A Path to Prostate Cancer Therapy Development

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‘Discovery is our Business’

Charles Huggins (1902-1997)
Nobel Prize in Medicine 1966
Prostate Cancer Therapeutics 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
- Castration
- Grey Zone
- Steroids
- Ketoconazole
- Estrogens??

March 2010
Cabazitaxel
Overall Survival Benefit in chemotreated mCRPC

Currently Investigating Known therapy Paradigm
Survival Improvement over Docetaxel

<table>
<thead>
<tr>
<th></th>
<th>CBZP</th>
<th>MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>15.1</td>
<td>12.7</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>
</tbody>
</table>

De Bono et al 2010.
Further androgen signaling inhibition prolongs life in chemotherapy-treated mCRPC

Abiraterone acetate + Prednisone

Enzalutamide

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
Abiraterone Acetate
Cabazitaxel
Alpharadin
MDV3100....

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.

- **Local Therapy**
- **Androgen Deprivation**
  - **Therapies After LHRH Agonists and Antiandrogens**
- **Chemotherapy**
- **Death**
- **Post-chemotherapy**

**Asymptomatic**
- **Nonmetastatic**
- **Castrate Sensitive**

**Symptomatic**
- **Metastatic**
- **Castrate Resistant**

**Time**

**Castration Intermittent for biochemical relapse**

**Continuous Castration**
- **mHSPC**

**Docetaxel**

**Abiraterone Acetate**
- **Cabazitaxel**
- **Alpharadin**
- **Enzalutamide**

**June 12**

**June 12**
## 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>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>18.9 vs. 16.5</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>15.1 vs. 12.7</td>
<td>2.4</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>14.8 vs. 10.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Alsympca</td>
<td>Alpharadin vs placebo</td>
<td>CRPC</td>
<td>0.695</td>
<td>809</td>
<td>14.0 vs 11.2</td>
<td>3.6</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>Enzalutamide 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

+ ≥21.2ms!!
We have a problem..

But it’s a good one !!

More reagents than we knowledge on how to use them..
Therapy Development
to be distinguished from
Drug Development
Therapy approach

How we treat patients

Vs

How we should treat patients!
Current Treatment Approach

• Access to reagents
• Reimbursement Status/ Ease to prescribe
• Discipline / Physician  (*urology*/*medical oncology*/ *radiation oncology*)
• Experience/ Evidence Driven- Solid Tumor Therapy Paradigm
• Disease Characteristics (bone tropism / anaplastic features)
• Patient Characteristics
• Safety Profile
• Patient Preference (*need to build on this*)
Treatment based predictors of outcome are required
Disease Heterogeneity may require combinatorial approach or guided sequencing
The significance of Prostate Cancer Chemotherapy Response Profile

Proposed New Therapy Paradigm

- Transition from endocrine to paracrine androgen signaling
- Microenvironment driven resistance to androgen signaling inhibition
- Epitheliocentric progression: Altered cell cycle
Solid Tumor Therapy Paradigm

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

**Docetaxel**

**TAX-327 Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median survival (months)</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel q3w</td>
<td>18.9</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>16.4</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Tannock et al NEJM 2004
Accepted Model of Cancer Progression

Treatment Sensitive           Treatment Resistant
Therapeutic agents effective in far-advanced disease states will be more effective in earlier states.
Accepted Model of Cancer Progression

Earlier Chemotherapy Does Not Prolong Survival!

Gravis et al Lancet Onc 2012

GETUG 15

Millikan et al JCO 2008

Proportion Free from AIPC

Years from Start of Hormonal Rx

Hormonal Rx Only
Chemohormonal Rx
Proposed Progression Model

- Autocrine
- Paracrine
- Epithelial dysregulation
- Lethality
- Time
- Microenvironment Dependence-Androgen Signaling Addiction

Efstathiou et al CCR 2010
Adaptive Response of Androgen Signaling in CRPC

Androgen rich

AR Genomic Signaling

AR

PSA

Intracrine steroid biosynthesis

CYP17

Aberrant AR activation

mAR

PSA

Interface with other pathways

Cell survival/anti-apoptotic

Castration Disease Progression

Androgen Independent

Adaptive Response of Androgen Signaling in CRPC
Chronic Myelogenous Leukemia

- "Oncogene Addiction"
- BCR-ABL

- "Blast Crisis"

Prostate Cancer

- "Microenvironment Dependence"
- Androgen Signaling Addiction

- Androgen Independent Progression

Elucidating signaling network will lead to combinatorial microenvironment targeting
Model for Reclassification of Prostate Cancer

DHT Dependent → Cyp17 → AR → Src → Oncogene Activation → Exit from spiral

Entry into spiral

(FGFR, c-Met, Akt, etc)
AR amplification, mutation paracrine factors

Altered Cell Cycle

Oncogene Activation
AR/oncogene cross talk microenvironment dependence
Imagine if we knew how to prioritize or/and combine agents to *effectively* and *anticipate* need before clinically apparent!
Do we have any predictors of outcome or resistance to proposed treatments?

Being Pragmatic!
Do we have any predictors of outcome or resistance to proposed treatments?

NO!

We only have some prognosticators of outcome
Predictor of outcome or resistance to a specific treatment

Prognosticator: provides prognosis of outcome irrespective of treatment used
Abiraterone Acetate chemo-naive mCRPC: Patients with **Low Serum Testosterone** perform poorly...

**OS Significantly Longer in HH Versus LH Groups in AA + P and Placebo + P Arms: Testosterone**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA + P; HH</td>
<td>17.8</td>
</tr>
<tr>
<td>PL + P; HH</td>
<td>15.8</td>
</tr>
<tr>
<td>AA + P; LH</td>
<td>13.6</td>
</tr>
<tr>
<td>PL + P; LH</td>
<td>9.3</td>
</tr>
</tbody>
</table>

**Survival (%) vs Time to Death (Months)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA HH vs AA LH</td>
<td>0.64 (0.53-0.77)</td>
</tr>
<tr>
<td>AA HH vs PL HH</td>
<td>0.81 (0.64-1.03)</td>
</tr>
<tr>
<td>AA LH vs PL LH</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>PL HH vs PL LH</td>
<td>0.51 (0.39-0.67)</td>
</tr>
</tbody>
</table>

HH, high hormone; LH, low hormone; PL, placebo.

*Ryan et al Proc AACR 2012*
Prognostic: Patients with **Low Serum Testosterone** perform poorly... but

**Still** Abiraterone better than Prednisone alone!!

Maybe Predictive of resistance to Hormonal Treatments... to be proven
....Sometimes we need to prove the Obvious...
Short Time to CRPC prognostic of poor outcome

Bournakis et al 2012
Circulating Tumor Cell Allures

• CTC a step for haematogenous metastatic spread Mechanism unclear

• CTC enumeration:
  – Might represent a prognostic tool
    • Identifying patients for adjuvant therapy- *is it adjuvant??*
  – *Accelerate confirmation of treatment efficacy in trials?*

• Molecular characterisation of CTC could be more representative than profile of primary tumor
  – Real-time

• Minimally invasive
Veridex CellSearch® is the only test Analytically Valid and FDA Cleared (Breast, Colorectal, and Prostate)

The Biomarker:
The “number” of intact; DAPI (+), EpCAM (+), CD45 (-)

Reported as number of cells/7.5 mL of blood
Favorable: < 5 CTC
Unfavorable: ≥ 5 CTC

must be analysed within 96 hours
CTC counts are **prognostic** & identify response to treatment in chemotherapy-treated pts

Breast

Colorectal

Prostate

Remain Favorable

Convert to Unfavorable

Remain Unfavorable

Convert to Favorable
In Chemotherapy-Treated Patients, CTC Number is Prognostic for Survival at Baseline

The results lead to a 510K clearance, but did not establish surrogacy as an efficacy-response biomarker

COUAA301: AA Improves Overall Survival in Patients with Favorable and Unfavorable CTC Counts at Baseline

No predictor there!

Baseline CTC < 5

AA Median (95% CI): 22.1 Mos (20.4-24.1)

Placebo Median (95% CI): 19.7 Mos (16.7-not estimable)

Baseline CTC ≥ 5

AA Median (95% CI): 10.9 Mos (9.9-12.0)

Placebo Median (95% CI): 8.2 Mos (7.4-9.3)

Scher et al ASCO 2011
Treatment, Baseline LDH and CTC Count Were **Prognostic** for Survival in the Multivariate Model While PSA Was Not

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.70 (0.59, 0.828)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LDH</td>
<td>2.98 (2.496, 3.565)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CTC count</td>
<td>1.19 (1.137, 1.245)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hgb</td>
<td>0.95 (0.891, 1.001)</td>
<td>0.0574</td>
</tr>
<tr>
<td>ALP</td>
<td>0.98 (0.874, 1.097)</td>
<td>0.7218</td>
</tr>
<tr>
<td>PSA</td>
<td>1.04 (0.983, 1.093)</td>
<td>0.1797</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; Hgb, hemoglobin; LDH, lactase dehydrogenase; ALP, alkaline phosphatase.
Candidate Clinical Predictors of Response (post hoc analyses)

- Gleason Score <8 vs high risk (baseline evaluation): Conflicting data Loriot et al vs Oudard et al
- prior lines of chemo ( >1 vs 1) –stating the obvious!
- time to crpc ( jury still out - shortcoming : definition of CRPC/retrospective data)

in line with protracted androgen signaling addiction vs autocrine/epitheliocentric progression
Gleason Score Criterion

Beware:

This is a morphology criterion

1. Gleason Grade 4 includes distinct morphologies with different behavior

2. Temporal heterogeneity and heterogeneity within disease warrants rebiopsy
Presence of Cribriform Gleason Score 4 predicts for relapse

\[ \text{Figure 4c} \]

**Proposed Grouping of Treated Prostate Cancer**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dominant Architectural Pattern</th>
<th>Cribriform Pattern or Intraductal Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cell clusters/cords, isolated cells</td>
<td>Absent</td>
</tr>
<tr>
<td>B</td>
<td>Small glands, fused glands</td>
<td>Absent</td>
</tr>
<tr>
<td>C</td>
<td>Any</td>
<td>Present</td>
</tr>
</tbody>
</table>

Efstathiou et al 2010 Eur Urology
What do we know ..?

Making a decision in the clinic- Based on clinical information-’physician algorithm’

Age vs Frailty-other comorbidities (Droz et al)

Disease Related Symptoms- Rapid Progression

Rapid radiologic progression

Presence of visceral metastases
Whatever happened to characterizing the tumor?

Facilitated by the advent of drugs that actually do work!
Adaptive Response of Androgen Signaling in Bone mCRPC

Androgen rich

AR Genomic Signaling

AR

PSA

Intracrine steroid biosynthesis

Androgen Independent

Castration Disease Progression

Aberrant AR activation

Interface with other pathways

Adaptive Response of Androgen Signaling in Bone mCRPC

Androgen rich

AR Genomic Signaling

AR

PSA

Intracrine steroid biosynthesis

Androgen Independent

Castration Disease Progression

Aberrant AR activation

Interface with other pathways
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 AND THUS ‘PRECISION THERAPY’ DEVELOPMENT
Informative Transilial Bone Marrow Biopsy

CT Directed

Adaptive Response of Androgen Signaling in Bone mCRPC

Androgen rich

AR Genomic Signaling

PSA

AR

CYP17

Intracrine steroid biosynthesis

Castration Disease Progression

Aberrant AR activation

Cell survival/anti-apoptotic

Interface with other pathways

Androgen Independent
BMA Abiraterone Acetate Study

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

Abiraterone Acetate

Efstathiou et al. J Clin Oncol
Predicting Outcome of Androgen Signaling Inhibition

Androgen Signaling Signature predictive of benefit: Overexpression of nuclear AR + CYP17 expression

Correlation of CYP17 expression to intracrine androgens

Efstathiou et al JCO 2012
BMA Study

Enzalutamide

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. in review
Increased pretreatment CYP17 expression and bone marrow testosterone concentration predict for benefit in the background of AR nuclear overexpression.

<table>
<thead>
<tr>
<th></th>
<th>Benefit</th>
<th>Primary Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggestive of overlap</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between reagents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean CYP17 Expression</strong></td>
<td>10 (0-30)</td>
<td>70 (0-90)</td>
</tr>
<tr>
<td>(%) (Range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Bone Marrow Aspirate Testosterone</strong></td>
<td>0.016 (0-0.077)</td>
<td>0.033 (0-0.105)</td>
</tr>
<tr>
<td>(Range)(ng/ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value
Wilcoxon’s rank test

0.002
0.019

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Androgen Receptor Subcellular Localization Shift following Enzalutamide

<table>
<thead>
<tr>
<th></th>
<th>Decrease in Nuclear AR (&gt;20%)</th>
<th>No Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% PSA decline</td>
<td>6</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>No PSA decline</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Efstathiou et al. J Clin Oncol 2011; 29(Suppl): Abstract 4501 (Oral Presentation)
Efstathiou et al under review
Candidate Predictors of primary resistance to Enzalutamide: ARV7 splice variant

<table>
<thead>
<tr>
<th></th>
<th>ARV7</th>
<th>No ARV7</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Resistance</td>
<td>7</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Benefit</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Resistance**

**Benefit**

Efstathiou et al under review
Adaptive Response of Androgen Signaling in CRPC

Halabi et al: Neither PSA decline (≥30% and ≥50%) nor PSA velocity within the first three months of therapy are surrogate endpoints for OS in pts receiving second line chemotherapy. (ASCO 2012)
“Altered Cell Cycle” & Adenocarcinoma
BMA Study

Cabazitaxel

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. in review
Antimitotic drugs bind to microtubules at diverse sites

Vinblastine

Colchicine

Tubulin-Colchicine complex

Taxanes

Impact of taxanes on cell cycle

• Androgens act earlier than taxanes in cell cycle
• Androgens given before taxanes will prevent their action

Taxanes stabilize microtubules leading to cell-cycle arrest in metaphase-anaphase

Normal cell cycle

a. Prometaphase
b. Metaphase
c. Anaphase
d. Telophase

Taxanes

Taxanes stabilize microtubules and inhibit disassembly: cell-cycle signal to pass from metaphase to anaphase is blocked and cells eventually die by apoptosis

Function of microtubules

- Cell shape
- Transport of vesicles
- Mitochondrial function
- Cell signalling
- Cell division and mitosis

Docetaxel suppresses androgen receptor nuclear translocation in PCa tumors

A. Similar AR levels in controls & docetaxel-treated PCa patients

B. 

C. Marked reduction of AR nuclear translocation with docetaxel

D. 

Microtubules facilitate AR nuclear translocation and enhance downstream AR transcriptional activity

Alternative taxane mechanism of action in prostate cancer Beyond Cell Cycle Arrest

Non clinical data

©2012 by American Association for Cancer Research
Chronic Myelogenous Leukemia

“Oncogene Addiction”
BCR-ABL

“Blast Crisis”

Prostate Cancer

“Microenvironment Dependence”
Androgen Signaling Addiction

Androgen Independent Progression
Identifying Predictors of Outcome and Resistance to therapy is essential to therapy development
**Integrated Management of Advanced Prostate Cancer**

Treatment based predictors of outcome are required.

Disease Heterogeneity may require combinatorial approach or guided sequencing.
WHAT IS “CURING” PROSTATE CANCER!
Prostate Cancer Mortality

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

*estimated for 2003
Acknowledgements

Medical Oncology
Christopher Logothetis
Ana Aparicio
John Araujo
Paul Corn
Lance Pagliaro
Shi Ming Tu
Amado Zurita

Stanford Alexander Lab
Maria Karlou PhD
Elsa Li Ning Tapia MD
Vaso Tzelepi MD
Anh Hoang HT
Odilia Leon

Laboratory investigators
Gary Gallick
Sue-Hwa Lin
Sankar Maity
Nora Navone
Mark Titus
Timothy Thompson
Patricia Troncoso

Urology
John Davis
Bryan Chapin
Louis Pisters
Curtis Pettaway

Funding
Prostate Cancer Foundation
CCSG (5 P30 CA016672-35)
MD Anderson Prostate Cancer SPORE
DOD Therapy Consortium
David H. Koch Center
Hellenic PCF
George Mitchell Foundation
DOD Therapy Consortium

Patients & Families