A Forward Look at Options for Prostate Cancer

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New Therapies in Advanced Prostate Cancer

Non-cytotoxics leading the way
Matching Drugs to Disease (and Androgen) Biology
Building on Docetaxel Backbone
Continued Promise of Immunotherapy

Castration Resistant Prostate Cancer: Standards of Care

1. Androgen Deprivation Therapy: Should be Maintained.
2. Secondary hormonal therapy (e.g. Ketoconazole), may be considered, not FDA approved.
3. Zoledronic Acid: Prevention of Skeletal Related Events
4. Docetaxel Chemotherapy: Survival Benefit, FDA approved
6. Not approved, may be beneficial, no definitive data – Carboplatin, etc
7. Palliative XRT, Radio-isotopes: Still useful in some.

The Development Landscape For Systemic Therapies In Prostate Cancer

Diagnoses

186,320

Castration resistant:
Docetaxel
Deaths From Disease

(bicalutamide)

Clinically Localized Disease
Rising PSA
Clinical Metastases: Non-Castrate

With detectable metastases: deaths from cancer exceed that from other causes

Deaths= 28,000

Continued Promise of Immunotherapy
Castration Resistance - Understanding of Biology is Leading to New Therapies

Genes Expressed at Higher Levels in AIPC BM Biopsies ( Compared to primaries - among others)

<table>
<thead>
<tr>
<th>Symbol (AIPC:Primary)</th>
<th>Gene Name</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>Androgen Receptor</td>
<td>AR</td>
</tr>
<tr>
<td>AKR1C3</td>
<td>Aldo-keto reductase family 1, member C3</td>
<td>Converts androstenedione to testosterone</td>
</tr>
<tr>
<td>SRD5A1</td>
<td>5 alpha reductase type 1</td>
<td>Converts T to DHT, Converts Androstenedione to Androstanedione</td>
</tr>
<tr>
<td>HSD3B2</td>
<td>3 Beta-hydroxysteroid dehydrogenase type 2</td>
<td>Converts DHEA to Androstanedione</td>
</tr>
<tr>
<td>AKR1C2</td>
<td>Aldo-keto reductase 2</td>
<td>Catabolizes DHT</td>
</tr>
<tr>
<td>AKR1C1</td>
<td>Aldo-keto reductase 1</td>
<td>Catabolizes DHT</td>
</tr>
</tbody>
</table>

The Biological Rationale for the Development of Secondary Hormonal Therapies

Adrenal Androgen Synthesis

Ketoconazole

Abiraterone

MDV3100
Both Ketoconazole and Abiraterone (CB760) Inhibit CYP17

Abiraterone – 4 years on, what do we know?

- Phase I Questions
  - Tox and PSA effects
  - Fasted vs Fed
  - Capsule vs Tablet
  - Adrenal Insufficiency?
  - Corticosteroids necessary?

- Phase II questions
  - Efficacy/Durability
    - Pre-chemotherapy with prednisone (02)
    - Post-chemotherapy without prednisone (03)
    - Post-chemotherapy with prednisone (04)

- Phase III questions
  - Efficacy/Durability
    - Survival vs Prednisone
    - Pre vs Post Docetaxel.

High Rate of Response to Abiraterone – Even Post Ketoconazole

- Ryan et al JCO 2010
- Danila et al JCO 2010
- Reid et al JCO 2010

Baseline

Post Cycle 6

50% PSA decline – 45.2%
50% PSA decline – 54.8%

Danila Et al JCO 2010
Ryan  Et al JCO 2010
**Cougar Biotechnology: Schematic of Phase III Trial Design (Trial 301)**

**RANDOMIZE**

1. **Progressive Prostate Cancer after Docetaxel based chemotherapy**
   
   **Arm A**
   - Abiraterone plus Prednisone

   **Arm B**
   - Placebo plus Prednisone

   **2:1 Randomization**
   
   Primary Endpoint - Overall Survival

**Cougar Biotechnology: Schematic of Phase III Trial Design (Trial 302)**

**RANDOMIZE**

1. **Progressive Prostate Cancer WITHOUT prior Docetaxel based chemotherapy**
   
   **Arm A**
   - Abiraterone plus Prednisone

   **Arm B**
   - Placebo plus Prednisone

   **Endpoints – PFS, Overall Survival**

**Higher AR levels in HRPC tumors**

Stanbrough et al Cancer Research 2006

- CKS2 and LRRC15 by quantitative real-time RT-PCR.
- Expression levels are in arbitrary units based on the lowest level expression being set at 10. Bars, mean expression.

**The Amplified AR As A Drug Target**

MDV-3100 and ARN-509

Both developed in model of AR amplification

MDV-3100 Phase III
ARN-509 – phase I pending
MDV3100
A Second-Generation Antiandrogen

1. Engineered for activity in prostate cancer cells that overexpress the androgen receptor (AR).
2. Binds the AR more potently than bicalutamide.
3. Unlike bicalutamide, MDV3100 inhibits nuclear translocation of the AR and its binding to DNA.
4. Induces apoptosis in prostate cancer cells.

AR Antagonism with MDV-3100
Possibly Related Grade 2/3 Adverse Events in >2 Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Doses (N = 140)</th>
<th>≤240 mg/day (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2</td>
<td>G3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (21%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8%)</td>
<td>–</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (3%)</td>
<td>–</td>
</tr>
<tr>
<td>Seizure</td>
<td>–</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

1. Only one subject discontinued treatment due to fatigue which coincided with disease progression
2. There were 2 witnessed seizures (1 each at 600 and 360 mg/day) and a possible un-witnessed seizure at 680 mg/day.
   - Both patients with witnessed seizures were taking concomitant medications that can cause seizures
3. MTD determined to be 240 mg/day; patients at higher doses were lowered to 240 mg/day

Waterfall Plot of Best Percent PSA Change from Baseline

Medivation: Schematic of Phase III Trial Design

- Progressive Prostate Cancer after Docetaxel based chemotherapy
- No prior Abiraterone or Ketoconazole

2:1 Randomization
Primary Endpoint - Overall Survival
Secondary aims – PFS and Pain control
Chemotherapy for CRPC

1. Survival Improvement shown (Docetaxel over Mitoxantrone) in 2004
2. To date, no proven benefit to additional therapy to docetaxel
3. Issues of Timing remain
4. Second line chemotherapy under development

Docetaxel HRPC Trials

TAX 327
N=1006

SWOG 9916
N=770


Can the Efficacy of Chemotherapy be enhanced?

- Addition of non-cytotoxic drugs
  - Bevacizumab – FAILED
  - Calcitriol – FAILED
  - Immunotherapy – GVAX - FAILED

Overall Survival — TAX 327

Docetaxel in earlier stage prostate cancer?

Early Docetaxel? ADT vs ADT + Chemotherapy in Non-met rising PSA

Arm A
- Docetaxel 75 mg/m² q 3 weeks x 6 months
- Leuprolide x 24 months

Arm B
- Leuprolide x 24 months

The study is designed to detect a hazard ratio of 1.5 with the median time to progression of 36 months vs. 54 months, as defined by a detectable PSA. Patients must have a testosterone ≥50 to be evaluable. QOL will be assessed in both arms.

CALGB 90203: Neoadjuvant Docetaxel

- Preoperative Estimate (Kattan Nomogram) of Biochemical RFS ≤ 60%
- Randomize
- 6 Cycles Chemotherapy
  - Docetaxel 70 mg/m² q 21 days
  - Prednisone 5 mg po bid
  - LHHRH Agonist x 4 months

- Surgical Intervention
  - Staging Pelvic Lymphadenopathy
  - Radical Prostatectomy*

- Open

*Patients with positive surgical margins will be allowed to receive immediate adjuvant external beam radiation to the prostatic fossa at the discretion of the treating physician. Adjuvant radiation must be initiated within 6 months of the date of surgery.
What about Taxane refractory disease??

- Unmet medical need
- Poor prognosis.
- Chemotherapy vs other approaches?

Cabazetaxel

- Microtubule Stabilizer
- Developed in Docetaxel resistant prostate cancer cell lines.

TROPIC – Cabazetaxel vs MP

- Cabazetaxel 25 mg/m² q 21 days
- Prednisone 10 mg daily
- Mitoxantrone
- Prednisone 10 mg daily

N=755

146 Sites/ 26 Countries

Tropic Phase III Trial - Results

<table>
<thead>
<tr>
<th>Pt Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBZ</td>
</tr>
<tr>
<td>PSA</td>
<td>128</td>
</tr>
<tr>
<td>Age</td>
<td>67</td>
</tr>
<tr>
<td>Prior docetaxel (cumulative dose)</td>
<td>576 mg</td>
</tr>
<tr>
<td>Last Docetaxel</td>
<td>0.8 years</td>
</tr>
<tr>
<td>Visceral Disease (%)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>OVERALL SURVIVAL</td>
</tr>
<tr>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td></td>
<td>PSA Response Rate (%)</td>
</tr>
<tr>
<td></td>
<td>TTP</td>
</tr>
<tr>
<td></td>
<td># Cycles (median)</td>
</tr>
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Primary Endpoint: Overall Survival (ITT Analysis)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td>0.59–0.83</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td></td>
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Number at risk: 80% 60% 40% 20%

0 months 6 months 12 months 18 months 24 months 30 months

Progression-Free Survival (PFS) Results

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<tr>
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<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.74</td>
<td>0.64–0.86</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

PFS composite endpoint: PSA progression, pain progression, tumor progression, symptom deterioration, or death.

Number at risk: 80% 60% 40% 20%

0 months 3 months 6 months 9 months 15 months 18 months 21 months

Total Deaths During Study Safety Population

<table>
<thead>
<tr>
<th></th>
<th>MP (n=371)</th>
<th>CBZP (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths during study</td>
<td>275 (74.1%)</td>
<td>227 (61.2%)</td>
</tr>
<tr>
<td>Due to progression</td>
<td>253 (68.2%)</td>
<td>197 (53.1%)</td>
</tr>
<tr>
<td>Due to AEs</td>
<td>7 (1.9%)</td>
<td>18 (4.9%)</td>
</tr>
<tr>
<td>Due to other reasons</td>
<td>15 (4.0%)</td>
<td>12 (3.2%)</td>
</tr>
</tbody>
</table>

Immunotherapy in CRPC – FDA Approval of Provenge 4-29-10
Theoretical Kinetics of Treatment Response:
Cytotoxic Therapy vs Immunotherapy

- Cytotoxic chemotherapy quickly debulks tumors
  - Resistance and tumor regrowth may occur
- Immunotherapy activates the immune system
  - Clinical effect may take time to develop
  - Responses may be sustained due to immunologic memory

Results: Overall Survival (ITT population)

- APC8015 (n=82)
- Placebo (n=45)

P = 0.01 (log-rank) HR = 1.7 (95% CI: 1.126, 2.563)

Small JCO 2006
Summary

In advanced CRPC – Docetaxel remains the standard of care

Many new agents in development – three in late stage and may gain approval in next 2-3 years.

Non-cytotoxic approaches leading the charge