Hormonal Therapy In the Setting of CRPC

Leonard G. Gomella, MD  
Chairman  
Department of Urology  
Sidney Kimmel Cancer Center  
Philadelphia, PA
Before 2010, the last agent approved for the treatment of CRPC was docetaxel.
ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC

- Maintaining castrate levels of serum testosterone
- Consider bone anti-resorptive 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 (see PROS-G)†
- Palliative RT for painful bony metastases
- Best supportive care

CRPC, studies positive² for metastases

Visceral metastases

No →
- Enzalutamide¹ (category 1)
- Abiraterone acetate¹,² with prednisone (category 1)
- Docetaxel¹,² with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)²
- Clinical trial
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Corticosteroids

Yes →
- Docetaxel¹,² with prednisone (category 1)
- Enzalutamide¹ (category 1)
- Abiraterone acetate¹,² with prednisone
- Alternative chemotherapy (mitoxantrone)¹,²
- Clinical trial

Progression after:
- Abiraterone acetate
- Enzalutamide
- Docetaxel

See Subsequent Therapy for CRPC (PROS-12)

Progression after all other therapies

---

¹See Principles of Imaging (PROS-B).
²See Principles of Androgen Deprivation Therapy (PROS-F).
³See Principles of Immunotherapy and Chemotherapy (PROS-G).
⁴Sipuleucel-T has not been studied in patients with visceral metastases.
⁵Radium-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).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Castration-Resistant Prostate Cancer (CRPC)

New Definition: 2 consecutive rises in PSA while on ADT and serum T <50 ng/mL
- Check serum T periodically on ADT

“Androgen resistant”, “androgen independent”, “hormone refractory” terms no longer used
- Prostate cancer in CRPC maintains response to hormonal axis

Do people who have a lower T with ADT do better?
- Some data suggests yes

LHRH agonists, antagonists or surgical castration do not ablate T to the lowest levels possible

ADT, androgen deprivation therapy; T, testosterone; LHRH, luteinizing hormone-releasing hormone
Treatment of Metastatic PC

Androgen Deprivation +/- AR antagonists

Cell Cycle Arrest/Death
(40/60%)

Remission

12-36 months

Relapse

Cell Cycle resumes

“Castration Resistant” (CRPC)

Castration +/- Antiandrogen

Patients that re-activate androgen pathways
Hormone Naïve Disease- Importance of Lower T Levels: A Hypothesis-Generation Analysis From a Retrospective Study

Retrospective analysis of 73 patients with nonmetastatic prostate cancer who received 3-month depot of LHRH agonist

Patients with testosterone levels <32 ng/dL had an average of an additional 4 years until castrate-resistant progression

Mean Time Free of Androgen-Independent Progression

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Time Free of Androgen-Independent Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>106 months</td>
</tr>
<tr>
<td>Group 2</td>
<td>90 months</td>
</tr>
<tr>
<td>Group 3</td>
<td>72 months</td>
</tr>
</tbody>
</table>
Secondary “Hormonal” Therapy: Responses Rarely Durable

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>30%-60%</td>
</tr>
<tr>
<td>Estrogens</td>
<td>40%-60%</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>20%</td>
</tr>
<tr>
<td>Anti-androgen Withdrawal</td>
<td>20% rarely durable</td>
</tr>
</tbody>
</table>

*Curr Oncol. 2010 Sept; 17(Supplement 2): S72–S79*
CRPC Maintains Sensitivity to Low Levels of Androgens

Androgen biosynthesis from adrenal precursors and De novo synthesis

Cells become hypersensitive to small amounts of androgen through alterations in the androgen receptor (AR), including

- Increase in the expression of ARs
- Mutations in the AR structure
- Activation of the AR independent of androgens

Reducing androgens to lowest levels possible is desirable in CRPC

CRPC Prostate Cancer: “Adapting” to castrate environment

Hormone Therapy

- MUTATION • gain of function
- Crosstalk AR –Sig Path
- Post-translational Modifications of AR
- AR SPLICE VARIANTS
- COFACTOR PERTURBATION •CoAct gain •CoR loss/dismissal
- INTRACRINE ANDROGEN SYNTHESIS
- Amplification\ Overexpression AR
- Alterations of Steroid Transporters

RESTORED AR ACTIVITY (rising PSA)

RECURRENT TUMOR DEVELOPMENT

Penning & Knudsen 2010
New Theories for CRPC
Based on Translational Discoveries

- CaP responds to castration by synthesizing androgens from weaker androgens and/or cholesterol
- Androgen Receptor (AR) may respond to castration with molecular and biochemical alterations that cause hypersensitivity to low levels of androgens
  - AR upregulation/mutations/promiscuous activation
- Progressing prostate cancer with low/castrate levels of testosterone is **STILL** sensitive to androgens
Newer CRPC “Hormonal Agents”
(Androgen Biosynthesis Inhibitors/Androgen Receptor Pathway)

FDA Approved*

- Abiraterone acetate (ABI)*
- Enzalutamide (MDV3100) (ARSI)*
- TOK001 (Galeterone: ABI/ ARSI/ AR degradation)
- ARN 509 (ARSI)
- EPI-001 (AR N-Terminal)
- SNARE-1 (selective nuclear receptor exporter-1)

Terminated:
- TAK700 (Orteronel: ABI) (ELM-PC4 pre chemo no survival advantage)
## Agents with OS Benefit in mCRPC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Comparator</th>
<th>Primary Endpoint</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy-naïve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate +</td>
<td>COU-AA-302</td>
<td>Placebo + prednisone</td>
<td>OS benefit 5.2 months*</td>
<td>2012</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>IMPACT</td>
<td>Placebo</td>
<td>OS benefit 4.1 months</td>
<td>2010</td>
</tr>
<tr>
<td>Radium-223</td>
<td>ALSYMPCA</td>
<td>Placebo</td>
<td>OS benefit 3.6 months</td>
<td>2013</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>PREVAIL</td>
<td>Placebo</td>
<td>OS benefit 4 months</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Post-chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate +</td>
<td>COU-AA-301</td>
<td>Placebo + prednisone</td>
<td>OS benefit 4.6 months</td>
<td>2011</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>AFFIRM</td>
<td>Placebo</td>
<td>OS benefit 4.8 months</td>
<td>2012</td>
</tr>
<tr>
<td>Cabazitaxel + prednisone</td>
<td>TROPIC</td>
<td>Mitoxantrone + prednisone</td>
<td>OS benefit 2.4 months</td>
<td>2010</td>
</tr>
<tr>
<td>Docetaxel + prednisone</td>
<td>TAX327</td>
<td>Mitoxantrone + prednisone</td>
<td>OS benefit 2.4 months</td>
<td>2004</td>
</tr>
</tbody>
</table>

*P=0.0151. Did not meet the prespecified value for statistical significance.

Abiraterone: Mechanism of Action

**Abiraterone**

**CYP17: 17α-hydroxylase**

**CYP17: C17,20-lyase**

**Cholesterol**

**Pregnenolone**

**Progesterone**

**17α-OH-Pregnenolone**

**17α-OH-Progesterone**

**DHEA**

**Androstenedione**

**Testosterone**

**DHT**

**Androgen Receptor**

**Testes**

**Tumor**

**Adrenal Glands**
Abiraterone Suppresses Steroids Downstream of C17,20-lyase

Testosterone (by LC-MS/MS)

Androstenedione

DHEA

Estradiol
Abiraterone Administration

• Administration
  – 1,000 mg (4, 250mg tablets) once daily on an empty stomach with prednisone 5mg BID
  – Monitor BP/LFT/potassium

• Dose Modifications
  – Dosage adjustment necessary if hepatotoxicity occurs
    • ALT/AST 5x NL or bilirubin 3x NL stop medication
    • Resume at 750mg daily once ALT/AST 2.5x NL or bilirubin 1.5x NL
Abiraterone Acetate
Adverse Effects

- Most AEs occurred during the first 3 months of treatment
- Most AEs are grade 1-2
- Most common AEs
  - Fatigue
  - Arthralgia
  - Fluid retention-peripheral edema
  - Hypokalemic
  - Hypertension
  - Cardiac Disorders
  - Atrial fibrillation
  - ALT and AST increased
  - Increased hot flashes

Abiraterone: Why with prednisone?

To block effects of decreased cortisol on increasing ACTH and increased mineralocorticoid effects

Incidence of CS-Associated AEs in mCRPC patients

- **Conclusion:** With a median exposure of 8.3 months (range, 0.1-34.9 months; total 2006 years), low-dose P given with or without AA is associated with an overall low incidence of CS-associated AEs, and long-term treatment with AA + P is well tolerated.

Assessment of Corticosteroid (CS)-Associated Adverse Events (AEs) With Long-Term Exposure to Low-Dose Prednisone (P) Given With Abiraterone Acetate (AA) to Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients

Gomella, et al AUA 2015
## testosterone Clinical Trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Description</th>
<th>Study ID</th>
<th>NCT Number</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Post-chemotherapy</td>
<td>COU-AA-301</td>
<td>NCT00638690</td>
<td>Completed</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Pre-chemotherapy</td>
<td>COU-AA-302</td>
<td>NCT00887198</td>
<td>Completed</td>
<td></td>
</tr>
<tr>
<td>Non-</td>
<td>M0 with rising PSA despite castrate levels of testosterone</td>
<td>IMAAGEN</td>
<td>NCT01314118</td>
<td>Ongoing, not recruiting</td>
<td></td>
</tr>
<tr>
<td>metastatic Prostate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>AA + Exemestane in postmenapausal women with ER+ metastatic breast cancer</td>
<td>BCA2001</td>
<td>NCT01381874</td>
<td>Ongoing, not recruiting</td>
<td></td>
</tr>
</tbody>
</table>

* Does not include IIT

---

2015 www.clinicaltrials.gov
IMAAGEN:
M0 CRPC PSA of $\geq 10$ ng/mL/ PSADT of $\leq 10$ mo

5 mg pred/day different than label

PSA Response During Cycles 1-6

- 91% subjects had ≥ 30% reduction
- 87% subjects had ≥ 50% reduction
- 60% subjects had ≥ 90% reduction

A Progression

- Median time to PSA progression was 28.7 months (85% CI: 21.2, NE)
- 45 (34.4%) subjects showed evidence of PSA progression as of this update

Radiographic Evidence of Disease Progression

- 21 (16.0%) subjects had radiographic evidence of disease progression as reported by investigators

MDV3100 (Enzalutamide)
Anti-Androgen with No Agonist Effects

1. MDV3100 oral hormonal agent to target androgen receptor (AR) signaling.

2. A new class of Androgen Receptor Signaling Inhibitors (ARSI) that affects multiple steps in the androgen receptor signaling pathway (translocation and DNA binding).

3. No impact on T
4. Does not require steroids

**Primary endpoint**
- Progression-free survival, defined as time from randomization to (whichever occurs first):
  - Radiographic progression
  - SRE
  - Initiation of new antineoplastic therapy
  - Death

**Secondary endpoints**
- PSA response
- Time to PSA progression
- Safety

---

**Patient population**
- 375 men with progressive mCRPC
- Asymptomatic/mildly symptomatic
- Chemotherapy-naïve
- No requirement for steroids

**Statistical design**
- Final analysis planned at ≥ 220 progression events with 85% power to detect a target hazard ratio of 0.67 (assuming a median PFS of 9 months versus 6 months)

---

mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; SRE = skeletal-related event


**TERRAIN: A Phase 2 Efficacy and Safety Study of Enzalutamide vs Bicalutamide in mCRPC:**

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>ENZA Patients at risk</th>
<th>BIC Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>184</td>
<td>191</td>
</tr>
<tr>
<td>3</td>
<td>159</td>
<td>133</td>
</tr>
<tr>
<td>6</td>
<td>131</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>107</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td>44</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>21</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>24</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Median 15.7 months (95% CI 11.5, 19.4) for ENZA

Median 5.8 months (95% CI 4.8, 8.1) for BIC

Hazard ratio 0.44 (95% CI 0.34, 0.57) with p < 0.0001

**BIC = bicalutamide; CI = confidence interval; ENZA = enzalutamide; mCRPC = metastatic castration-resistant prostate cancer**

Primary Endpoint
Progression-free survival (PFS):
Radiographic progression
or
PSA progression
or
Death

Key secondary endpoints:
- Time to PSA progression
- PSA response
- rPFS (M1 population only)

Patient Population
- 396 men with progressive CRPC
  - M0 or M1
- Asymptomatic/mildly symptomatic
- Chemotherapy-naïve
- Ongoing ADT
- No prior progression on bicalutamide

Randomized 1:1

Enzalutamide 160 mg/day (n = 198)

Bicalutamide 50 mg/day (n = 198)

ClinicalTrials.gov identifier: NCT01664923

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; M0 = nonmetastatic; M1 = metastatic; PSA = prostate-specific antigen; rPFS = radiographic PFS.

Enzalutamide 160 mg
Bicalutamide 50 mg

Median 19.4 months
(95% CI: 16.5, NR)

100
90
80 70
60
50 40 30
20
10
0

PFS (%)

0 3 6 9 12 15 18 21 24 27 30

HR, 0.24 (95% CI: 0.18, 0.32); P < 0.0001

Median 5.7 months
(95% CI: 5.6, 8.1)

Patients at Risk
Enzalutamide: 198 171 150 131 101 66 43 24 16 5 0
Bicalutamide: 198 138 80 51 29 17 9 5 3 1 0

CI = confidence interval; HR = hazard ratio; NR = not reached

STRIVE: rPFS (radiographic) in M1

- rPFS defined as the time from randomization to the first objective evidence of radiographic progression (soft tissue or bone) or death from any cause

CI = confidence interval; HR = hazard ratio; M1 = metastatic; NR = not reached; rPFS = radiographic PFS

TRIVE Conclusions

First trial to demonstrate that enza + ADT more efficacious than bicalutamide plus ADT in M0 and M1 CRPC patients:

- Prolonged PFS
- Prolonged time to PSA progression
- Higher PSA response rates
- Prolonged rPFS

More profound androgen blockade, enza had more fatigue, hot flashes, hypertension more falls and dizziness.

More constipation, diarrhea, anemia, and urinary tract infections were observed in the bicalutamide arm.

Follow up PROSPER phase 3 trial includes only M0 CRPC

Enzalutamide Administration

• Administration
  – 160mg (4, 40mg capsules) once daily
  – May be taken with or without food
  – Do not chew, crush, dissolve or open the capsule.

• Dose Modifications
  – If ≥ grade 3 toxicity, delay for 1 week or until symptoms improve to ≤ grade 2, then continue at same or reduced dose

Enzalutamide
Adverse Events

- Fatigue
- Dizziness
- Hot flash
- Headache
- Peripheral edema
- Infections
- Falls and related injuries
- Lowers seizure threshold
- Diarrhea
- Muscoskeletal Pain
  - Hypertension
- LFT abnormalities
- Hallucinations

# Ongoing Enzalutamide Clinical Trials

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Phase</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERRAIN</td>
<td>2</td>
<td>ENZA vs. bicalutamide after ADT in mCRPC</td>
<td>Data available</td>
</tr>
<tr>
<td>STRIVE</td>
<td>2</td>
<td>ENZA vs. bicalutamide after ADT in M0/M1 CRPC</td>
<td>Data available</td>
</tr>
<tr>
<td>oadjuvant</td>
<td>2</td>
<td>Randomized, open-label ENZA neoadj therapy for patients undergoing RP for localized PC</td>
<td>Data available</td>
</tr>
<tr>
<td>ATO (TBP)</td>
<td>2</td>
<td>Abiraterone + prednisone ± ENZA in patients progressing on ENZA</td>
<td>In follow up</td>
</tr>
<tr>
<td>ROSPER</td>
<td>3</td>
<td>ADT ± ENZA in M0 CRPC without prior chemotherapy</td>
<td>Open</td>
</tr>
<tr>
<td>PWARD</td>
<td>2</td>
<td>Open-label extension in CRPC patients</td>
<td>Open</td>
</tr>
<tr>
<td>RUMPET</td>
<td>4</td>
<td>Prospective observational cohort study</td>
<td>Open</td>
</tr>
</tbody>
</table>

Not including IIT’s
## Ongoing Enzalutamide Clinical Trials

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Phase</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMBARK</td>
<td>3</td>
<td>Randomized, 3-arm trial of ENZA vs. ENZA + Leuprolide vs. Placebo + Leuprolide for patients with non-metastatic prostate cancer and rapidly rising PSA after initial local therapy</td>
<td>Open</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>4</td>
<td>International Prostate Cancer Registry</td>
<td>Open</td>
</tr>
</tbody>
</table>
# Comparison of Abiraterone Acetate and Enzalutamide

<table>
<thead>
<tr>
<th>Feature</th>
<th>Abiraterone acetate</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>CYP17 inhibition</td>
<td>Antiandrogen</td>
</tr>
<tr>
<td>Efficacy after docetaxel</td>
<td>OS, PFS</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>Efficacy before docetaxel</td>
<td>PFS, OS (NS)</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>Major potential adverse effects</td>
<td>Hypertension</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>LFT abnormalities</td>
<td>ALT elevation</td>
</tr>
<tr>
<td>Requires prednisone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$$$/-</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>
ARN-509 Antagonizes and Blocks Androgen Receptor/DNA Binding and Inhibits Tumor Growth

- ARN-509: competitively inhibits AR-androgen binding; 7-10 X higher affinity than bicalutamide
- AR antagonism impairs AR activation and AR signaling
- ARN-509 inhibits AR-mediated nuclear localization and DNA binding/transcription

## N-509 Clinical Trials

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Description</th>
<th>Study ID</th>
<th>NCT Number</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-metastatic CRPC</td>
<td>M0 patients</td>
<td>SPARTAN</td>
<td>NCT01946204</td>
<td></td>
<td></td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>M1</td>
<td>ARN-509 vs LHRH agonist</td>
<td>-</td>
<td>NCT01790126</td>
<td></td>
<td></td>
<td>Currently recruiting</td>
</tr>
<tr>
<td>mCRPC</td>
<td>Combo w/abiraterone</td>
<td>-</td>
<td>NCT02123758</td>
<td></td>
<td></td>
<td>Currently recruiting</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Molecular Profiling
Precision/Personalized Therapy

• AR-V7: an Androgen Receptor splice variant expressed about 20-fold higher in patients with CRPC

• If present, may indicate resistance to abiraterone or enzalutamide

• May allow more targeted therapies

Antonarakis, ES J Clin Oncol 32:5s, 2014 (suppl; abstr 5001)
Abiraterone/Enzalutamide Combo Trials

Phase 2, single-arm combo safety study

ALLIANCE (formerly ACOSOG, CALGB, NCCTG)
- Phase 3, randomized, open-label
- Estimated completion December 2019

**Patients**
- 1224 patients with progressive mCRPC
- No prior taxane-based chemotherapy or abiraterone

**Primary Endpoint:**
- Overall survival

**Secondary Endpoints:**
- ≥ Grade 3 AEs
- PSA response
- PFS, rPFS
- Objective response rate
- Tumor burden and bone activity

How to administer, when to administer, and how to combine these newer agents will be an ongoing challenge in the coming years.

Prostate cancer patients have good reason to hope

New treatments show promise in slowing disease

Karen Weintraub
Special for USA TODAY

Jim Kiefert of Olympia, Wash., has been battling prostate cancer for 23 years. The retired school administrator, 74, has never been more optimistic about his prospects.

For the first time, thanks to a handful of drug approvals over the past 2½ years, there are now multiple options for treating advanced prostate cancer. The newest drug, enzalutamide (brand name Xtandi), came on the market in September with the best survival data ever for prostate cancer.

None of the new drugs is a cure. Re-

Jim Kiefert, 74, is still rowing and exercising 23 years after his cancer diagnosis. He has benefited from two drug trials in the past decade.
END
Intratumoral Androgen Levels Are Increased Due To Overexpression of The Androgen Synthetic Enzymes

Gerald et al, Amer J Pathol 164:217, 2004

Intracrine Synthesis of Androgens

A mutation in 3βHSD1 occurs in a subset of human CRPC tumors that blocks degradation of the enzyme

Abiraterone acetate

Yuan et al., Oncogene, 10 June 2013; doi: 10.1038/onc.2013.235
AR amplifications and overexpression

- Overexpression of AR occurs in the majority of CRPC
  - Elevated gene copy number ~80%
  - High-level of amplification ~30%
  - CTC from mCRPC found high level of gene amplification in 38-63% of the cases
  - AR amplification has correlated to response to second endocrine treatment

- AR gene amplification only partially explains AR overexpression
  - AR regulating miRNAs
  - Deregulation of transcription factors and/or co-regulators
    - NF-κB binds to AR promoter and increases AR mRNA\protein levels
    - Loss RB1 associated with overexpression of AR via increase in E2F1

Mohler et al., Clin Cancer Res. 10(2):440-8, 2004

Walting et al., Molecular and Cellular Endocrinology 360 (2012) 38-43
## Agents with OS Benefit in mCRPC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Comparator</th>
<th>Primary Endpoint</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy-naïve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate +</td>
<td>COU-AA-302</td>
<td>Placebo + prednisone</td>
<td>OS benefit 5.2 months*</td>
<td>2012</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>IMPACT</td>
<td>Placebo</td>
<td>OS benefit 4.1 months</td>
<td>2010</td>
</tr>
<tr>
<td>Radium-223</td>
<td>ALSYMPCA</td>
<td>Placebo</td>
<td>OS benefit 3.6 months</td>
<td>2013</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>PREVAIL</td>
<td>Placebo</td>
<td>OS benefit 2.2 months (interim analysis)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Post-chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone acetate +</td>
<td>COU-AA-301</td>
<td>Placebo + prednisone</td>
<td>OS benefit 4.6 months</td>
<td>2011</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>AFFIRM</td>
<td>Placebo</td>
<td>OS benefit 4.8 months</td>
<td>2012</td>
</tr>
<tr>
<td>Cabazitaxel + prednisone</td>
<td>TROPIC</td>
<td>Mitoxantrone + prednisone</td>
<td>OS benefit 2.4 months</td>
<td>2010</td>
</tr>
<tr>
<td>Docetaxel + prednisone</td>
<td>TAX327</td>
<td>Mitoxantrone + prednisone</td>
<td>OS benefit 2.4 months</td>
<td>2004</td>
</tr>
</tbody>
</table>

*P=0.0151. Did not meet the prespecified value for statistical significance.

NCI Intergroup Trial – ALLIANCE
PI- Michael Morris

Design Schematic

Metastatic progressive CRPC:
• No prior chemo for mets
• <1 wk prior keto
• No significant pain

RANDOMIZE

Arm A:
MDV3100 160mg po daily

Arm B:
Abiraterone 1000 mg po daily
Prednisone 5 mg po twice daily
MDV3100 160 mg po daily

Anticipated HR of 0.77 in favor of Arm B. N=1224. Final analysis to be conducted after 616 deaths. A one-sided type 1 error rate of 0.025, power of 0.90, accrual rate of 34 patients/month
### Novel Agents Targeting the Androgen Pathway

<table>
<thead>
<tr>
<th>Agent</th>
<th>Function</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone Acetate</td>
<td>CYP 17 $\alpha$-hydroxylase\12,20-lyase inhibitor</td>
<td>FDA approved</td>
</tr>
<tr>
<td>TAK-700</td>
<td>CYP 17,20 lyase inhibitor</td>
<td>-Phase III</td>
</tr>
<tr>
<td>Enzalutamide (MDV3100)</td>
<td>Anti-androgen\androgen receptor signaling inhibitor</td>
<td>FDA Approved</td>
</tr>
<tr>
<td>ARN-509</td>
<td>Anti-androgen</td>
<td>-Phase III</td>
</tr>
<tr>
<td>AZD3514</td>
<td>AR down-regulator\anti-androgen</td>
<td>-Phase I</td>
</tr>
<tr>
<td>TOK-001</td>
<td>Anti-androgen\CYP 17 inhibitor</td>
<td>-Phase I-II</td>
</tr>
<tr>
<td>EPI-001</td>
<td>Anti-androgen\N-terminal Domain</td>
<td>-pending clinical trials</td>
</tr>
</tbody>
</table>
Hormone Naïve Disease- Percentage of patients who fail to reach testosterone ≤ 20 ng/dL with LH-RH agonists


Adapted from Tombal B & Berges R. Eur Urol Suppl 2005;4:30-6
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Testosterone Levels with GnRH Agents

Retrospective data: less than half of men taking GnRH analogs have a serum T consistently < 20 ng/dL; Agonists may be better

Breakthrough (>50 ng/dL) in about 25% of patients on GnRH analogs

Currently, castrate level of serum testosterone is defined as ≤50 ng/dL

- Current definition of castrate level is based on older detection technology (isotope derivative technique)
- Actual castrate level may be much lower using newer methodologies (e.g., radioimmunoassay, chemiluminescence)

015 CRPC Treatment Options

- Secondary hormonal manipulation
- Androgen/androgen receptor manipulation
  - Enzalutamide (anti-androgen)
  - Abiraterone Acetate (CYP17 inhibitor, stops adrenal androgens)
- Radiopharmaceuticals
  - Radium 223
- Immunotherapy
  - Sipuleucel-T
- Chemotherapy
  - Docetaxel (1\textsuperscript{st} line)
  - Cabazitaxel (2\textsuperscript{nd} line)