Prostate Cancer: Castrate Resistant

Andrew J. Armstrong, MD, ScM
Duke Cancer Institute

Bridget Koontz, MD
Duke Cancer Institute

May 17, 2016

Moderated by Mark Geisler
NCCN, Conferences and Meetings Department

This activity is supported by educational grants from BTG; Bristol-Myers Squibb; Celgene Corporation; Genomic Health, Inc.; Lilly; Merck; Novartis Oncology; Prometheus Laboratories; Spectrum Pharmaceuticals, and by a grant from AstraZeneca, and an independent educational grant from Boehinger Ingelheim Pharmaceuticals, Inc.

Faculty Biography

Andrew J. Armstrong, MD, ScM, is Associate Professor of Medicine and Co-Director of the Clinical Research Program at Duke Cancer Institute. He is a medical oncologist and an internationally recognized expert in experimental therapeutics and biomarker development in genitourinary cancers, particularly prostate cancer. Dr. Armstrong trained at Duke University as a biomedical engineer and received his medical degree at the University of Virginia School of Medicine. He completed a residency in internal medicine at the Hospital of the University of Pennsylvania and a fellowship at Johns Hopkins Hospital, followed by public health clinical investigation training at the Bloomberg School of Public Health. Dr. Armstrong joined Duke’s faculty in 2006, where he has subsequently remained.

As a clinical and translational investigator, Dr. Armstrong’s research examines experimental therapeutics for patients with advanced genitourinary malignancies, particularly with a focus on prostate cancer and the investigation of biomarkers of response and benefit. His research for circulating tumor cell biology and epithelial plasticity is funded by the US Department of Defense, the Prostate Cancer Foundation and Movember, the NIH, and the American Cancer Society. He has developed a number of experimental agents in prostate and renal cell cancer, including completed or ongoing trials of mTOR inhibitors and PI3 kinase inhibitors, immunomodulatory agents, hormonal therapies, and anti-angiogenic agents. He also is heavily involved in the leadership of several phase 3 studies in advanced prostate cancer (dasatinib, tasquinimod, enzalutamide) in CRPC and is principal investigator on 8 investigator-initiated clinical trials and approximately 12 industry or cooperative group sponsored clinical trials.

Dr. Armstrong is a member of the NCCN Prostate Cancer Panel. He also contributes to the NCCN Oncology Research Program (ORP) by serving on the Enzalutamide Scientific Review Committee and the Temsirolimus Scientific Advisory Board and Scientific Review Committee.
Faculty Biography

Bridget Koontz, MD, is Associate Professor in the Department of Radiation Oncology at Duke University Medical Center and Medical Director of Radiation Oncology Services at Durham Regional Hospital.

Dr. Koontz earned her medical degree from Harvard Medical School. She completed an internship in internal medicine at UNC-Chapel Hill Hospitals and a residency in radiation oncology at Duke University Medical Center, during which she served as Chief Resident in her final year. She went on to complete a fellowship in low-dose rate (LDR) brachytherapy through the American Brachytherapy Society and the Seattle Prostate Institute.

Dr. Koontz's research and clinical interest is in genitourinary cancers, with a specific focus on minimizing the side effects of radiotherapy in the treatment of prostate cancer. Collaborating with a multidisciplinary team, her laboratory studies the mechanisms of radiation-induced erectile dysfunction and tests interventions to treat and prevent this devastating side effect. As part of her work, Dr. Koontz works to improve patient-provider interactions when discussing how cancer therapies affect sexuality and intimacy during and after treatment.

Dr. Koontz is a member of several professional organizations, including the American Society for Radiation Oncology, the American Society of Clinical Oncology, the American Urological Association, the International Society of Sexual Medicine, and the Sexual Medicine Society of North America. She also serves on a number of committees, including the Sexual Medicine Society of North America Basic Science Committee, the ASTRO Education Committee, the NRG Cancer Prevention and Control Committee, and the NRG Cooperative Group GU Steering Committee. Additionally, she serves as Co-Chair for the Integrating the Healthcare Enterprise – Radiation Oncology (IHE-RO) Planning Committee and Vice-Chair for the ASTRO Clinical Translational Basic Science Advisory Committee.

In addition to her professional memberships, Dr. Koontz serves as Associate Senior Editor of the International Journal of Radiation Oncology, Biology, Physics. She also has served as a reviewer for a number of prominent academic journals, including European Urology, Journal of Sexual Medicine, Practical Radiation Oncology, Cancer and Prostatic Disease, the Journal of Urology, and Annals of Urology.

Learning Objectives

• Outline novel therapies for castrate-resistant prostate cancer (CRPC) that received approval in recent years

• Assess available treatment options appropriate to different settings based on symptoms, overall health, and risk-benefit ratios
Illustrative Case #1

- 70yo white male with prostate cancer:
  - October 2004 – cT2b G4+3 7/10, 50% to 75% cores, PSA 15 ng/mL
  - Metastatic workup: negative
- February 2005 – Combined brachytherapy (Pd103) and external beam radiation therapy (EBXRT [IMRT])
- 2005 through 2006 – GnRH agonist monotherapy
  - PSA decreases to <0.01 but rises 6 years later in the setting of normal testosterone levels to 2.6
  - Restaging scans are normal, no evidence of local recurrence or adenopathy, visceral or bony metastases
- August 2012 – Bicalutamide and leuprolide
  - PSA dropped <0.1 ng/mL
- Late 2012-early 2013 – PSA rise; rapid PSA doubling time (PSADT) = 3 months

NCCN Schema: M0 CRPC

- No level 1 evidence with survival data
- Improved response and PFS (PSA, radiographic) with enzalutamide over bicalutamide
- Unclear if early M0 vs standard M1 CRPC use of enzalutamide is more advantageous
- Ongoing phase 3 trials in M0 CRPC setting will address this, and trial enrollment is encouraged
Secondary hormonal manipulations (excluding abiraterone, enzalutamide)

- Median duration of PSA response
  - 3-6 months, but some respond for >1 year
- Objective responses uncommon

- STRIVE trial is first randomized trial to include M0 CRPC patients

---

**STRIVE: Enzalutamide vs. Bicalutamide**

- **Medians**
  - Enzalutamide: 5.7 months (95% CI: 5.6, 8.1)
  - Bicalutamide: 19.4 months (95% CI: 16.5, NR)

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

---

Similar results observed with TERRAIN in M1 CSPC (n=375):
- Median PFS 5.8 → 15.7 months with enzalutamide vs. bicalutamide (HR = 0.44; 95% CI, 0.34-0.57; $P < .0001$), time to FACT-P deterioration 8.5 → 13.8 months

---

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

---

*Penson D, Armstrong AJ et al, JCO 2016*
# Activity in M0 CRPC

<table>
<thead>
<tr>
<th>End Point</th>
<th>Enalatamide (n = 198)</th>
<th>Bicalutamide (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>19.4 (16.5 to NR)</td>
<td>5.7 (5.6 to 8.1)</td>
</tr>
<tr>
<td>Median time to PSA progression, months</td>
<td>19.4 (19.4 to NR)</td>
<td>8.3 (5.7 to 8.5)</td>
</tr>
<tr>
<td>PSA response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥ 1 postbaseline PSA assessment</td>
<td>157</td>
<td>156</td>
</tr>
<tr>
<td>Confirmed PSA decline ≥ 50% from baseline</td>
<td>156/152 (61)</td>
<td>61/156 (39)</td>
</tr>
<tr>
<td>Confirmed PSA decline ≥ 30% from baseline</td>
<td>198/198 (100)</td>
<td>198/198 (100)</td>
</tr>
<tr>
<td>Median, months</td>
<td>198</td>
<td>198</td>
</tr>
<tr>
<td>Nometastatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>NR (18.4 to NR)</td>
<td>8.9 (6 to 11.1)</td>
</tr>
<tr>
<td>Median time to PSA progression, months</td>
<td>NR (11.1 to NR)</td>
<td>11.1 (8.4 to 15.9)</td>
</tr>
<tr>
<td>PSA response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥ 1 postbaseline PSA assessment</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Confirmed PSA decline ≥ 50% from baseline</td>
<td>26/69 (38)</td>
<td>26/69 (38)</td>
</tr>
<tr>
<td>Confirmed PSA decline ≥ 30% from baseline</td>
<td>50/95 (52)</td>
<td>50/95 (52)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>NR (14.1 to NR)</td>
<td>NR (14.1 to NR)</td>
</tr>
</tbody>
</table>

Penson D, Armstrong AJ et al, JCO 2016

---

# Illustrative Case #1 (cont)

- Taken off antiandrogen but no withdrawal response
  - testosterone 25 ng/dL
- May 2013 – 11.2 ng/mL
- Imaging:
  - Bone scan: widespread osseous metastases
  - CT AP: no visceral involvement (subcentimeter pulmonary nodules and mesenteric nodes)
- Asymptomatic
Multiple Treatment Options Are Now Available for Men With Metastatic Prostate Cancer
Pattern of Spread is Important for Prognosis

Note: the expected survival of men with mCRPC and lung metastases is similar to that of men with mCRPC and bone metastases, while men with liver metastases have the poorest survival

Zoledronic Acid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Core plus Extension Phase</th>
<th>Zoledronic Acid, 4 mg (n = 214)</th>
<th>Placebo (n = 208)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 Skeletal-Related Event (%)</td>
<td>81 (38)</td>
<td>101 (49)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Median Time to First Skeletal-Related Event (Days)</td>
<td>488</td>
<td>321</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Mean Incidence of Skeletal-Related Events per Year</td>
<td>0.77</td>
<td>1.47</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Multiple-Event Analysis (Risk Ratio)</td>
<td>0.64</td>
<td>−</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>BPI Score (Mean Increase from Baseline)*</td>
<td>0.58</td>
<td>1.05</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Analgesic Score (Mean Increase from Baseline)*</td>
<td>1.04</td>
<td>1.17</td>
<td>0.491</td>
<td></td>
</tr>
</tbody>
</table>

Saad et al Clin GU Cancers 2005, JNCI 2004
Denosumab: RANKL mAb

Positive phase III data in solid tumors to prevent SREs

Phase 3 RCTs of Osteoclast-Targeted Therapy: Time to First Skeletal Related Event

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Phase 3 RCT of Denosumab versus Zoledronic Acid

**Overall Survival**

![Graph showing overall survival comparison between Denosumab and Zoledronic Acid]

**Time to Disease Progression**

![Graph showing time to disease progression comparison between Denosumab and Zoledronic Acid]

Fizazi et al. Lancet 2011

---

**Risk / Benefit Profile for Denosumab vs. Zoledronic Acid**

<table>
<thead>
<tr>
<th>Event</th>
<th>Zoledronic Acid (n=951)</th>
<th>Denosumab (n=950)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall safety summary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events occurring ≥10% frequency in either treatment group</td>
<td>144 (16%)</td>
<td>147 (16%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (1.4%)</td>
<td>15 (1.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Back pain</td>
<td>21 (2.2%)</td>
<td>35 (3.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (2.4%)</td>
<td>21 (2.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (2.3%)</td>
<td>26 (2.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>38 (4.0%)</td>
<td>38 (4.1%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (2.6%)</td>
<td>25 (2.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 (2.3%)</td>
<td>22 (2.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Acute phase reactions</td>
<td>28 (2.9%)</td>
<td>32 (3.4%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Acute phase reactions</td>
<td>28 (2.9%)</td>
<td>32 (3.4%)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Fizazi et al. Lancet 2011

---

**Acute phase reactions:** 18 vs. 8% favoring denosumab

**Renal impairment:** 15 vs. 16%
CALGB/ALLIANCE 90202: RCT of Early Versus Standard Zoledronic Acid

SRE-Free Survival

Overall Survival

SRE, skeletal-related event

Smith et al JCO 2014

STAMPEDE: Zoledronic Acid

Overall Survival

Failure-Free Survival

SOC, standard of care

James et al Proc ASCO 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
NCCN Guidance for Bone Anti-Resorptive Therapies

- Both zoledronic acid and denosumab are effective at delaying the time to skeletal related events (spinal cord compression, radiation, surgery to bone, pathologic fractures) in men with mCRPC
- **No known clinical activity in hormone-sensitive disease and not recommended in this setting regardless of bone metastases**
- These agents do not improve survival or delay progression-free survival
- Risk of osteonecrosis of the jaw (ONJ) increases over time and with more frequent dosing

Sipuleucel-T: Mechanism of Action

- Antigen (PAP-GMCSF) is exposed to an Antigen Presenting Cell (APC)
- APC takes up the antigen
- Antigen is processed and presented on surface of the APC
- Fully activated, the APC is now sipuleucel-T and is collected
- INFUSE PATIENT
- T-cells proliferate and attack cancer cells
- sipuleucel-T activates T-cells in the body
**IMPACT Overall Survival**

Survival (months)

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.

---

**IMPACT: Sipuleucel-T Trend Toward Greater Survival Benefit With Lower Baseline PSA**

<table>
<thead>
<tr>
<th>Baseline PSA, ng/mL</th>
<th>≤22.1 (n=128)</th>
<th>&gt;22.1-50.1 (n=128)</th>
<th>&gt;50.1-134.1 (n=128)</th>
<th>&gt;134.1 (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference</td>
<td>13.0</td>
<td>7.0</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.51</td>
<td>0.74</td>
<td>0.81</td>
<td>0.84</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.31-0.85)</td>
<td>(0.47-1.17)</td>
<td>(0.52-1.24)</td>
<td>(0.55-1.29)</td>
</tr>
</tbody>
</table>

- Earlier use of sipuleucel-T prior to abiraterone/rozalutamide is preferred, given lack of short term benefits on PSA, disease control and possible improved survival impact earlier in the disease course

---

Kantoff et al NEJM 2010

Schellhammer et al Urology 2013
Sipuleucel-T

- FDA Approved April 2010
- Toxicities are mild, infusion related: fever, chills
- Slightly higher risk of spinal cord compression in men treated with sipuleucel-T, thus consideration of spinal imaging (MRI) in men with higher volume spinal disease
- Ideally used early with lower volume disease or before numerous other therapies
- No impact on PSA or radiographic response, PFS
- NCCN category 1 recommendation if asymptomatic to minimally symptomatic (no opiates for cancer pain), no liver metastases, life expectancy >6 mo, ECOG 0-1

Illustrative Case #1 (cont)

- Immunotherapy:
  - June 2013 – Sipuleucel-T x 3 infusions
    - Leuprolide continued
    - Denosumab q4weeks

- Surveillance post-sipuleucel-T:
  - July 2014 – Bone scan: progression of osseous metastatic disease
  - CT a/p: Unchanged subcentimeter pulmonary nodules and mesenteric nodes
  - PSA 114 ng/mL, testosterone 15 ng/dL
  - LDH 261, Alk phos 264, Hgb 13.1, LFTs NL
  - Remains minimally symptomatic

- Discussion point:
  - Options and timing for next systemic therapy in mCRPC—abiraterone/encealutamide vs docetaxel vs radium-223 vs clinical trials
**Enzalutamide:** Second Generation Androgen Receptor Inhibitor

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding

**PREVAIL: Chemo-Naïve CRPC**

- **Overall survival**
- **rPFS**

*N=1717, randomized 1:1 Enzalutamide vs placebo*

- All subgroups benefited
- rPFS 3.9→NYR (15–19 mo)
- PSA PFS 2.8→11.2 months
- OS updated 2015 35.3 vs. 31.3 months (HR 0.77 p=0.002)
- PSA 50/90% or greater decline in 78/47%
- RECIST responses in 59%
- Time to chemo: 28 vs. 10.8 months
- QOL responses in 40 vs. 23%, TTQOL decline 11.3 vs. 5.6 mo

Beer, Armstrong et al NEJM 2014
Activity of Enzalutamide in Men with mCRPC Based on Pattern of Spread

Chemo-Naïve Enzalutamide Risks

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Enzalutamide (N=871)</th>
<th>Placebo (N=864)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>170 (19)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>235 (27)</td>
<td>22 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>189 (22)</td>
<td>4 (0-7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>177 (20)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>356 (41)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>177 (20)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Itch</td>
<td>147 (17)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>177 (20)</td>
<td>5 (0-7)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>11 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fat</td>
<td>190 (22)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>200 (23)</td>
<td>5 (0-3)</td>
</tr>
<tr>
<td>Edema of peripheral structures</td>
<td>91 (11)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>Headache</td>
<td>91 (11)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>Specific adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiac adverse event</td>
<td>84 (10)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (2)</td>
<td>3 (0-3)</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>7 (0)</td>
<td>7 (0-3)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>32 (4)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Ischemic or hemorrhagic cerebrovascular event</td>
<td>12 (1)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Ectopic or placental membrane tumor</td>
<td>1 (0)</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td>Urine</td>
<td>16 (2)</td>
<td>3 (0-10)</td>
</tr>
</tbody>
</table>

Beer, Armstrong et al NEJM 2014
Abiraterone Acetate + Prednisone

![Chemical diagram showing the conversion of various steroids through the action of various enzymes such as CYP17, 17α-hydroxylase, and 11β-Hydroxylase.]

**Abiraterone Acetate**

- Superiority over prednisone demonstrated post-docetaxel and in chemo-naïve men with mCRPC
- Dose is 1000 mg daily without food plus prednisone 5 mg bid
- Improved OS accompanied by improvements in QOL, pain, PFS, response rates, and fewer adverse events than placebo
- Prevention of pain, performance status deterioration, need for chemotherapy improved pre-docetaxel
- Abiraterone acetate with prednisone is now FDA approved for men with metastatic CRPC prior to docetaxel

**OS** 30.2 → 34.7 months
**HR** 0.81 *p*=0.0033

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
# Abiraterone acetate side effects

<table>
<thead>
<tr>
<th>Abiraterone acetate group (n=542)</th>
<th>Placebo group (n=540)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1-2</td>
<td>Grades 3-5</td>
</tr>
<tr>
<td>Fluid retention/electrolytes</td>
<td>Fluid retention/electrolytes</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>ALT increased</td>
<td>ALT increased</td>
</tr>
<tr>
<td>AST increased</td>
<td>AST increased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Data are n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase. *Before crossover.

Ryan et al, Lancet Oncol 2015

# Abiraterone vs. Enzalutamide in Chemotherapy Naïve Men with mCRPC

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone Acetate</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires prednisone</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>May cause mineralocorticoid excess</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Evaluated in visceral disease</td>
<td>Y (post-chemo only)</td>
<td>Y (pre/post chemo)</td>
</tr>
<tr>
<td>Major side effects</td>
<td>Hypertension, hypokalemia, LFTs, edema, some cardiac, fatigue, hot flush</td>
<td>Hypertension, rare seizures (&lt;0.2%), some cardiac, fatigue, falls (19%), hot flush</td>
</tr>
<tr>
<td>Grade 3-4 AE Risk (%)</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>PSA response rate (&gt;50%)</td>
<td>62%</td>
<td>78%</td>
</tr>
<tr>
<td>Radiographic response rate</td>
<td>36%</td>
<td>59%</td>
</tr>
<tr>
<td>rPFS</td>
<td>16.5 months</td>
<td>15-18 months</td>
</tr>
<tr>
<td>OS</td>
<td>34.7 months</td>
<td>35.3 months</td>
</tr>
<tr>
<td>Time to chemotherapy</td>
<td>25 months</td>
<td>28 months</td>
</tr>
</tbody>
</table>

Zhang, Armstrong et al, Exp Opin Pharmacother 2015
Timing and Selection of Secondary Androgen Receptor (AR)-Directed Therapies

• Choice of abiraterone vs. enzalutamide cannot be dictated based on differences in efficacy
  – Similar OS, PFS from cross-trial comparisons
  – Enzalutamide has been evaluated in men with visceral metastases in the chemo-naïve setting
  – Both considered category 1 recommendations in NCCN guidelines

• Therefore choice is based on differential toxicity
  – Abiraterone acetate for seizure-prone men and those more frail elderly (>75y) men at high risk for falls
  – Enzalutamide for men with significant CV risk factors, contraindications to prednisone, brittle diabetes and metabolic syndrome, contraindications to prednisone

Practical Aspects of Enzalutamide Use

• NCCN category 1 recommendation in 2016 in the mCRPC setting regardless of prior docetaxel, pattern of spread, symptoms
• Prescription is for 4 40-mg capsules taken once daily, with or without food
• I recommend home BP monitoring given the 7% risk of severe HTN with enzalutamide (160/100) of unclear cause
• Exercise encouraged to reduce fall risk
• No driving restrictions given rare seizure risk but important to avoid enzalutamide in patients with a prior history of seizures or epilepsy or those men at very high risk of seizures (brain tumors, prior major strokes, CNS metastases, taking concurrent medications that lower the seizure threshold)
Practical Aspects of Abiraterone Acetate with Prednisone Use

• NCCN category 1 recommendation in 2016 in the mCRPC setting regardless of prior docetaxel, symptoms
• Prescription is for 4 500-mg tablets taken once daily, 1 hour prior to food intake or 2 hours after food (water OK)
  – Taking with food increases bioavailability substantially, may increase toxicity
• I recommend home BP monitoring given the 5-10% risk of severe HTN with abiraterone (160/100) due to mineralocorticoid excess
  – Eplerenone may reverse this (mineralocorticoid antagonist)
• Exercise encouraged to reduce fall risk, fatigue
• Liver function and electrolyte, renal monitoring every 6 weeks initially, then every 12 weeks
  – Treatment of fluid retention, hypokalemia is common
• Pre-treatment cardiac evaluation reasonable in patients with significant underlying congestive heart failure (CHF), coronary artery disease (CAD), or arrhythmias

Practical Aspects of Abiraterone/Enzalutamide Use: Follow-up

• I check PSA at 6 weeks and then every 12 weeks and perform CT, bone scans every 12 weeks
• Radiographic progression typically follows PSA progression, but occasionally radiographic progression can be observed first
• Bone scan progression can be misclassified due to healing response, so confirmation of additional new lesions over time is needed before declaring progression based on bone scan alone
• CT remains important to document soft tissue/visceral metastases which can develop over time
• I do not stop abiraterone/enzalutamide for PSA-only progression because there is clear clinical benefit of these agents for multiple other disease manifestations (pain, QOL, radiologic)
Bone Scans in CRPC

1. Difficult to interpret
2. Images osteoblast activity
3. Healing may appear more intense!
4. New lesions are best measures of progression vs. flare (within clinical context)
5. Confirmation scans showing continued additional new lesions required—flare is common (40% with abiraterone/enzalutamide!)
6. Prostate Cancer Working Group 2 Guidelines are new criteria for determining progression
7. Often will be performed on site and centrally along with clinical read
8. Thus, misclassification of progression is common!

Cross-Resistance in the Clinic

- **Enzalutamide after abiraterone**
  can result in PSA responses (>50% decline) but this was observed in <1/3 of men in the post-docetaxel CRPC setting with a short TTP of 4 months and rare radiographic responses
- Similar for abiraterone after enzalutamide and in pre-docetaxel setting
- Response to enzalutamide was **not** possible to predict based on prior response to abiraterone
Abiraterone Acetate

Androgen and Androgen Synthesis →

Enzalutamide

Progesterone

AR F876L
AR H875Y, L702H, T878A

Dimerization

Nuclear Translocation

Enzalutamide

Nucleus

DNA binding

Cryptic exon

AR-variants (i.e. AR-v7)

N

AR

N

AR

C

C

C

C

Survival PSA secretion Proliferation Invasion Metastasis

Taxane Chemotherapy

Microtubule binding

Others:
NF-κB, PI3K pathways
Epithelial Plasticity/Stemness

Zhang, Armstrong Exp Opin Pharmacother 2015

Limitation: not yet externally validated in a multicenter trial
Antonarakis et al NEJM September 2014

AR-v7 and Cross-Resistance

Measured through a circulating tumor cell (CTC) assay and an AR-v7 rt-PCR based probe

Enzalutamide-Treated Patients

Abiraterone-Treated Patients

AR-v7 positive

AR-v7 negative

Base PSA Response (%) change

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
AR-v7 and Cross-Resistance

Note: CTC AR-V7 test has not yet been externally validated and thus remains a research biomarker at this time (ongoing studies)

HR, 6-16!
Associated with prediction of poor OS or clinical benefit

Illustrative Case #2

- 69yo male with prostate cancer:
  - cT2b G9 PSA 2.4 ng/mL
  - Metastatic workup: negative
- RP: pT3a GS4+3, tertiary 5, R1
- Adjuvant XRT
- One year later, PSA rise from 0.1→9→44
- Restaging scans:
  - CT/BS shows multiple bone mets and bulky RP nodes up to 7.7cm
- ADT + docetaxel initiated

Antonarakis et al NEJM September 2014
Images

Illustrative Case #2 (cont)

- Restaging after docetaxel induction chemotherapy/ADT reveals resolution of adenopathy, persistent bone metastases, PSA is 2.0
- Within 12 months, PSA rises to 14 and diffuse bone pain develops. Staging confirms additional new bone lesions in axial spine, no visceral/nodal metastases
- Patient is treated with enzalutamide and responds but progresses within 6 months
How to treat Men with mCRPC who progress following docetaxel?

SUBSEQUENT SYSTEMIC THERAPY FOR M1 CRPC

- Docetaxel with prednisone (category 1)
- Abiraterone with prednisone
- Enzalutamide
- Radium-223 for symptomatic bone metastases (category 1)
- Spinal cord, T1 if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0-1

No visceral metastases

- Enzalutamide (category 1)
- Abiraterone with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)
- Cabazitaxel with prednisone (category 1)
- Clinical trial

Prior therapy docetaxel

- Docetaxel and cabazitaxel
- Alternative chemotherapy (mitoxantrone with prednisone)
- Other secondary hormone therapy
- Antiandrogen
- Antiandrogen withdrawal
- Ketychoenolase a hydrocoritzone
- Corticosteroids
- DES or other estrogen
- Best supportive care

Range of α-emitting Radiopharmaceutical Compared with β-emitter

Short range of α-particles reduces bone marrow exposure

Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium

**Unfit for docetaxel** includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.

**Best standard of care** defined as a routine standard of care at each center, eg, local external-beam radiotherapy, corticosteroids, antiandrogens, estrogens (e.g., diethylstilbestrol or estramustine), or ketoconazole.

**Primary endpoint:** overall survival

Radium (Ra 223 dichloride) prescribing information, 2013.

**PARKER ET AL NEJM 2013**

**NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST) UPDATE 2016**
**ALSYMPCA Updated Analysis: OS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Radium-223 (n = 614)</th>
<th>Placebo (n = 307)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>14.9</td>
<td>11.3</td>
<td>0.70 (0.58–0.83)</td>
</tr>
<tr>
<td>Total ALP level at baseline</td>
<td>0.70</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;220 U/liter</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥220 U/liter</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Current high phosphonate use</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Previous discontinued use</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Previous discontinued use</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG performance status score</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;6 metastases</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥6 metastases</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Supravisceral</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**Median Δ: 3.6 months**

**30% reduction in risk of death**

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Radium-223 Updated Analysis
Adverse Events (AEs) of Interest

<table>
<thead>
<tr>
<th>Patients with AEs</th>
<th>Radium-223 (n = 600)</th>
<th>Placebo (n = 301)</th>
<th>Radium-223 (n = 600)</th>
<th>Placebo (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>122 (31)</td>
<td>77 (13)</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
<td>13 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>17 (6)</td>
<td>38 (6)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
<td>125 (21)</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>45 (15)</td>
<td>9 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>104 (35)</td>
<td>13 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (19)</td>
<td>41 (14)</td>
<td>10 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
<td>6 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

The safety of taxane chemotherapy following radium-223 has not been well characterized

Radium-223 and Prior Docetaxel Use

Hoskin et al Lancet Oncol 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Subgroup Analysis of Hazard Ratios for Death in the Two Study Groups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ALP level at baseline</td>
<td>No differences in hazard ratios for death between Radium-223 and Placebo groups.</td>
<td></td>
</tr>
<tr>
<td>Baseline ECGG performance-status score</td>
<td>No differences in hazard ratios for death between Radium-223 and Placebo groups.</td>
<td></td>
</tr>
<tr>
<td>Intent of disease</td>
<td>No differences in hazard ratios for death between Radium-223 and Placebo groups.</td>
<td></td>
</tr>
<tr>
<td>Opioid use</td>
<td>No differences in hazard ratios for death between Radium-223 and Placebo groups.</td>
<td></td>
</tr>
</tbody>
</table>

Radium-223: Summary

Administration:
- Once every 4 weeks for 6 months
- 60 second IV infusion
- Given by radiation oncologist or nuclear medicine radiologist
- Enteric excretion
- No pre-medication, no post-medication
- CBC check before each treatment

Clinical Benefit:
- Primary endpoint of improvement in symptomatic SRE
- 3.6 month benefit in OS
- Perhaps greater in men with high alkaline phosphatase
- Should be considered in symptomatic men with bone-predominant mCRPC
- Consider spinal imaging for epidural disease in men with high burden of disease and rapid progression; palliative EBXRT should be used if high risk for spinal cord compression
- No head to head data vs. docetaxel yet, and optimal timing/sequencing/combinations with hormonal therapies and chemotherapy is currently being established
NCCN Guidelines

- Radium-223 recommended for men with symptomatic bone-predominant mCRPC
- Can be used before or after docetaxel given similar survival benefit
- Patients should be followed carefully for bone marrow toxicity prior to dosing and over time
- Concurrent use of hormonal therapies, external beam palliative radiation, steroids are reasonable given the lack of drug interactions and safety, palliative goals

NCCN Summary Recommendations: M1 CRPC

<table>
<thead>
<tr>
<th>Drug</th>
<th>NO VISCERAL METASTASES</th>
<th>WITH VISCERAL METASTASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone with prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel with prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole + hydrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone with prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radium-223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>