Improving Treatment Strategies in the Management of Castrate-Resistant Prostate Cancer

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Genmab, Exelixis, GE
Prostate Cancer Disease States

- Clinically Localized Disease
- Rising PSA
- Clinical Metastatic Castrate
- Non Metastatic Rising PSA – Castrate
- Clinical Metastatic Castrate prechemo
- Clinical Metastatic Castrate Post chemo
- Death from other causes
- Death of Disease

Approximately 1/3 of patients will develop PSA-only recurrence following primary therapy.

Metastatic Prostate Cancer
The Lethal Phenotype

29,720 estimated deaths in 2013
Metastatic Prostate Cancer
The Lethal Phenotype

- Hormone dependent disease
- Treatment strategies tested over the past 7 decades:
  - Surgical vs medical castration
  - Combined androgen deprivation (AD) vs monotherapy
  - Gonadal suppression vs peripheral blockade
  - LHRH-agonists vs Antagonist
  - Intermittent AD vs Continuous AD
  - AD +/- chemotherapy

- Despite a high response rate most patients will progress to castration resistance.
- The median survival is about 4 years

Mechanisms of Castration Resistance

Clonal selection:
- Nobel 1977\(^1\);
- Isaacs & Coffey 1981\(^2\)

Molecular adaptation:\(^3\)
- Androgen receptor
  - Gene amplification
  - Mutations
- Alteration in survival pathways bypassing AR

1. Nobel RL. Hormonal control of growth and progression tumors of NB rates and theory of action. 1977
2. Isaacs J, Coffey D. Cancer Res 1981
**Castration Resistant Prostate Cancer**

**Plethora of Targets and Agents**

### Pathway | Target | Agents
--- | --- | ---
Angiogenesis | PDGF receptor | Olaratumab
Unknown | Tasquinimod
VEGF | Aflibercept
VEGF receptor | Ramucirumab

Androgen signaling * | Androgen receptor | ARN-509, MDV3100
CYP17 | Abiraterone, Orteronel

Apoptosis | BCL-2 | AT-101
Clusterin, MDM2 | Custirsen, MI-773

Cell Cycle * | Microtubules | Eribulin, Taxanes

DNA repair | PARP | Veliparib

Bone * | Osteoclast, RANKL, Integrins | Radium 223, Zoledronic acid, Denosumab, EMD 525797

Immune modulation * | Vaccine, CTLA-4 | Sipuleucel-T, Ipilimumab
Multiple | Lenalidomide

Other Pathways | HSP27, IGF-1R, Src, MET +/-VEGFR2 | OGX-427, Cixutumumab, Dasatinib, Cabozantinib, LY2875358

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**Metastatic Castration Resistant Prostate Cancer**

- **13 positive trials, 12 FDA approvals since 1996**

  - **Survival Improvement (2 – 5 months)**
    - Docetaxel
    - Sipuleucel-T
    - Cabazitaxel
    - Abiraterone
    - Enzalutamide*
    - Radium-223

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

  - **Skeletal related events**
    - Zoledronic acid, Denusomab
Docetaxel + Prednisone or Mitoxantrone + Prednisone for Castration Resistant Prostate Cancer: Overall Survival

Pre Docetaxel: Sipuleucel-T vs. Placebo Overall Survival

<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 mos</td>
<td>21.7 mos</td>
<td>0.032</td>
</tr>
<tr>
<td>Time to Progression</td>
<td>3.7 mos</td>
<td>3.6 mos</td>
<td>0.630</td>
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<tr>
<td>≥ 50% PSA Reduction</td>
<td>2.6%</td>
<td>1.3%</td>
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</table>
Post Docetaxel: Cabazitaxel/Prednisone vs Mitoxantrone/Prednisone

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</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>
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</table>

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
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<tbody>
<tr>
<td>377</td>
<td>289</td>
<td>195</td>
</tr>
<tr>
<td>185</td>
<td>94</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>19</td>
</tr>
</tbody>
</table>

de Bono, et al. Lancet 2010; 376: 1147

“Castration Resistant” vs “Hormone Refractory”

“AR Signalling Still Matters”

Steroid Hormone Synthesis Pathway

"AR Signalling Still Matters"

**Abiraterone/prednisone: Post-Docetaxel Overall Survival**

- **Abiraterone acetate:**
  - **Overall Survival:** HR = 0.65 (0.54-0.77) \( P < 0.0001 \)
  - Survival: 14.8 months (95%CI: 14.1, 15.4)

- **Placebo:**
  - Survival: 10.9 months (95%CI: 10.2, 12.0)

2 Prior Chemo OS:
- Abiraterone: 14.0 mos AA vs 10.3 mos placebo
- Placebo: 15.4 mos AA vs 11.5 mos placebo

de Bono, et al. NEJM 2011; 364: 2055

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**Enzalutamide: Post-Docetaxel Overall Survival**

- **Overall Survival**
  - Hazard ratio: 0.63 (95% CI: 0.53-0.75) \( P=0.001 \)

- **Time to PSA Progression**
  - Hazard ratio: 0.26 (95% CI: 0.20-0.35) \( P<0.001 \)

- **Radiographic Progression-Free Survival**
  - Hazard ratio: 0.40 (95% CI: 0.35-0.47) \( P<0.001 \)

Scher et al: NEJM 2012
Abiraterone/prednisone: Pre-Docetaxel Radiographic Progression-free Survival & Overall Survival

A  Radiographic Progression-free Survival

B  Overall Survival


Bone: The Hallmark of Metastatic Prostate Cancer
Clinical Manifestations of Bone Metastasis

Pain, cord compression, fractures, myelothesis, constitutional symptoms

- Radiation to bone
- Pathologic fracture
- Spinal cord compression
- Surgery to bone
- Change in antineoplastic therapy

Skeletal related events (SRE)

A randomized, Placebo-Controlled Trial of Zoledronic acid in metastatic CRPC

SRE: ZA: 38% vs P: 49% (P = .028)

Denosumab vs Zoledronic Acid

Time to first on-study skeletal-related event

Fizazi K et al. The Lancet 2011

Radium-223: Overall Survival and Time to First Symptomatic Skeletal Event in mCRPC

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)

Parker C et al. NEJM 2013
Targeting the BONE alone is “NOT Enough”

Bone is NOT the only site of disease

- Lung/Liver: 19% vs. 22%
- Nodes: 24% vs. 18%
- Bone: 88% vs. 93%

mCRPC: Standards in 2013

mCRPC Progressing on Hormonal Therapy

Clinical Considerations:
- Performance status
- Symptoms
- Extent of metastatic disease
- Co-morbidities
- Patient preferences
- Cost/Logistics

- Clinical Trial
- Abiraterone/Prednisone
- Sipuleucel-T
- Docetaxel/Prednisone
- Alpharadin

mCRPC Progressing on Docetaxel/Prednisone

- Clinical Trial
- Abiraterone/Prednisone
- Enzalutamide
- Cabazitaxel/Prednisone
- Mitoxantrone
### Pending Phase III Trials

<table>
<thead>
<tr>
<th>Chemotherapy-Naïve</th>
<th>First-Line Chemotherapy</th>
<th>Post-Docetaxel</th>
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<tbody>
<tr>
<td>• MDV3100</td>
<td>• Docetaxel/Prednisone +/- Zibotentan</td>
<td>• TAK-700/Pred</td>
</tr>
<tr>
<td>• TAK-700/Pred</td>
<td>• Docetaxel/Prednisone +/- Custirsen</td>
<td>• Ipilimumab</td>
</tr>
<tr>
<td></td>
<td>• Docetaxel vs Cabazitaxel</td>
<td>• Cabozantinib vs Mitoxantrone</td>
</tr>
<tr>
<td>• Ipilimumab</td>
<td></td>
<td></td>
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<tr>
<td>• Tasquinimod</td>
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### So Are We There Yet?

- **Good news:** “Embarrassment of riches”
- **The glaring deficiency:**
  - Impact on survival is relatively modest
  - *All new agents tested against placebo*
  - We still use a “one size fit all” treatment approaches (“0” predictive biomarkers & no personalized therapeutics)
- **Continued Challenges:**
  - How to maximize therapeutic efficacy
  - How to best sequence current approved agents
  - *Who will fund such trials?*
  - How to define best “cost” effectiveness
  - Where/How best to develop new agents/combinations

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- Where/How best to develop new agents/combinations
What about Cost?

Average Wholesaler Price Per Cycle of Drug Only

- Docetaxel 150 mg IV (75 mg/m2 x 2 m2) = $2921.20
  median 6 cycles
- Cabazitaxel 50 mg IV(25 mg/m2 x 2 m2) = $8408.08
  median 6 cycles
- Abiraterone 1000 mg PO (30-day) = $8203.91
  median 8 months
- Enzalutamide 160 mg PO (30-day) = $9467.46
  median 8 months
- Provenge 37,200 X 3 = $123,922.80
- Radium 223 : $ 28,173 (X 6)
- Denusomab 120 mg SC = $2017.68
- Zoledronic Acid 4 mg IV = $360 - $1196.56 (available as generic)

Too Many Negative Phase III Trials:
Importance of Understanding the Biological Context

- GVAX X 2
- Satraplatin
- Docetaxel + DN101
- Bone
  - Docetaxel +/- Dasatinib
  - Atrasentan X 2
  - Docetaxel +/- Atrasentan
  - Zibotenan
- VEGF/Angiogenesis
  - Taxotere +/- Bevacizumab
  - Taxotere +/- Sunitinib
  - Docetaxel +/- aflibercept
  - Docetaxel +/- Lenalidomide
Identification of “active” drugs

Appropriate Phase III studies in advanced disease

Identification of active and safe combinations

Adjuvant

Neoadjuvant

This = Decades & $$$$$$
Biomarkers  
Prognosis and Prediction

A Biomarker is:

- **Prognostic**: correlates with outcome, independent of treatment effects (PS, stage, Gleason’s score, PSA)
- **Predictive**: Provides evidence about the probability of benefit or toxicity from a specific intervention (ER/PR, HER-2, KRAS mutations)
- A factor can be:
  - Prognostic but not predictive
  - Predictive but not prognostic
  - Predictive and prognostic
  - Neither

When is a Marker Clinically Useful?

- It is either **Prognostic** or **Predictive**
- The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
  - Greater chance for benefit
  - Smaller toxicity risk
- The estimate of magnitude of effect is **reliable**
  - Assay is reproducible
  - Clinical trial/marker study design is appropriate
  - Results are validated in subsequent well-designed studies (Levels of Evidence I or II)

Modified from D. Hayes
PSA
The “most” widely used Biomarker in Prostate Cancer

- A biomarker for detection, diagnosis, prognosis & monitoring of disease activity.
- PSA decline has been used as an “efficacy” indicator and PSA increase has been associated with disease “progression”
  - To date no prospectively validated data exist regarding “response or progression” by PSA
  - Criteria have been generally consensus based using best clinical judgment (PSAWG JCO 1999 & PCWG JCO 2008)

PSA vs Overall Survival: S9346 & S9916 Post Hoc Analyses

OS by PSA progression
A. S9346
B. S9916

OS by PSA decline
C. S9346
D. S9916

Hussain M et al. JCO 2009;27:2450-2456
Circulating Tumor Cells as a Biomarker

One Size Does Not Fit All

20 + years of investigations: No predictive biomarker
Example # 1: ETS Gene Fusions as Potential Predictive Biomarker

- ~50% of prostate cancers have ETS gene fusions
- The predominant ETS fusion (80-90%) is TMPRSS2:ERG

Gene 1
(with androgen-sensitive promoter)
Gene 2
( encoding ETS transcription factor)

ETS Gene Fusion
(with androgen-sensitive promoter driving overexpression of ETS transcription factor)

Tomlins et al. Science 2005

NCI Study # 9012: Study Schema
N=148

Registration

Metastatic tissue biopsy adequate for ETS fusion status evaluation
Metastatic tissue biopsy inadequate for ETS fusion status evaluation

Stratification

ETS fusion-positive (~50% of cases)
ETS fusion-negative (~50% of cases)

Abiraterone
Abiraterone + PARP1 inhibitor
Abiraterone
Abiraterone + PARP1 inhibitor

Multicenter (12 Centers) UM- Lead
Funding: CTEP Sponsored, DoD PC080189, N01 Early Therapeutic Development, SU2C
Example 2: Targeting RB
A Randomized Phase II Study of Androgen Deprivation +/- PD 0332991 in Metastatic Hormone-Sensitive Prostate Cancer

New M1 PCa

Biopsy

RB Positive patients (60)

Randomize 1:2

Control Arm (ADT) (N=20)

ADT + PD 0332991 (ADT) (N=40)

PCF Challenge Award 2013

Key Landmarks in Prostate Cancer

1941 Orchiectomy
1985 LHRH agonist
1986 PSA
1996 Mitoxantrone
1997 Sa-153
2002 Zoledronic Acid
2004 Docetaxel
2008 Degarelix
2011 Abiraterone Acetate
2010 Sipuleucel-T Cabazitaxel Denosumab
2013 Radium 223

<1984 Estramustine
1989 Flutamide
2004 Docetaxel
2010 Sipuleucel-T Cabazitaxel Denosumab
2012 Enzalutamide


**Relative Survival Rates:**
- 5-y: nearly 100%,
- 10-y: 98%,
- 15-y: 93%

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**Movember**