors(^14); co-occurs with MYC in 40% of neuroendocrine prostate cancers</td>
</tr>
<tr>
<td><strong>AKT</strong></td>
<td>Mutation</td>
<td>1 to 2(^15)</td>
<td>AKT inhibitors</td>
</tr>
<tr>
<td><strong>RAF</strong></td>
<td>Rearrangement</td>
<td>1 to 2(^16)</td>
<td>RAF inhibitors</td>
</tr>
<tr>
<td></td>
<td>Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>Mutation</td>
<td>1(^9,17,18)</td>
<td>RAF, MEK, or PI3K inhibitors</td>
</tr>
<tr>
<td></td>
<td>Rearrangement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Summarizes alterations in prostate cancer that have a treatment hypothesis currently being explored preclinically or in clinical trials. The most common alterations with a treatment hypothesis involve ETS rearrangements, androgen receptor, and PTEN loss. With only a limited number of samples assessed, a majority of these alterations are not necessarily mutually exclusive.

**Abbreviation:** PI3K, phosphatidylinositol 3-kinase.
<table>
<thead>
<tr>
<th>Target</th>
<th>Ongoing Trials</th>
<th>Therapies</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Genome-Based Enrichment or Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETS fusions</strong></td>
<td>Study combining ABT-888, oral PARP inhibitor, with temozolomide in patients with metastatic prostate cancer</td>
<td>ABT-888, PARP inhibitor</td>
<td>NCT01085422</td>
<td>ETS randomization</td>
</tr>
<tr>
<td></td>
<td>Study to assess safety and tolerability of oral CC-115 for patients with advanced solid tumors, non-Hodgkin lymphoma, or multiple myeloma</td>
<td>CC-115, DNAPK, and mTOR inhibitor</td>
<td>NCT01353625</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Abiraterone acetate with or without veliparib in treating patients with metastatic prostate cancer</td>
<td>Veliparib, PARP inhibitor</td>
<td>NCT01576172</td>
<td>None</td>
</tr>
<tr>
<td><strong>PI3K/mTOR/AKT pathway</strong></td>
<td>Phase II study of BKM120 in men with metastatic CRPC</td>
<td>BKM120, PI3K inhibitor</td>
<td>NCT01385293</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Phase II/IIIa, first time in human study of GSK2636771 in patients with advanced solid tumors with PTEN deficiency</td>
<td>GSK2636771, PI3K inhibitor</td>
<td>NCT01458067</td>
<td>PTEN deficiency by immunohistochemistry</td>
</tr>
<tr>
<td></td>
<td>Phase II study of the efficacy and safety of AP23573 in patients with taxane-resistant AIPC</td>
<td>Ridaforolimus, mTOR inhibitor</td>
<td>NCT00110188</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus to reverse androgen insensitivity for CRPC</td>
<td>Temsirolimus, mTOR inhibitor</td>
<td>NCT01020305</td>
<td>None</td>
</tr>
<tr>
<td><strong>Androgen signaling</strong></td>
<td>Determine effect of MDV3100 on androgen signaling pathway in correlation with anti-tumor effects of MDV3100 to identify potential predictors of response or resistance to therapy</td>
<td>MDV3100, second-generation AR antagonist</td>
<td>NCT01091103</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Safety and efficacy study of MDV3100 in patients with CRPC who have been previously treated with docetaxel-based chemotherapy (AFFIRM)</td>
<td>MDV3100, second-generation AR antagonist</td>
<td>NCT00974311</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Safety, pharmacokinetic and proof-of-concept study of ARN-509 in CRPC</td>
<td>ARN 509, second-generation AR antagonist</td>
<td>NCT01171898</td>
<td>None</td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td>Bicalutamide with or without MK2206 in treating patients with previously treated prostate cancer</td>
<td>Bicalutamide plus MK2206, AKT inhibitor</td>
<td>NCT01251861</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus to reverse androgen insensitivity for CRPC</td>
<td>Temsirolimus (mTOR)</td>
<td>NCT01020305</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Study of GDC-0086 or GDC-0089 with abiraterone acetate versus abiraterone acetate in patients with CRPC previously treated with docetaxel chemotherapy</td>
<td>Abiraterone plus GDC-0086 (AKT inhibitor) or GDC-0089 (PI3K/mTOR)</td>
<td>NCT01485681</td>
<td>None</td>
</tr>
<tr>
<td><strong>Private driver mutations</strong></td>
<td>Abiraterone acetate with or without veliparib in treating patients with metastatic prostate cancer</td>
<td>Vemurafenib, RAF inhibitor</td>
<td>NCT01085422</td>
<td>BRAF subset receives vemurafenib</td>
</tr>
</tbody>
</table>

NOTE: There are multiple ongoing trials involving novel agents targeting ETS, PI3K pathway, and AR signaling in prostate cancer. Few studies are beginning to target multiple pathways through combination therapies. Although this table is not comprehensive, it is meant to provide an overview of directions for targeted therapies in prostate cancer.

**Abbreviations:** AFFIRM, A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100; AIPC, androgen-independent prostate cancer; AR, androgen receptor; CRPC, castration-resistant prostate cancer; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin homolog.
Fig 1. Pathway-guided treatment in prostate cancer. This diagram highlights pathways for targeting in prostate cancer, including the phosphatidylinositol 3-kinase (PI3K) pathway, ETS rearrangements, and androgen signaling. Green indicates putative treatment hypotheses for relevant pathways. Each of these pathways can be driven by genomic aberrations, such as point mutations, copy number alterations, and rearrangements. The diagram also highlights less common driving mutations involving RAS, RAF, and AKT oncogenes. Furthermore, there is potential for cooperation between pathways because these are not necessarily mutually exclusive. Genes highlighted in gold have known genomic alterations. AR, androgen receptor; mTOR, mammalian target of rapamycin, PARP, poly (ADP-ribose) polymerase; RTK, receptor tyrosine kinase.
AR Splice Variants

AR splice variants are associated with poor prognosis and Treatment resistance

- The translation of splice variants results in proteins with altered activity and regulation\(^1\)

- Exons 4-8 of AR are not required for transcriptional activity and splice variants lacking this region may be constitutively active\(^2\)

- In one study, expression of AR variants lacking the ligand-binding domain in CRPC bone metastases was associated with poor prognosis\(^2\)

- Detection of AR-V7 in tumor cells is associated with treatment resistance\(^3,4\)

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Lack of Response Associated with AR-V7 (Johns Hopkins University)

- Prospective study of M1 CRPC patients eligible for abiraterone (N=31) and enzalutamide (N=31) treatment; AR-V7 identified in CTC samples pretreatment
- None (0/18) of the AR-V7 positive patients achieved a PSA50
  - Only 1 AR-V7 positive patient showed any PSA reduction (enzalutamide)
- AR-V7 prevalence increased post additional treatments

<table>
<thead>
<tr>
<th>Treatment¹</th>
<th>Baseline AR-V7+</th>
<th>AR-V7 status</th>
<th>PSA50</th>
<th>P- value</th>
<th>rPFS</th>
<th>P- value</th>
<th>OS (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (N=31)</td>
<td>19% (6/31)</td>
<td>+</td>
<td>0% (0/6)</td>
<td>.004</td>
<td>2.3 mos</td>
<td>&lt;.001</td>
<td>10.6 mos (8.5–NR)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–</td>
<td>68% (17/25)</td>
<td></td>
<td>&gt;6.3 mos</td>
<td></td>
<td>&gt;11.9 mos (11.9–NR)</td>
<td></td>
</tr>
<tr>
<td>Enzalutamide (N=31)</td>
<td>39% (12/31)</td>
<td>+</td>
<td>0% (0/12)</td>
<td>.004</td>
<td>2.1 mos</td>
<td>&lt;.001</td>
<td>5.5 mos (3.9–NR)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–</td>
<td>53% (10/19)</td>
<td></td>
<td>6.1 mos</td>
<td></td>
<td>NR (NR–NR)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Treatment Status²</th>
<th>Before enzalutamide or abiraterone</th>
<th>Post enzalutamide</th>
<th>Post abiraterone</th>
<th>Post abiraterone &amp; enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-V7 Prevalence</td>
<td>12%</td>
<td>25%</td>
<td>51%</td>
<td>67%</td>
</tr>
</tbody>
</table>

CRPC=castration-resistant prostate cancer; CTC=circulating tumor cell; M1=metastatic disease; NR=not reached; OS=overall survival; PSA=prostate specific antigen; rPFS=radiographic progression-free survival. 1. Antonarakis ES et al. NEJM. 201410.1056/NEJMoa1315815. 2. Antonarakis ES et al. ASCO 2014
A  Enzalutamide-Treated Patients

B  Abiraterone-Treated Patients

Antonarakis et al
NEJM 2014
A Gain-of-Function Mutation in DHT Synthesis in Castration-Resistant Prostate Cancer

Kai-Hsiung Chang¹,²,³,⁴, Rui Li⁴, Barbara Kuri¹,²,³, Yair Lotan⁵, Claus G. Roehrborn⁶, Jiayan Liu⁵, Robert Vessella⁹, Peter S. Nelson⁹,¹⁰, Payal Kapur⁵, Xiaofeng Guo⁷, Hamid Mirzaei⁷, Richard J. Auchus⁸, Nima Sharifi¹,²,³,⁴, 🇮🇷, 🇺🇸
Mutation in 3BHSD1 Facilitates Conversion of Precursors to DHT
Glucocorticoid Receptor Confers Resistance to Antiandrogens by Bypassing Androgen Receptor Blockade

Vivek K. Arora¹,², Emily Schenkein¹, Rajmohan Murali¹,³, Sumit K. Subudhi², John Wongvipat¹, Minna D. Balbas¹,⁴, Neel Shah¹,⁴, Ling Cai¹, Eleni Efstathiou⁵, Chris Logothetis⁵, Deyou Zheng⁶, Charles L. Sawyers¹,⁷.
Glucocorticoid Receptor Activation Post-Enzalutamide Treatment

- Acquired resistance to enzalutamide can be associated with increased expression of the glucocorticoid receptor (GR)

<table>
<thead>
<tr>
<th>PSA decline</th>
<th>Good</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50%</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>
Integrative Clinical Genomics of Advanced Prostate Cancer

**Graphical Abstract**

**Authors**
Dan Robinson, Eliezer M. Van Allen, ..., Charles L. Sawyers, Arul M. Chinnaiyan

**Correspondence**
sawyersc@mskcc.org (C.L.S.), arul@umich.edu (A.M.C.)

**In Brief**
A multi-institutional integrative clinical sequencing analysis reveals that the majority of affected individuals with metastatic castration-resistant prostate cancer harbor clinically actionable molecular alterations, highlighting the need for genetic counseling to inform precision medicine in affected individuals with advanced prostate cancer.

**Highlights**
- A multi-institutional integrative clinical sequencing of mCRPC
- Approximately 90% of mCRPC harbor clinically actionable molecular alterations
- mCRPC harbors genomic alterations in *PIK3CA/B, RSPO, RAF, APC, β-catenin, and ZBTB16*
- 23% of mCRPC harbor DNA repair pathway aberrations, and 8% harbor germline findings
Sequence or Layering?

D. Lorente, J.S. De Bono, Eur J Cancer 2014;50:753
THE GENE
AN INTIMATE HISTORY

SIDDHARTHA MUKHERJEE
PULITZER PRIZE-WINNING AUTHOR OF THE EMPEROR OF ALL MALADIES
Conclusions

• The AR continues to be a major driver in the growth and survival of prostate CA cells, even in the CRPC patient.

• As urologists, we need to understand the nuances of resistance mechanisms and genomic alterations.

• Despite all the recent advances, there remains multiple challenges and opportunities for researchers to better understand the disease and possible development of novel targeted agents.