Mapping the Complexity of Androgen Signaling In Prostate Cancer Progression

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Prostate Cancer Evolution

NOTE: This diagram represents typical disease progression. Some patients are metastatic at diagnosis and are thus still castrate sensitive.

Local Therapy

Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Chemotherapy

Death

Post-chemotherapy

Asymptomatic

Nonmetastatic

Castrate Sensitive

Castrate Resistant

Symptomatic

Metastatic

Time

Grey Zone

Local Therapy

Castration

Steroids

Ketoconazole

Estrogens??

Docetaxel

March 2010
Prostate cancer drug development

NOTE: This diagram represents typical disease progression. Some patients are metastatic at diagnosis and are thus still castrate sensitive.

- Castration
- Sipuleucel-T
- Docetaxel
- Chemotherapy
- Death
- Post-chemotherapy
- Abiraterone Acetate
- Cabazitaxel
- Alpharadin
- MDV3100...

Local Therapy
Androgen Deprivation
Therapies After LHRH Agonists and Antiandrogens
Chemotherapy
Death

Asymptomatic
Nonmetastatic
Castrate Sensitive

Symptomatic
Metastatic
Castrate Resistant

Time

November 11
Prostate cancer drug development

NOTE: This diagram represents typical disease progression. Some patients are metastatic at diagnosis and are thus still castrate sensitive.

Castration

Docetaxel

Abiraterone Acetate
Sipeuleucel-T

March 12

Abiraterone Acetate
Cabazitaxel
Alpharadin
MDV3100
Prostate cancer therapy development?

Local Therapy

Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Chemotherapy

Death

Asymptomatic

Nonmetastatic

Castrate Sensitive

Symptomatic

Metastatic

Castrate Resistant

Castration

Abiraterone Acetate

MDV3100 (Intermittent)

Sipeuleucel-T

Cabazitaxel

Docetaxel

Alpharadin

Short term expectation
Therapy development
to be distinguished from drug
development

Priority: predictors of outcome and
resistance to treatment
Solid Tumor Therapy Paradigm

*Therapeutic agents effective in far-advanced disease states will be more effective in earlier states.*
Standard of Care in Metastatic Castrate Resistant Prostate Cancer

![Graph showing survival rates for different treatments]

- **Docetaxel + estramustine**
  - 217 deaths; median, 17.5 mo
  - Survival rate: 80% at 12 months

- **Mitoxantrone + prednisone**
  - 235 deaths; median, 15.6 mo
  - Survival rate: 70% at 12 months

<table>
<thead>
<tr>
<th>Months after Enrollment</th>
<th>Docetaxel + estramustine</th>
<th>Mitoxantrone + prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>338</td>
<td>336</td>
</tr>
<tr>
<td>12</td>
<td>218</td>
<td>185</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

*P = 0.02*
Accepted Solid Tumor Therapy Paradigm

Treatment Sensitive  Treatment Resistant

GETUG12 trial results in line! (Fizazi et al ASCO 2011)
Proposed Progression Model

Efstathiou et al 2010 CCR
Proposed Progression Model

- Autocrine
- Paracrine
- Epithelial dysregulation
- Physiological changes
- Lethality
- Chemotherapy resistance

Microenvironment Dependence

Efstathiou et al. CCR 2010
Prostate Cancer Progression

Efstathiou et al CCR 2010
Endocrine-to-Paracrine Androgen Signaling Transition

Proposed Model of Prostate Cancer Progression

Role of endocrine-to-paracrine androgen signaling transition

Elucidating the link of androgen signaling to milestones of prostate cancer progression will serve as the foundation for the individualized microenvironment targeted therapies.
Androgen Signaling in Prostate Cancer

Endocrine

Gonads

Adrenals

Testosterone

AR

Efstathiou et al ASCO 2010
Androgen Signaling in CRPC

Endocrine

Gonads

Adrenals

Microenvironment

‘Intracrine’

Testosterone

Steroid Metabolome

Efstathiou et al ASCO 2010
Molecular Profiling Studies Identified Overexpressed AR as a Frequent Molecular Alteration in CRPC That Is Infrequent in Primary Tumors

Abbreviations: AR=androgen receptor; CRPC=castration-resistant prostate cancer.

Adaptive Response of Androgen Signaling in CRPC

- Androgen-rich
- AR Genomic Signaling
  - AR
  - PSA
- AR Genomic Signaling

- Intracrine steroid biosynthesis
- Aberrant AR activation
- Interface with other pathways

Castration Disease Progression

Androgen Independent

Adaptive Response of Androgen Signaling in CRPC

- AR
- PSA
- SRC/SH2
- Cell survival/anti-apoptotic

Aberrant AR activation

Intracrine steroid biosynthesis
Adaptive Response of Androgen Signaling in CRPC

AR Genomic Signaling

Castration/ Disease Progression

Increased Intracrine steroid biosynthesis
Required Androgen Inhibition in CRPC

Endocrine

Gonads

Adrenals

Microenvironment
‘Intracrine’

Testosterone

Steroid Metabolome

Efstathiou et al ASCO
Abiraterone Acetate: A Rationally Designed Androgen Biosynthesis Inhibitor

• Inhibition of CYP17 has been shown to block production of androgens from all sources in the body—testes, adrenal glands, and the CaP tumor

• Molecular modeling was used to design a compound that could act as a substrate for CYP17

• The resulting analog, abiraterone acetate, is a highly specific, potent inhibitor of CYP17

3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene
Molecular Weight=391.55
Abiraterone Acetate: Androgen Biosynthesis Inhibitor

Androgens produced at 3 critical sites lead to tumor growth
- Testes
- Adrenal glands
- Prostate tumor cells

Abiraterone inhibits biosynthesis of androgens that stimulate tumor cell growth\(^1-5\)

Endocrinology Driven Treatment

Low-dose steroid replacement minimizes mineralocorticoid-related toxicity

Cholesterol

Desmolase

Pregnenolone → Progesterone → Deoxy-corticosterone → Corticosterone

17α-OH-pregnenolone

CYP17

17α-hydroxylase

17α-OH-progesterone → 11-Deoxy-cortisol → Cortisol

ACTH

DHEA → Androstenedione → Testosterone → DHT

5α-reductase

CYP19: aromatase

Estradiol

Informative Transilial Bone Marrow Biopsy

CT Directed

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
BMA Abiraterone Acetate Study

Abiraterone Acetate

Baseline*  Week 8*  Maximum Response*/**  Discontinuation*

*Tissue:
1) Serum and plasma blood and bone marrow aspirate
2) Transilial bone marrow biopsy

**Variable time point/optional

Efstathiou et al. J Clin Oncol
Modulation of Serum in PSA

30% Reduction: 59% (34/56)
50% Reduction: 48% (28/56)
90% Reduction: 16% (9/56)

median PS-ECOG : 2 (range 0-2)

Efstathiou et al. J Clin Oncol
Liver Metastasis Major Response coupled with Symptomatic Improvement and PSA reduction

Baseline  Month 6

Patient stayed on treatment for 16 months. Upon clinical, imaging (liver) and PSA progression given chemo. survived 28 months
Time to Treatment Discontinuation

Median time-to treatment discontinuation: 233 days,
95%CI: 196 – 400 days

Primary Resistance: Treatment discontinuation within 4 months. 16/56 pts (28.6%)
Off-Study Criterion: Symptomatic Progression (PSA or/and imaging progression not required)
Imaging reevaluation: "Standard of Care"

Efstathiou et al. J Clin Oncol in press
Median survival: 555 days, 95% CI: 440 – 965+ days
Median Follow up 673 days

On treatment <4ms OS : 208ds
On treatment >4ms OS : 812ds
Persistent Androgen Signaling in CRPC With Bone Metastases

AR

CYP17

Efstathiou et al. J Clin Oncol
Pretreatment CYP17 Expression in the Tumor Correlates with Increased BMA Testosterone Concentration (MS)

<table>
<thead>
<tr>
<th>CYP17 expression in the tumor ≥10%</th>
<th>no CYP17 expression in the tumor</th>
<th>p-value. Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMA-T (ng/ml)</td>
<td>Mean BMA-T (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>0.074 (0.070)</td>
<td>0.026 (0.019)</td>
<td>0.045</td>
</tr>
</tbody>
</table>
Intense and Homogeneous Nuclear AR Expression With CYP17 Co-expression Correlate With Longer Treatment Duration

<table>
<thead>
<tr>
<th></th>
<th>Primary Resistance*</th>
<th>Stable Response</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>&gt;90% nuclear AR</td>
<td>1 (7)</td>
<td>13 (93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 10% )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP17 expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>epithelium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of one or</td>
<td>10 (91)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Time to treatment discontinuation <4 months (122 days)
Modulation of AR Copy Number

qPCR on ≥500 cells.

Efstathiou et al. J Clin Oncol
Sustained Depletion of Testosterone Following Abiraterone Acetate

Efstathiou et al. J Clin Oncol
COU-AA-301: Abiraterone Acetate Improves Overall Survival in Metastatic CRPC

HR = 0.646 (0.54-0.77)  \( P < 0.0001 \)

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

Abiraterone acetate:
14.8 months (95% CI: 14.1-15.4)

CRPC, castrate resistant prostate cancer.


FDA Approved Apr 28, 2011
EMEA Approved Sep 2011
“Earlier” Use of Androgen Biosynthesis Inhibitor

Abiraterone Acetate

Undetectable PSA >2 years! Asymptomatic no imaging progression
Potential Survival Benefit now Confirmed by Study 302!!
Adaptive Response of Androgen Signaling in CRPC

Androgen-rich

AR Genomic Signaling

AR

PSA

AR

CYP17

Increase steroid biosynthesis

Castration/ Disease Progression

Aberrant AR Activation

mAR

mAR

PSA

m

mAR
Intense AR expression Persists at Progression (Abiraterone Acetate)

Efstadhio et al. Am Assoc Can Res 2011; LB421 (oral presentation)
MDV3100: Second Generation Antiandrogen
Phase I-II MDV3100 Clinical Activity

Chemo naïve; N=65

Chemo exposed; N=75

PSA progression by PCWG2
- Total, N=140
- Chemo naive, N=65
- Post chemo, N=75

Pre-chemo median - 45 wk
All subjects median - 27 wk
Post-chemo median - 23 wk

Overall Radiographic Progression
- Pre-chemo median - not reached
- All subjects median - 47 wk
- Post-chemo median - 28 wk

Scher et al Lancet 2010
**Bone Marrow Biopsy Study**

**MDV 3100 (160mg qd)**

- **Baseline**
- **Week 8**
- **Discontinuation**

**Planned Accrual:** 30 Evaluable Patients/ maximum 60 accrued

**Off-Study Criterion:** Symptomatic or/and Imaging Progression

_Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)_
Similar PSA modulation profile by MDV3100 and Abiraterone Acetate

Abiraterone Acetate

MDV 3100

Efstathiou et al. J Clin Oncol in press
Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Increased pretreatment CYP17 expression and testosterone concentration predict for ≥50% PSA decline

<table>
<thead>
<tr>
<th></th>
<th>Not ≥50% PSA Decline</th>
<th>≥50% PSA Decline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CYP17 Expression (%)</td>
<td>10 (0-30)</td>
<td>70 (0-90)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean Bone Marrow Aspirate Testosterone (Range)(ng/ml)</td>
<td>0.016 (0-0.077)</td>
<td>0.033 (0-0.105)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Androgen Receptor Subcellular Localization Shift (Patients with ≥50% PSA decline)

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Nuclear</th>
<th></th>
<th>Week 8</th>
<th></th>
<th>Cytoplasmic</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Decrease in Nuclear AR (&gt;20%)</td>
<td>No Decrease in nuclear AR</td>
<td>P value</td>
<td>Fisher’s</td>
<td></td>
</tr>
<tr>
<td>≥50% PSA decline</td>
<td>6</td>
<td>2</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>No(≥50%) PSA decline</td>
<td>2</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Modulation of Bone marrow Testosterone by Abiraterone Acetate & MDV 3100 in CRPC

Efstathiou et al. J Clin Oncol 12/2012
Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
MDV3100 prolonged survival by a median of 4.8 months in the Phase 3 AFFIRM trial.

HR = 0.631 (0.529, 0.752)  P < 0.0001

37% reduction in risk of death

MDV3100: 18.4 months
(95% CI: 17.3, NYR)

Placebo: 13.6 months
(95% CI: 11.3, 15.8)
Adaptive Response of Androgen Signaling in CRPC

AR Genomic Signaling

Castration/ Disease Progression

Non-genomic AR signaling
Activation of SRC kinase, cMET, Hh

Cell survival/anti-apoptotic
Increased pSrc expression correlates with resistance to both Androgen Signaling Inhibitors (Abiraterone Acetate & MDV3100)

<table>
<thead>
<tr>
<th>Mean pSrc Expression (%)</th>
<th>Non responders</th>
<th>Responders</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Range)</td>
<td>70 (0-90)</td>
<td>10 (0-30)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Therapy Development
Proposed Combinatorial Strategy in CRPC

Androgen Signaling

Castration

Targeting Src Kinase

Targeting the Androgen Receptor

Androgen Biosynthesis Inhibition
Adaptive Response of Androgen Signaling in CRPC

Androgen-rich

AR Genomic Signaling

CAstration
Disease Progression

Intracrine
steroid biosynthesis

Aberrant AR activation

Interface with other pathways

Androgen Independent

Cell survival/anti-apoptotic

Adaptive Response of Androgen Signaling in CRPC
Chronic Myelogenous Leukemia

"Oncogene Addiction"

"Blast Crisis"

BCR-ABL

Prostate Cancer

"Microenvironment Dependence"

Androgen Independent Progression

S-E Signaling Network

Elucidating signaling network will lead to combinatorial microenvironment targeting
Prostate cancer therapy development?

The Future is here  Microenvironment Targeting
## Survival in patients with mCRPC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Pts</th>
<th>HR</th>
<th>N</th>
<th>Survival (months)</th>
<th>Delta (mo’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T</td>
<td>CRPC</td>
<td>0.78</td>
<td>512</td>
<td>25.8 vs. 21.7</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.9 vs. 16.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Tax 327, Tannock NEJM, 2004</td>
<td>Docetaxel/pred vs. mito/pred</td>
<td>CRPC, chemo naïve</td>
<td>0.76</td>
<td>1006</td>
<td>15.1 vs. 12.7</td>
<td>2.4</td>
</tr>
<tr>
<td>TROPIC, Sartor Lancet 2010</td>
<td>CBZ/pred vs. mito/pred</td>
<td>CRPC, post-docetaxel</td>
<td>0.70</td>
<td>755</td>
<td>14.8 vs. 10.9</td>
<td>3.9</td>
</tr>
<tr>
<td>COUGAR 301 NEJM 2011</td>
<td>Abiraterone Acetate /pred vs. Pred</td>
<td>CRPC, post-docetaxel</td>
<td>0.64</td>
<td>1195</td>
<td>14.0 vs 11.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Alsymppca</td>
<td>Alpharadin vs placebo</td>
<td>CRPC</td>
<td>0.695</td>
<td>809</td>
<td>18.4 vs 13.6</td>
<td>4.8</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>MDV3100 vs placebo</td>
<td>CRPC post docetaxel</td>
<td>0.63</td>
<td>1199</td>
<td>18.4 vs 13.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Overall Survival increase: Can we add it up or do even better with the right sequence or combination

+ ≥20.4ms!!
Integrated Management of Advanced Prostate Cancer

Treatment based predictors of outcome are required: INDIVIDUALISED THERAPY!!
Disease Heterogeneity may require combinatorial approach
Prostate Cancer Mortality

Number of Deaths

1981: 23,370
1985: 25,943
1990: 32,378
1995: 34,475
2000: 31,078
2005: 28,900*

*estimated for 2003

Sources: Ca-A Cancer Journal for Clinicians (ACS); Vital Statistics of the United States; SEER

PSA
TRUS
Magic of Collaboration!

- Patient Advocates
- Laboratory Scientists
- Computer Scientists
- Mathematicians
- Clinicians
Acknowledgments

MD Anderson Cancer Center
Stanford Alexander Tissue Der. Laboratory
• Anh Hoang, HT
• Maria Karlou, PhD
• Odilia Leon
• Vassiliki Tzelepi, MD, PhD

GU Center Clinicians
• Christopher Logothetis, MD
• Shi-Ming Tu, MD
• Ana Aparicio, MD

GU Pathology
• Patricia Troncoso, MD

Roswell Park
• Mark Titus, PhD
• James Mohler, MD

University of Athens
Dept of Clinical Therapeutics
• Meletios A Dimopoulos MD
• Evangelos Bournakis MD

Prostate Cancer Foundation
Stanford Alexander
David H. Koch Center for Applied Research of Genitourinary Cancers
MD Anderson Prostate Cancer SPORE

Patients