Systemic Approaches for the Treatment of Advanced Disease: Biology Dictates Therapy

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1. A framework and the systemic therapy standards.

2. Castration resistant prostate cancers are not “hormone refractory”.


4. The landscape is changing indeed.
A Framework for Management and The Development Of Systemic Therapies For Prostate Cancer

Diagnoses
186, 320

Clinically Localized Disease

Rising PSA

Clinical Metastases: Non-Castrate

Non-Castrate Androgen depletion /blockade (bicalutamide)

Castration resistant: Docetaxel
Deaths From Disease
28,660

Clinical Metastases: Castrate Pre-1st Line
Docetaxel

Clinical Metastases: Castrate Post-No Standard

Hormone Therapy for Prostate Cancer: Reducing Ligand Levels and/or Blocking Androgen Receptor Binding

Adrenal Androgens

ANDROGEN RECEPTOR

DHT ligand
LHRH agonists
Bicalutamide
Flutamide

P

Pol II
CoR
NCOr/HDAC

AR responsive gene signature
AR protein
TMPRSS2-Erg fusion mRNA, etc
A Rising PSA Following Androgen Depletion Is A Transition to a Lethal Disease Phenotype

T < 50 ng/dl

For Castration Resistant Prostate Cancers Q3 Week Docetaxel Can Prolong Life And Is the First Line Standard of Care

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs</th>
<th>No.</th>
<th>Median Survival</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>99-16</td>
<td>D+E</td>
<td>386</td>
<td>18 mos.</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>M+P</td>
<td>384</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>327</td>
<td>D</td>
<td>335</td>
<td>18.9</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>M+P</td>
<td>337</td>
<td>16.4</td>
<td></td>
</tr>
</tbody>
</table>

D = docetaxel, E = estramustine, M = mitoxantrone, P = prednisone

Petrylak et al., and Tannock et al., NEJM, 2004

Pivotal trials that have led to many hypotheses for testing.
**Systemic Approaches for the Treatment of Advanced Disease: Biology Dictates Therapy**

1. A framework and the systemic therapy standards.

2. *Castration resistant prostate cancers are not “hormone refractory”.*

3. Building on the “first line” standard..

4. The landscape is changing indeed.

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**A Rising PSA Following Androgen Depletion Is A Surrogate for Restored AR Signaling and a Transition to a Lethal Disease Phenotype**

At relapse, AR signaling contributes to progression.

Incomplete suppression or early resistance?

Antagonist-agonist conversion: anti-androgen withdrawal responses
The Oncogenic Changes in the Androgen Receptor of Castration Resistant Prostate Cancers Are Targets for Therapy

Increased AR protein
AR mRNA overexpression
Increased AR DNA copy number
Overexpressed androgen synthetic enzymes
Elevated androgens in tumor

Abiraterone Acetate Inhibits Androgen Synthesis in The Adrenal Gland and in The Tumor

Chen et al. Curr Opin Pharm, 2008
Clinical Contexts for Use and Testing Androgen Receptor Signaling Directed Therapies

UNMET NEED:
Effective therapies for castration resistant disease.
Delay the “need” for chemotherapy.

OBJECTIVE:
Is there a role for AR directed therapies in CRPC?
Development new biomarkers of prognosis, efficacy, and for treatment selection.

The 17,20 Lyase Inhibitor Abiraterone Acetate Lowers Ligand Levels and Is Active in CRPC Both Pre- and Post-Chemotherapy

MW = 391.55

1. C17,20 lyase inhibitor: blocks selectively & irreversibly 17a-hydroxylase / C17,20 lyase
2. Inhibits androgen generation in the testis, adrenals and tumor.
3. Orally administered.
4. Effects on androgen synthesis shown in Proof-of-concept phase 1 trials.
The 17,20 Lyase Inhibitor Abiraterone Acetate Is Active in CRPC Both *Pre-* and *Post-*Chemotherapy: These tumors are not hormone-refractory!

<table>
<thead>
<tr>
<th></th>
<th>&gt;50% PSA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Trial No. Pts.</td>
</tr>
<tr>
<td><strong>Pre-Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td><strong>Post-Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
</tr>
</tbody>
</table>

Considering a tumor to be hormone refractory a priori, is not only a misnomer, but can deprive a patient of potentially useful therapy.

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**Phase III Registration Trial of Abiraterone Acetate in Post-Chemotherapy Setting (NCT 00638690) Is Accrued**

- **Abiraterone 1000 mg daily**
- **Prednisone 10 mg daily**

**Primary Endpoint:** 25% survival increase

- **Sample size:** 1158 (772 and 386)
- **Statistics:** 85% Power; (HR = 0.80), p=0.05, two sided
- **Biomarkers:** CTC

**DeBono, J (Europe) and Scher, H. (North America)  Co-PI, Cougar Biotechnology**
The Phase III Registration Trial of Abiraterone Acetate in Pre-Chemotherapy (Cougar 301): Start May, 2008: Co-Primary Endpoints Are PFS and Overall Survival

- Abiraterone 1000 mg daily
- Prednisone 10 mg daily
- Placebo daily
- Prednisone 10 mg daily

**STATISTICS**

- Primary: 25% survival increase
- Statistics: Enrolled - 1200

1. Fully accrued ahead of schedule.
2. Trial results available 2Q2009.

DeBono, J (Europe) and Scher, H. (North America) Co-PI, OrthoBiotech Oncology Research & Development (A Unit of Cougar Biotechnology)

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**Abiraterone Acetate in CRPC**

1. The “decision” to offer chemotherapy does not mean a tumor is refractory to hormones.

2. PSA declines are an on-target effect: clinical benefits are yet to be “proven”.

3. A prospective randomized phase 3 registration trial was initiated in the 3rd quarter of 2008 in the post-taxane setting (Cougar 301).

4. Accrual is near completion and pre-chemotherapy trial is under regulatory review (Cougar 302).
MDV3100: A Novel Anti-Androgen Engineered to Address Deficiencies in the Currently Available Agents in The Class

Androgen precursors → Androgens → Tumor synthesis → Cell surface ligand/receptor

AR degraded

HSP90

LIA: Truncated AR: LDB Deletions Splice Variants
LBD: PROMISCUTY: antiandrogens, progestins, glucocorticoids

MDV-3100

AR

Nuclear Localization

Overexpression

Transcription of TMPRSS-ETS, etc for growth and survival

Chen et al. Curr Opin Pharm, 2008

RD-162 → MDV3100 Identified in A Screen For Stronger Antagonism and No Agonism in Prostate Cancer Model Systems with Overexpressed AR Blocks

- Crystal structure
- Homology modeling
- Binding affinity

High AR binding affinity with no agonistic activity

Science (in press)
**MDV3100** Which is Active in Tumors With Overexpressed AR Blocks FDHT Uptake in Tumor and Produces Declines in PSA in Pre- and Post-Chemotherapy CRPC (N=140)

Waterfall Plot of Percent PSA Change from Baseline

Pre-Treatment

Post-Treatment

Scher et al. for the PCCTC, ASCO, June 2009

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**Efficacy-Response #2:** Phase III Registration Trial of MDV3100 in CRPC Post-Chemotherapy *(AFFIRM)* Also Includes the Prospective Evaluation of CTC Number as a Biomarker

**STATISTICS**

- **Primary:** 25% survival increase
- **Secondary:** CTC number
- **Sample size:** Approximately 1200
- **Biomarkers:** CTC enumeration Profiling

1. IRB approved.
3. CTC sampling mirrors Cougar 301.

Scher H. (North America) and DeBono, J (Europe) Co-PI
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4. The landscape is changing indeed.

Building on Docetaxel As the First-Line Standard of Care

1. New agents: many classes:
   - cytotoxics, biologics, signaling inhibitors, proapoptotic - microenvironment directed

2. Combinations:
# A Partial List of Taxotere Combinations Under Evaluation

## As First-Line Therapy: A “Theme” of Targeting the Tumor Microenvironment and Survival Pathways

### Phase 3

<table>
<thead>
<tr>
<th>No.</th>
<th>Combination</th>
<th>Company/Study</th>
<th>Company/Study Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>+ Avastin (anti-VEGF Ab)</td>
<td>Genentech</td>
<td>Genentech (CALGB)</td>
</tr>
<tr>
<td>2.</td>
<td>+ Afibercept (VEGF-trap)</td>
<td>Sanofi-Aventis</td>
<td></td>
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<tr>
<td>3.</td>
<td>+ Atrasentan (endothelin)</td>
<td>Abbott</td>
<td>Abbott (SWOG)</td>
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<tr>
<td>4.</td>
<td>+ ZD4054</td>
<td>Astra-Zeneca</td>
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<tr>
<td>5.</td>
<td>+ Dasatinib (src)</td>
<td>Bristol-Myers-Squibb</td>
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<tr>
<td>6.</td>
<td>+ IGF1R antibody</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>+ clusterin antisense</td>
<td>Oncogenex</td>
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### Phase 2

<table>
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<th>Company/Study Abbreviation</th>
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<tbody>
<tr>
<td>1.</td>
<td>+ LBH-589</td>
<td>Novartis</td>
<td>Novartis - Phase 1/2</td>
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<tr>
<td>2.</td>
<td>+ RAD-001</td>
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<tr>
<td>3.</td>
<td>+ Sunitinib</td>
<td>Pfizer</td>
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<tr>
<td>4.</td>
<td>+ quadramet</td>
<td>Cytogen</td>
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<tr>
<td>5.</td>
<td>+ alfaradin</td>
<td>Bayer</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>+ AT-101 (bcl-2)</td>
<td>Ascenta</td>
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</tbody>
</table>

## CALGB 9040: Randomized Double Blinded Placebo controlled Phase III Trial Comparing Docetaxel + Prednisone with or without Bevacizumab in men with HRPC

### Eligibility
- Metastatic PC
- T <50 ng/ml
- No prior chemo
- Adequate hem, renal, and liver function

### Stratification
- Halabi nomogram

### Endpoint:
- Overall survival; progression free survival
- Hazard Ratio = 1.26 (19 months to 24 months), 90% power

N = 1020 patients
- CALGB, ECOG, NCIC

### RANDOMIZE
- Docetaxel q 3 wks + Prednisone + Placebo
- Docetaxel q 3 wks + bevacizumab + prednisone
Docetaxel +/- Avastin

A negative trial.

Targeting the Bidirectional Tumor-Host Interaction in Bone

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Building on Docetaxel As the First-Line Standard of Care

1. New agents: many classes: cytotoxics, biologics, signaling inhibitors, proapoptotic - microenvironment directed

2. Combinations:
Cabazitaxel + prednisone (CBZP) versus mitoxantrone + prednisone (MP) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-based regimen

Final Results of the Phase III TROPIC Trial

Oliver Sartor, MD
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Johann de Bono, MD, PhD
Reader in Experimental Cancer Medicine
The Institute of Cancer Research
The Royal Marsden Hospital
Surrey, UK

On behalf of the TROPIC Investigators

2010 Genitourinary Cancers Symposium
Progress in Multidisciplinary Management

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Cabazitaxel: A Next-Generation Taxane

- New semi-synthetic taxane
  - Selected to overcome the emergence of taxane resistance
  - Microtubule stabilizer

- Preclinical data
  - As potent as docetaxel against sensitive cell lines and tumor models
  - Activity against tumor cells and tumor models that are resistant to, or not sensitive to currently available taxanes

- Clinical data
  - In Phase I trials DLT was neutropenia
  - Antitumor activity in mCRPC in Phase I including docetaxel-resistant disease

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TROPIC: Phase III Registration Study
146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors
ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

- cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
- mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

Primary Endpoint: Overall Survival (ITT Analysis)

Proportion of OS (%)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CRZP</th>
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<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></td>
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<tr>
<td>95% CI</td>
<td>0.59-0.83</td>
<td></td>
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<tr>
<td>P-value</td>
<td>&lt;.0001</td>
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Number at risk

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CRZP</th>
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<tbody>
<tr>
<td>0 months</td>
<td>377</td>
<td>378</td>
</tr>
<tr>
<td>6 months</td>
<td>300</td>
<td>321</td>
</tr>
<tr>
<td>12 months</td>
<td>188</td>
<td>231</td>
</tr>
<tr>
<td>18 months</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>24 months</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>30 months</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
Sipuleucel-T Immunotherapy for Advanced Prostate Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

IMPACT STUDY

**Sipuleucel-T: Patient-Specific Therapy**

**Day 1**
- Leukapheresis

**Day 2-3**
- Sipuleucel-T is manufactured

**Day 3-4**
- Patient is infused

**Apheresis Center**

**Dendreon**

**Doctor’s Office**

COMPLETE COURSE OF THERAPY:
- Weeks 0, 2, 4
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=512)

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression

Median Survival Benefit = 4.1 Mos.

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

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

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
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4. The landscape is changing indeed.

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