Prostate Cancer: State of a Rapidly Evolving Art

Advances in Hormonal Therapy for Advanced Prostate Cancer

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Disclosure Slide

• I have received travel support and honoraria from:
  – Janssen
  – Sanofi
  – Astellas
  – Novartis
  – Pfizer
Key Points:

- Hormonal agents remain important therapeutic options in advanced prostate cancer (too).
- Hormonal signalling pathways are complex.
- One size does not (should not / will not) fit all.
- Further progress will come from learning how to better use agents we currently have – and those coming.
The Evolution of Hormonal Targeting

Timeline: Evolution of hormone strategies to treat prostate cancer

- Huggins and colleagues demonstrate the beneficial effect of androgen ablation in patients with metastatic prostate cancer using either surgical castration by orchietomy or medical castration by oestrogen therapy.
- Anderson, Bruchovsky, Mainwaring and colleagues discover and characterize the androgen receptor and investigate ways to produce synthetic peptide agonists of LHRH.
- Schally characterizes the structure of the luteinizing hormone-releasing hormone (LHRH; also known as gonadotropin-releasing hormone), and investigates ways to produce synthetic peptide agonists of LHRH.
- First antiandrogen approved: Flutamide
- First LHRH antagonist approved: Degarelix
- Abiraterone obtains FDA approval for treatment of metastatic castrate resistant prostate cancer (CRPC) before chemotherapy
- Enzalutamide obtains FDA approval for treatment of metastatic CRPC before chemotherapy

Key Events:
- 1941: The Veterans Administration Cooperative Urologic Research Group (VACURG) deems oral oestrogen diethylstilbestrol (DES) treatment is as effective as orchietomy in the treatment of prostate cancer.
- 1954: Schally receives the Nobel Prize in Physiology and Medicine for his revolutionary work.
- Late 1960s: Schally characterizes the structure of the luteinizing hormone-releasing hormone (LHRH).
- 1977: Case report of ketoconazole used for prostate cancer, resulting in rapid and sustained reduction in serum androgens and rapid induction of a clinical remission.
- 1983: First LHRH analogue approved: Leuprolide
- 1985: First antiandrogen approved: Flutamide
- 1990: First LHRH antagonist approved: Degarelix
- 2008: Enzalutamide obtains FDA approval for treatment of metastatic CRPC before chemotherapy
- 2011: Abiraterone obtains FDA approval for treatment of metastatic castrate resistant prostate cancer (CRPC) before chemotherapy
- 2012: Miller and Hinman try to produce ‘medical adrenalectomy’ by using large doses of cortisone, resulting in subjective and objective improvement.
Currently We Face a Choice Paradox in CRPC

Currently, we face a choice paradox in Castrate-Resistant Prostate Cancer (CRPC) as we transition from Castration Sensitive to Castration Resistant states.

**Diagnosis**

- Surgery/Radiation
- Androgen Ablation
- (Metastatic) Castrate-Resistant Prostate Cancer (CRPC)

**Androgen Ablation Therapy**

- Normal
- Localised
- Advanced

- Castration Sensitive
- Castration Resistant

**Chemotherapies**

- **‘Pre-chemotherapy’**
  - Abiraterone acetate
  - Enzalutamide
  - Sipuleucel-T
  - Trial therapies

- **‘Post-chemotherapy’**
  - Abiraterone acetate
  - Enzalutamide
  - Cabazitaxel
  - Radium²²³
  - Trial therapies
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Androgen Receptor (AR) in Prostate Cancer

- AR activated in cytoplasm, translocated to nucleus, binds and activates AR-target genes
- AR addiction is a hard habit to break

Hormonal Targets Remain Relevant in Advanced Prostate Cancer

Pezaro & Omlin 2013.

MONASH University
Medicine, Nursing and Health Sciences

Pezaro & Omlin 2013.
Abiraterone Acetate: Androgen Biosynthesis Inhibitor

- Androgens produced at 3 critical sites lead to tumor proliferation
- Abiraterone inhibits biosynthesis of androgens

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Endpoints</th>
<th>Analyses</th>
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<tbody>
<tr>
<td><strong>Post-chemotherapy 301:</strong> Abiraterone/Pred vs. Placebo/Pred</td>
<td>1195</td>
<td>Overall survival</td>
<td>15.8 vs. 11.2m (HR 0.74, 95% CI 0.64 – 0.86) *final analysis</td>
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<tr>
<td><strong>Pre-chemotherapy 302:</strong> Abiraterone/Pred vs. Placebo/Pred</td>
<td>1088</td>
<td>Overall survival</td>
<td>34.7 vs. 30.3m (HR 0.8, 95% CI 0.69-0.34) **final analysis</td>
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<td>Radiographic PFS</td>
<td>16.5 vs. 8.3m (HR 0.53, 95% CI 0.45 – 0.62)</td>
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Abiraterone: Mechanism of Action + Toxicity

ACTH

Pregnenolone

Deoxycorticosterone $\times 10$

Corticosterone $\times 40$

Aldosterone $\div 1.5$

Hypokalemia

Hypertension

Fluid overload

Suppression of renin

Negative feedback

CYP17: 17α-hydroxylase

17OH-Pregnenolone $\rightarrow$ 17OH-Progesterone $\rightarrow$ 11-deoxycortisol $\rightarrow$ Cortisol $\div 2$

Testosterone $\div 1$ ng/dL

Estradiol $\div 80$ ng/dL

DHEA $\times 3$

Androstenedione $\div 2$ ng/dL

CYP17: C17,20-lyase

Positive drive

x 5

Hypokalemia

Hypertension

Fluid overload

### Enzalutamide: Second Generation Anti-Androgen

**Study** | **N** | **Endpoints** | **Analyses**
--- | --- | --- | ---
**Post-chemo AFFIRM:** Enzalutamide vs. Placebo | 1199 | Overall survival | 18.4 vs. 13.6m (HR 0.63, 95% CI 0.53 – 0.75)
**Pre-chemo PREVAIL:** Enzalutamide vs. Placebo | 1717 | Overall survival | 35.3 vs. 31.3m (HR 0.77, 95% CI 0.67-0.88)
 |  | rPFS | *Final analysis
 NR vs. 3.9m (HR 0.19, 95% CI 0.15 – 0.23)
• **In vitro:** Confocal microscopy

Red = tubulin  
Green = AR

Arrowheads: microtubule bundles

A: Control  
B: DHT analogue  
C: Paclitaxel + DHT analogue  
D: Paclitaxel

• AR in Circulating Tumour Cells:
  – 14 pts receiving taxanes.
  – 13/18 samples during ‘clinical progression’ showed NUCLEAR AR localisation.
  – 12/17 samples during ‘response/stable disease’ showed CYTOPLASMIC AR localisation.
  – Cytoplasmic AR localisation seen as early as 1-hour post taxane.
Additional AR-Targeting Agents in Development

Circulating testosterone
- LHRH analogues

CYP17A1 inhibitors
- Abiraterone
- Orteronel (TAK-700)
- VT-464
- Galeterone (TOK-001)

Adrenal androgens

Androgen biosynthesis inhibitors
- Dutasteride
- ASP9521

Steroidogenic enzyme up-regulation
- DHT biosynthesis

Second generation anti-androgens
- Enzalutamide
- ARN-509
- ODM-201

AR overexpression
- ligand hypersensitivity

AR mutation
- ligand promiscuity

AR truncation
- constitutively active

AR mRNA inhibitors
- ISIS-ARRx

AR N-terminal inhibitors
- EPI-001

Nucleus

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Increasingly Complex Models = Increased Variability of Response
Mechanisms of Castration Resistance

Cytoplasm

1. AR Promiscuity

2. Modification of Co-regulators

3. Aberrant Activation

4. Adrenal androgens

5α-reductase

5α-dione “backdoor” pathway

SHBG

Ligand-dependent

Ligand-independent

Nucleus

1. AR amplification

Growth and Survival regulation

Transcriptional Regulation

Genome

Cofactor recruitment

Co-activators

Co-activators

Co-activators

AR production

wtAR

mutAR

hsp90

wtAR

hsp90

wtAR

hsp90

wtAR

hsp90

ARV

ARV

ARV

ARV

p52

MAPK

AKT

Non-Receptor Tyrosine kinases

Receptor Tyrosine kinases

Chandrasekar: Transl Androl Urol 2015.
AR Pathway Aberrations Increased in CRPC

Robinson: Cell 2015.
Genomic Landscape Reveals CRPC Complexity
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Looking Beyond the Bottom Line in Clinical Trials

PSA Decline on Abiraterone Phase II Trial

Progression-Free Survival on Abiraterone-301 Trial

Reid: J Clin Oncol 2010; de Bono: NEJM 2011
Sequencing Cohorts Reveal Further Heterogeneity

Case series: 35 patients Abi - Enza
How Do We Approach Individualised Treatment?

BIOMARKERS REQUIRED

Laboratory e.g. Presence of AR mutations?

Clinical e.g. Long response to prior treatment?

Imaging e.g. Differential activity?

Response patterns to AR targeting treatments in advanced prostate cancer

- Refractory
- Acquired resistance
- Continued sensitivity to sequential AR therapies
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State-of-the-Art Treatment Requires State-of-the-Art Assessments

- Out with old imaging!
  - Bone scan: ‘better than an x-ray’ = 3 monthly on-trial assessments??
  - CT/BS: progression focus
  - Unreliable

  …Cabozantanib

- Newer technologies: response + progression data:
  - Diffusion-weighted MRI
  - PSMA/Na/F/Cl PET

- Bring in biomarkers!
  - PSA ≠ survival surrogate
  - PFS unreliable (TAK-700)

  - Hb, ALP, albumin slow and late

  - CTC / cfDNA easily accessible, promising (but may still hide heterogeneity)

  - Need validating across trials / populations / platforms
Where Are Current Hormonal Agents Moving?

• Combinations:
  – Upfront
  – Addition on progression

• Earlier in disease:
  – M0 CRPC (if this really exists)
  – Hormone-sensitive
  – Biochemical recurrence
  – Neo-adjuvant
~50 Abi-combo trials on Clinical Trials, ~35 Enza-combinations

Docetaxel / Cabazitaxel
Enzalutamide / ARN509 (JNJ56021927)
Radium-223
Ipilimumab
HSP90 inhibitors
VEGFR inhibitors
PSA-TRICOM
PI3K / mTOR / AKT inhibitors

Reciprocal regulation in PTEN-deficient prostate cancer

DOCETAXEL + GRAVEYARD

www.clinicaltrials.gov; Carver Cancer Cell 2011
Liquid Biomarkers May Predict Efficacy of AR Targeting

- PSA response by ARv7 status ➔ ARMOR3-SV Trial

**Key Inclusion:**
- Progressive metastatic (M1) disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

**Key Exclusion:**
- Prior treatment with second generation anti-androgens (e.g. Zytiga, Xtandi)
- Prior treatment with chemotherapy for CRPC

**Primary Endpoint:**
- Radiographic Progression Free Survival (rPFS)

**Secondary Endpoints:**
- Overall Survival (OS)
- PSA Changes
- Safety

- AR amplification:
  - Associated with treatment resistance in abiraterone and enzalutamide cohorts

Biomarker-Embedded Research

**OZM-054: A phase 2, randomized, multicenter study**

- **Whole Blood:** cfDNA Collection
- **Whole Blood:** RNA Collection

**1st Line Therapy**

- **Arm A:** CBZP
- **Arm B:** AA or ENZA (n = 50)

**2nd Line Therapy**

- **Arm A:** CROSSOVER TO AA or ENZA
- **Arm B:** CROSSOVER TO CBZP

**mCRPC**
- Liver metastases
- CRPC <12 mo from initial ADT
- Poor prognosis by index

**CBZP:** cabazitaxel; **ENZA:** enzalutamide
**ClinicalTrials.gov:** NCT02254785; **PI:** K. Chi
Should We Challenge the Basic Premise of Castration?

- **Enzalutamide monotherapy:**
  - 62 of 67 men in phase II trial has PSA decline ≥80% at week 25
  - Most common adverse events G1-2 gynaecomastia, fatigue
  - LH and testosterone increased from baseline

- **Bipolar androgen therapy:**
  - Castration with intermittent supraphysiologic testosterone
  - PSA response in 7 of 14 evaluable patients
  - ?Improved sensitivity to subsequent ADT

_Tombal: Lancet Oncol 2014; Schweizer: Sci Trans Med 2015._
Conclusions

• Hormonal treatment options for men with advanced prostate cancer have markedly improved in the past decade.

• It is extremely unlikely that there is an optimal ‘one size fits all’ sequence.

• We must prioritise initiatives that enable treatment prediction and earlier recognition of progression.

• Further innovation will result from identifying patient subtypes for current and new hormonal treatments AND from improved methods of assessing treatment response.
THANK YOU