Advanced Prostate Cancer: Role of Clinical Trials

Dr. Pawel Zalewski, Medical Oncologist, CERCP
Faculty/Presenter Disclosure

Faculty/Presenter: **Dr. Pawel Zalewski**

Relationship with commercial interests:

- Grants/Research Supports:
- Speaker bureau/Honoraria:
- Consulting Fees:
- Clinical trials: Participates in trials sponsored by various pharmaceutical companies without receiving direct payment
The DRCC Research Program: Historical & Current Activity

- Oncology Clinical Trials Unit formed in mid 1990s with a focus on breast, CRC, and lung
- 1st Clinical Trial conducted in 1994 (NCIC MA.12):
  - Double-blind randomized trial of Tamoxifen vs. PLA in patients with node + or high risk node – Bca
- Over the last decade clinical trials have been extended to all cancer types within Medical & Radiation Oncology
- From 1994 until present, 255 studies have been conducted
- Currently 57 active clinical trials (prostate, breast, lung, GI, GU, melanoma, hematology, radiation)
DRCC Research Team

- 2 Clinical Trials Medical Leads & 25+ Investigators who conduct clinical trials in medical and radiation oncology
- Research Director & Oncology Research Coordinator
- RNs, RPNs, Radiation Coordinator
- Ethics Associate, Admin Assistant & Clinical Research Assistant
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Target</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogenesis</td>
<td>PDGF receptor</td>
<td>Olaratumab</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Tasquinimod</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Aflibercept</td>
</tr>
<tr>
<td></td>
<td>VEGF receptor</td>
<td>Ramucirumab</td>
</tr>
<tr>
<td>Androgen signaling</td>
<td>Androgen receptor</td>
<td>ARN-509, <strong>Enzalutamide</strong></td>
</tr>
<tr>
<td></td>
<td>CYP17</td>
<td><strong>Abiraterone</strong>, Orteronel</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>BCL-2</td>
<td>AT-101</td>
</tr>
<tr>
<td></td>
<td>Clusterin, MDM2</td>
<td>Custirsen, MI-773</td>
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<tr>
<td>Cell cycle*</td>
<td>Microtubules</td>
<td>Docetaxel, Cabazitaxel, Eribulin</td>
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<tr>
<td>DNA repair</td>
<td>PARP</td>
<td>Veliparib</td>
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<tr>
<td>Bone*</td>
<td>Osteoclast, RANKL</td>
<td>Radium-223, Zoledronic Acid, Denosumab, EMD 525797</td>
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<tr>
<td></td>
<td>Integrins</td>
<td></td>
</tr>
<tr>
<td>Immune modulation*</td>
<td>Vaccine, CTLA-4</td>
<td>Sipuleucel-T, Ipilimumab</td>
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<tr>
<td></td>
<td>Multiple</td>
<td>Lenalidomide</td>
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<tr>
<td>Other Pathways</td>
<td>HSP27, IGF-1R, Src MET +/-VEGFR2</td>
<td>OGX-427, Cixutumumab Cabozantinib, LY2875358 PAM4983g</td>
</tr>
</tbody>
</table>
Metastatic Castration-Resistant Prostate Cancer: 13 Positive Trials → 12 FDA Approvals Since 1996

- **Survival Improvement**
  - Docetaxel
  - Sipuleucel-T
  - Cabazitaxel
  - Abiraterone X 2
  - Enzalutamide X 1
  - Radium-223

- **Pain**
  - *Mitoxantrone, Strontium, Samarium*

- **Skeletal-related events**
  - *Zoledronic acid, Denosumab*
Docetaxel + Prednisone or Mitoxantrone + Prednisone for Castration-Resistant Prostate Cancer

Overall Survival

No at Risk
Docetaxel every 3 wk
Wkly docetaxel
Mitoxantrone

335 296 217 104 37 5
334 297 200 105 29 4
337 297 192 95 29 3

No at Risk
Docetaxel + estramustine
Mitoxantrone + prednisone

338 218 60 13
185 50 10

P = .02

Docetaxel + estramustine (217 deaths; median: 17.5 months)
Mitoxantrone + prednisone (235 deaths; median: 15.6 months)

Post Docetaxel: Cabazitaxel/Prednisone vs Mitoxantrone/Prednisone

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
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</thead>
<tbody>
<tr>
<td>Median OS (mos)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59-0.83</td>
<td></td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
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</table>

Combined median follow-up: 13.7 months

Pre Docetaxel: Sipuleucel-T vs Placebo

Overall Survival

Median Survival
25.8 m vs 21.7 m

Table:

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T (n = 341)</th>
<th>Placebo (n = 171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>25.8 ms</td>
<td>21.7 ms</td>
<td>.032</td>
</tr>
<tr>
<td>Time to Progression</td>
<td>3.7 ms</td>
<td>3.6 ms</td>
<td>.630</td>
</tr>
<tr>
<td>≥50% PSA Reduction</td>
<td>2.6%</td>
<td>1.3%</td>
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</tbody>
</table>

Progression to Castration Resistance

Progression to castration resistance is an adaptive process secondary to AD via androgen receptor (AR)-dependent & independent mechanisms.

- Androgen receptor
  - Gene amplification
  - Mutations
- Alteration in survival pathways bypassing AR

Progression to Castration Resistance

“Castration Resistant” vs “Hormone Refractory”
AR Signaling Still Matters
**AR Signalling Still Matters**

**Abiraterone/Prednisone & Enzalutamide: Overall Survival Post-Docetaxel**

**Overall Survival**

- **Abiraterone acetate**
  - No at risk: 797
  - Months: 100 - 0
- **Placebo**
  - No at risk: 398
  - Months: 100 - 0

Hazard ratio, 0.63 (95% CI, 0.53-0.75) \( P < .001 \)

**Time to PSA Progression**

- **Abiraterone acetate**
  - No at risk: 797
  - Months: 100 - 0
- **Placebo**
  - No at risk: 398
  - Months: 100 - 0

Hazard ratio, 0.25 (95% CI, 0.20-0.30) \( P < .001 \)

**Radiographic Progression-Free Survival**

- **Abiraterone acetate**
  - No at risk: 797
  - Months: 100 - 0
- **Placebo**
  - No at risk: 398
  - Months: 100 - 0

Hazard ratio, 0.40 (95% CI, 0.35-0.47) \( P < .001 \)

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A Phase III Trial of Enzalutamide After Progression on Androgen Deprivation Therapy in Men With Metastatic Prostate Cancer

Hazard Ratio: 0.706 (95% CI: 0.60, 0.84) \( P < .0001 \)

Patients still alive at data cut off
Enzalutamide: 72%; Placebo: 63%

Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

Bone Metastases: The Hallmark of Metastatic Prostate Cancer

Tumor-Bone Cell Interactions

Prostate Cancer cells

Bone-derived growth factors

Osteolytic factors e.g., PTHrP

Osteoblastic factors e.g., ET-1

Growth factors

Osteoclasts

Osteoblasts

Mineralized bone matrix

New bone

Osteoblast maturation
Radium-223 (a targeted alpha emitter): Bone-seeking calcium mimetic, which selectively binds to areas of increased bone turnover in bone metastases (newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases)

So Are We There Yet?

**Good news:** “Embarrassment of riches”

**Glarling deficiency:**
- **Impact on survival in mCRPC is modest** (2-5 months)
  - All non-chemo agents tested against placebo
- **We still use a “one size fits all” treatment approach**
  (No predictive biomarkers & no personalized therapeutics)

**Opportunities:**
- How to maximize therapeutic efficacy
- How to best sequence/combine current approved agents
  - Who will fund such trials?
- Where/How best to develop new agents/combinations
- Need more focus on hormone-sensitive metastatic PCa
- How to control escalating costs
“Price is what you pay. Value is what you get”
(W. Buffett)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>AWS Cost per cycle - Drug Only</th>
<th># of Cycles</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Docetaxel</td>
<td>150 mg IV (75 mg/m² x 2 m²)</td>
<td>$2921.20</td>
<td>Median: 6</td>
<td>Yes</td>
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<tr>
<td>Cabazitaxel</td>
<td>50 mg IV (25 mg/m² x 2 m²)</td>
<td>$8408.08</td>
<td>Median: 6</td>
<td>Yes</td>
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<tr>
<td>Abiraterone</td>
<td>1000 mg PO (30-day)</td>
<td>$8203.91</td>
<td>Median 8 ms</td>
<td>Yes</td>
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<tr>
<td>Enzalutamide</td>
<td>160 mg PO (30-day)</td>
<td>$9467.46</td>
<td>Median 8 ms</td>
<td>Yes</td>
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<tr>
<td>Sipuleucel-T</td>
<td>IV</td>
<td>$37,200</td>
<td>3 cycles</td>
<td>Yes</td>
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<tr>
<td>Radium-223</td>
<td>IV</td>
<td>$28,173</td>
<td>6 cycles</td>
<td>Yes</td>
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<tr>
<td>Denosumab</td>
<td>120 mg SC</td>
<td>$2017.68</td>
<td>Monthly</td>
<td>No</td>
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<tr>
<td>Zoledronic Acid</td>
<td>4 mg IV</td>
<td>$360 (generic) - $1196.56</td>
<td>Monthly</td>
<td>No</td>
</tr>
</tbody>
</table>
Too Many Negative Phase III Trials

- Allogeneic prostate cancer cell-line vaccine X 2
- Satraplatin
- Docetaxel + DN101
- TAK700 X 2
- Ipilimumab
- Custirsen

Bone
- Docetaxel +/- dasatinib
- Atrasentan X 2
- Docetaxel +/- atrasentan
- Zibotentan

VEGF/Angiogenesis
- Docetaxel +/- bevacizumab
- Docetaxel +/- aflibercept
- Docetaxel +/- lenalidomide
- Sunitinib

Importance of the Biological Context
Targeting ETS Fusions
NCI9012: Randomized ETS Gene Fusions Stratified Trial of Abiraterone +/- ABT888 for Patients With mCRPC

Registration

Metastatic tissue biopsy adequate for ETS fusion status evaluation

Stratification

ETS fusion-positive (~50% of cases)

Abiraterone

ETS fusion-negative (~50% of cases)

Abiraterone + PARP1 inhibitor

Metastatic tissue biopsy inadequate for ETS fusion status evaluation

Off Protocol

Abiraterone

Abiraterone + PARP1 inhibitor

Multicenter (12 Centers)

Funding: CTEP Sponsored, DoD PC080189, N01 Early Therapeutic Development, PCF, SU2C
Ongoing Phase III Trials in Advanced Prostate Cancer

- **Hormone Sensitive**
  - *SWOG1216: ADT +/- Orteronel*

- **Nonmetastatic CRPC**
  - *Enzalutamide, ARN-509*

- **Metastatic CRPC**

<table>
<thead>
<tr>
<th>Chemotherapy-Naive</th>
<th>First-Line Chemotherapy</th>
<th>Post-Docetaxel</th>
</tr>
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<tbody>
<tr>
<td>• Tasquinimod</td>
<td>• Docetaxel/Prednisone +/- Zibotentan</td>
<td>• Cabozantinib vs Mitoxantrone</td>
</tr>
<tr>
<td>• Ipitilumab</td>
<td>• Docetaxel vs Cabazitaxel</td>
<td>• Cabazitaxel +/- Custirsen</td>
</tr>
<tr>
<td>• Abiraterone +/- Radium</td>
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<td></td>
</tr>
</tbody>
</table>
Metastatic Hormone-Sensitive Prostate Cancer: Standards in 2014

1. Continuous androgen deprivation therapy (ADT) is the standard based on optimal survival outcomes
   • Patients interested in intermittent ADT should be counseled regarding potential negative impact on survival and modest impact on QoL

2. Patients with new high-volume M1 prostate cancer should be offered combination ADT + docetaxel

3. Patients should be offered access to clinical trials
Metastatic Castration Resistant Prostate Cancer: Standards in 2014

- Symptoms
- Performance status & comorbidities
- Sites/extent of metastatic disease
- Prior therapy and quality of response & tolerance
- Cost/logistics
- Patient preferences
mCRPC: Standards in 2014

mCRPC Progressing on Hormonal Therapy

- Clinical Trial

mCRPC Progressing on Docetaxel/Prednisone

- Sipuleucel-T
- Enzalutamide
- Abiraterone/Prednisone
- Docetaxel/Prednisone
- Radium-223
- Cabazitaxel/Prednisone
- Mitoxantrone
Clinical Scenario 3
How I Would Treat This Patient

• 75-year-old man with known bone metastases from prostate cancer
• Coronary artery bypass graft 8 years ago
  - No cardiac symptoms
• 3-year remission on ADT
• PSA slowly rising for past 6 months
• Pain-free until 4 weeks ago
  - Left hip pain relieved by NSAIDs
• PSA doubling time 8 months
• Bone scan shows multiple pelvic and spinal metastases
• CT - no visceral disease
• Renal, hepatic, and bone marrow function normal
Clinical Scenario 3
How I Would Treat This Patient

- Received 7 cycles of docetaxel
  - Discontinued following two neutropenic septic episodes
- 9 months later disease progressing
  - Received palliative radiotherapy to spine
  - Commenced abiraterone
  - Changed from zoledronic acid to denosumab
- 8 months later has further symptomatic progression
  - Widespread bone involvement
  - No visceral metastases
Questions About Clinical Trials