Advances in Prostate Cancer
(Localized to Newly metastatic)

Christopher Sweeney, MBBS
Dana Farber Cancer Institute
Prostate Cancer: A Disease with Many States

- Organ Confined Low Risk
- Clinically Localized - Risk of Mets
- Metastatic Disease
- Castration Resistant Prostate Cancer

- Risk of cancer
- Rising PSA no mets
- Rising PSA no/min mets
Improving Patient Selection for Localized Therapy

- Organ Confined Low Risk
- Risk of cancer
- Clinically Localized - Risk of Mets
- Prostate Cancer
- Rising PSA no mets
- Metastatic Disease
- Rising PSA no/min mets
- Castration Resistant Prostate Cancer
Low Risk and High Risk Localized Prostate Cancer

Outcome with surgery

- **Gleason 8-10**: 10% of all cases
  - 49% 15-year PCSM
  - 45% of all cancer deaths
- **Gleason 7**: 40% of all cases
  - 8% 15-year PCSM
  - 50% of all cancer deaths
- **Gleason 6**: 50% of all cases
  - <1% 15-year PCSM
  - 1 of 3756 patients with organ-confined, Gleason 6 cancer died of prostate cancer
Current Prostate Cancer Therapies for Localized Disease

- Active Surveillance
- Surgery
- Radiation (+/- testosterone suppression)
Current Prostate Cancer Therapies for Localized Disease

- **Active Surveillance**
- Patients with Biopsy low volume Gl 6 and PSA < 10 (rarely patient with low volume Gl 3+4=7)
- PSA and DRE every 3 months; TRUS biopsy annually
- 450 patients
  - 117 went on to surgery or radiation over ~ 5 year period of time
Current Prostate Cancer Therapies for Localized Disease

- **Surgery**
- Patients with nodule on DRE and watchful waiting (ie not get surgery if progressed) vs surgery
- Mostly low to intermediate risk disease
Current Prostate Cancer Therapies for Localized Disease

• **Radiation plus Testosterone suppression**

• Patients with intermediate risk disease
  – Gl 7, PSA 10 to 20
  – Radiation plus testosterone suppression results in less patients dying of prostate cancer
Current Prostate Cancer Therapies for Localized Disease

- **Radiation plus Testosterone suppression**
- Patients with high risk disease
  - GI 8, PSA > 20
- 3 years testosterone suppression
  - Markedly better than none
  - Modestly better than 6 mos
The Need to Improve Prostate Cancer Risk Stratification

60 yo man presents to PCP for check-up:
Pt: “Do I have PrCa?”
Doc: “Probable but only a few are dangerous”

PSA
DRE
TRUS Pr Biopsy

High risk:
PSA > 20; large nodule; Gl > 8: No question -- treat

Intermediate risk:
Small nodule; Gl 7:
May need treatment and even if Rx, some relapse

Low risk: No nodule; Gl 6:
Many never need treatment and even if Rx, impair QOL (incontinence/impotence”

No Cancer:
Serial PSA and DRE until life expectancy < 10 yrs
60 yo man presents to PCP for check-up:
Pt: “Do I have PrCa?”
Doc: “Probable but only a few are dangerous”
PSA, DRE and TRUS Bx

High risk:
PSA > 20; large nodule;
Gl > 8
No question -- treat

Intermediate risk:
Small nodule; Gl 7:
May need treatment
Some relapse

Low risk: No nodule; Gl 6:
May never need treatment and even if Rx, Impair QOL (incontinence/impotence”

No Cancer:
Serial PSA and DRE until life expectancy < 10 yrs

Most of the Pts With PrCa & Need Refined knowledge
-Avoid Treatment
-Adjuvant Rx to Prevent relapse
Genomic Risk Stratification

- 349 men with genes associated with pushing cells through growth cycle measured on biopsy and managed without surgery or radiation

*Cuzick et al BJC 2012*
Proposition

• By increasing the intensity / efficacy of therapy for patients with localized disease we will decrease the death rate from prostate cancer
  – 33,000 deaths (~ 7,000 from de novo mets)
    • ~ 26,000 from relapsed disease / prevent 50% relapse = save 13,000 lives per year
    • Decrease # deaths from 33,000 to 20,000 per year

• Bring treatments effective for highly resistant incurable CRPC earlier to eradicate curable micrometastatic disease
## The New Agents

<table>
<thead>
<tr>
<th>Trial/Agent Approved</th>
<th>Disease State</th>
<th>Comparator</th>
<th>Median Months Benefit</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel+Pred</td>
<td>Pre-Docetaxel CRPC</td>
<td>Mitoxantrone Pred</td>
<td>2.5</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>Pre-Docetaxel mCRPC</td>
<td>Placebo</td>
<td>4.1</td>
<td>0.775</td>
<td>0.032</td>
</tr>
<tr>
<td>Abiraterone+Pred</td>
<td>Pre-Docetaxel mCRPC</td>
<td>Pred</td>
<td>NR</td>
<td>0.75</td>
<td>0.0097</td>
</tr>
<tr>
<td>Enzalutimide</td>
<td>Post-Docetaxel CRPC</td>
<td>Placebo</td>
<td>4.8</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alpharadin</td>
<td>Pre and Post-Docetaxel</td>
<td>Placebo</td>
<td>2.8</td>
<td>0.69</td>
<td>0.00185</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Post-Chemotherapy</td>
<td>Mitoxantrone Pred</td>
<td>2.4</td>
<td>0.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(Abiraterone+Pred) 2011</td>
<td>Post-Docetaxel CRPC</td>
<td>Pred</td>
<td>3.9</td>
<td>0.646</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Intense hormonal therapy with new agent plus testosterone suppression results in less cancer at surgery: Pathology Results

<table>
<thead>
<tr>
<th>Results</th>
<th>12 weeks AA/24 weeks LHRHa (n = 28)</th>
<th>24 weeks AA/24 weeks LHRHa (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>1/27 (4%)</td>
<td>3/29 (10%)</td>
<td>0.6120</td>
</tr>
<tr>
<td>Near CR (tumor ≤ 5 mm)</td>
<td>3/27 (11%)</td>
<td>7/29 (24%)</td>
<td>0.2992</td>
</tr>
<tr>
<td>Total pCR/near pCR</td>
<td>4/27 (15%)</td>
<td>10/29 (34%)</td>
<td>0.0894</td>
</tr>
</tbody>
</table>
Intense hormonal therapy with new agent plus testosterone suppression results in less cancer at surgery: Blood Hormone Levels

**Dihydrotestosterone**

- **LHRHa**
- **AA/LHRHa/pred**
- **LHRHa + AA/LHRHa/pred**

**DHEA**

- **LHRHa**
- **AA/LHRHa/pred**
- **LHRHa + AA/LHRHa/pred**

- **p < 0.0001**
- **p = 0.0004**
- **p < 0.0001**
- **p < 0.0001**

- **12 week**
- **24 week**

- At 12 weeks, AA/LHRHa/pred significantly reduced serum DHT and DHEA levels compared with LHRHa.
- Addition of AA/pred to LHRHa at 12 weeks led to significantly reduced DHT and DHEA levels at 24 weeks compared with LHRHa alone at 12 weeks.

*P values from log-transformation of data.*

More Patients Will Be Cured of Prostate Cancer If We Prevent Relapses After Local Therapy

Total US Prostate Cancer Cases
N=240,800 in 2012

Localized disease
- Avoid treatment of those who don’t need Rx and provide enough Rx to those who need it

Metastatic Disease
- Relapsed from localized
- DeNovo Met

~3% of all PrCa
~ 7,000 of 33K deaths

Total US Prostate Cancer Death
N=33,270 in 2011
More Patients Will Be Cured of Prostate Cancer If We Prevent Relapses After Local Therapy

Total US Prostate Cancer Cases
N=240,800 in 2012

Localized disease
- Avoid treatment of those who don’t need Rx and provide enough Rx to those who need it

• Fewer patients who relapse
• Fewer patients who present with metastatic disease

Prevent 50% Relapses will lead to decrease US death rate
From 33,000 to 20,000
Problem

• The ability to show improvement in overall survival (cure rate) from adjuvant prostate cancer trials takes longer than a decade

• Men with aggressive localized prostate cancer with more than 20 year life expectancy could be cured with our current Rx but we have to wait greater than a decade to bring the treatments to them
Potential Solution

• Development of an intermediate clinical endpoint which accurately reflects the improvement in overall survival / cure rate

• Eg biochemical free survival at year X
• Eg metastasis free survival at year X
• An example...adjuvant radiation studies
Rising PSA after local therapy

- Organ Confined - Low Risk
- Clinically Localized - Risk of Mets
- Rising PSA no mets
- Metastatic Disease - Rising PSA no/min mets
- Castration Resistant Prostate Cancer

Prostate Cancer
Salvage radiation therapy (sRT) - “Stephenson’s” data

- Retrospective review of 1,540 pts with BCR after RP from 17 institutions (1987-2005)
- PSA > 0.2 ng/mL prior to sRT

**Progression**
- PSA > 0.2 above nadir after sRT, start of systemic Rx, clinical progression

Stephenson et al; *J Clin Oncol* 25:2035-2041. 2007
**Radiation Rx +/- Hormonal Therapy**

- **RTOG 9601**
  - 771 pts post RP
  - Med F-up of 7.1 yrs
  - Med age: 65 yo
  - pT3 or T2 with +ve TM, N0
  - PSA > 0.4
  - 64.8 Gy XRT
  - +/- 2 yrs of 150 mg bicalutamide alone
  - Placebo controlled

<table>
<thead>
<tr>
<th></th>
<th>Rads + Bic</th>
<th>Rads Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Late Gde 3 or 4 Toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>GI</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% free PSA progression</td>
<td>57%</td>
<td>40%</td>
</tr>
<tr>
<td>% with mets</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>7 yr Overall Survival</td>
<td>91%</td>
<td>86%</td>
</tr>
</tbody>
</table>
Intermittent vs Continuous ADT for D0 Prostate Cancer

- NCI-C PR.7/CTSU/UK
- 1386 pt with PSA > 3 1 yr post RT (salvage/primary)
- Med F-up 6.9 yrs
- IAS: 8 mos ADT and reRxn with PSA > 10
- Intermittent:
  - Less Hot flashes
  - On ADT for 27% of the time
  - 15 mos on 37 mos off

<table>
<thead>
<tr>
<th></th>
<th>IAS</th>
<th>CAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Deaths</td>
<td>122</td>
<td>97</td>
</tr>
<tr>
<td>(9%)</td>
<td></td>
<td>(8%)</td>
</tr>
<tr>
<td>Unrelated Deaths</td>
<td>134</td>
<td>146</td>
</tr>
</tbody>
</table>
Metastatic Disease Starting Hormonal Therapy

- Organ Confined Low Risk
- Clinically Localized - Risk of Mets
- Metastatic Disease
- Castration Resistant Prostate Cancer

- Risk of cancer
- Rising PSA no mets
- Rising PSA no/min mets

Prostate Cancer
Historical Perspective: Understanding Testosterone Endocrinology
Historical Perspective: Combined Androgen Blockade

- How real is the testosterone surge issue with LHRH agonists? **Clinical data from early studies**

- **Number of pts with worse pain @ week 4**
  - **Week 4:** LHRH 33 pts vs CAB 20 pts (p=0.013)
    - Intergroup 0036, Crawford NEJM, 1989, N = 603

- 7 month inc in MST in SWOG/Intergp of LHRH vs LHRH + CAB
- ? Early disease control accounts for benefit of CAB with anti-androgens in meta-analysis
Historical Perspective: Combined Androgen Blockade

- How real is the testosterone surge issue with LHRH agonists? **Role of LHRH Antagonists**

<table>
<thead>
<tr>
<th></th>
<th>CAB N=200</th>
<th>Degarelix N=400</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone D#3 &lt; 50 ng/mL</td>
<td>0%</td>
<td>96%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Klotz et al, BJU Intl, 2008
Historical Perspective: Combined Androgen Blockade

- Long term efficacy data of CAB: Meta-analysis

Contention: Off target effects of cyproterone on adrenal steroids effected outcome

Conclusion: Small (3%) benefit with long term CAB with non-steroidal anti-androgen (range of uncertainty 0% to 5%)

Prostate Cancer Trialists’ Collaborative Group*, Lancet 2000
Historical Perspective:
Testosterone Suppression vs Anti-Androgen Monotherapy

Conclusion:
LHRH Rx = Orch
Castration > Anti And Mono

Seidenfeld et al, Ann Int Med 2000; Meta-Analysis
Newly Metastatic Hormone Sensitive Disease

Deeper PSA Nadir: Better outcome to ADT

Hussain et al.

*J Clin Oncol*, 2006
Intermittent vs Continuous

SWOG led Intergroup trial
Metastatic Prostate Ca
-Starting ADT (3040 men)
-PSA < 4 (1535 men = selected group)
-Randomized to continuous Vs Int ADT

Hazard Ratio for death with Int Rx 1.10; 90% CI - 0.99 to 1.23

Exceeded the upper boundary for Noninferiority (cannot rule out a 20% greater risk of death with Int Rx vs Cont than with continuous therapy but too few events occurred to rule out significant inferiority of intermittent therapy

Hussain et al, NEJM 2013
A. Patients with Minimal Disease

- **Continuous therapy**: 220 deaths, Median Survival 6.9 yr
- **Intermittent therapy**: 231 deaths, Median Survival 5.4 yr

---

**Extensive Disease**

- **Continuous therapy**: 225 deaths, Median Survival 4.4 yr
- **Intermittent therapy**: 252 deaths, Median Survival 4.9 yr

---

**No. at Risk**

- **Continuous therapy**
  - Initial: 403, Years 208, 39
- **Intermittent therapy**
  - Initial: 389, Years 160, 39

---

**No. at Risk**

- **Continuous therapy**: 362, Years 116, 24
- **Intermittent therapy**: 381, Years 130, 12
QOL Analyses

ADT restarted with PSA > 20 ng/mL or preRx level if < 20;
(At the discretion of the investigator could be reinitiated when PSA level reached 10 ng/mL or when symptoms developed)
Restart another 7 months dosing and hold when < 4

<table>
<thead>
<tr>
<th>Functioning after Randomization</th>
<th>Erectile Function</th>
<th>Libido</th>
<th>Vitality</th>
<th>Mental Health</th>
<th>Physical Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>++</td>
<td>+</td>
<td>same</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Month 9</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Month 15</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>+</td>
</tr>
</tbody>
</table>

(+)=Int better
Intermittent ADT for metastatic disease

• Not superior cancer control
  – Preclinical models suggested

• Better QOL
  – A worthy endpoint

• Some patients have miserable experience
  – Metabolically unwell
  – Major QOL decline

• OK to do intermittent after r/v pros and cons
  – Restart sooner than the study suggested?
Hormone Sensitive Newly Metastatic Prostate Cancer: ADT +/- Docetaxel

Gravis et al Lancet Oncology 2012
French Study of 385 patients

9 cycles of q 3 week docetaxel

Sample size provided 80% power to assess whether early docetaxel could decrease the rate of death by 38% (hazard ratio of 0.62).
Hormone Sensitive Newly Metastatic Prostate Cancer: ADT +/- Docetaxel

In this study docetaxel did not reduce early deaths despite delay of progression.
- the efficacy of docetaxel fell before progression

? non-cancer deaths of elderly men with important comorbidities

? exacerbated by the adverse effects of cytotoxic therapy.
Other observations:
Fewer deaths in ADT plus docetaxel were caused by disease progression (68 [77%] of 88) than in the group given ADT alone (75 [85%] of 88),

4 deaths (5%) ADT plus docetaxel were treatment related toxic effects vs none in the group given ADT alone.

Lack of early survival benefit could be from disease that is resistant to both ADT and chemotherapy.

120 (62%) of 193 patients given ADT alone received docetaxel at progression, vs 54 (28%) of 192 given ADT plus docetaxel who were re-treated with docetaxel.
Hormone Sensitive Newly Metastatic Prostate Cancer: Clinical Trials

ECOG: CHAARTED Study; PI: Sweeney

Stratify
Age
≥ 70 vs < 70

ECOG PS
0-1 vs 2

CAB\(^1\) > 30 DAYS
Yes
No

Prior Adjuvant Hormonal Therapy
> 12 months
≤12 months

Bisphosphonate\(^2\)
Yes
No

Randomize

ARM A:
Androgen Deprivation\(^3\)
plus
Docetaxel 75 mg/m\(^2\)
every 21 days for maximum of 6 cycles

Evaluate every 3 weeks while receiving Docetaxel and at week 24 then every 12 weeks*

ARM B:
Androgen Deprivation Alone

Evaluate every 12 weeks*

N=780; 790 accrued
Whole blood, Tissue
Serum/Plasma – Baseline, 6 mos, CRPC
**Hormone Sensitive Newly Metastatic Prostate Cancer: Clinical Trials**

**CALGB 90202: PI Smith**

- **Randomize**
  - ADT + placebo q4w
  - ADT + zoledronic acid q4w

- **Progressive Disease**
  - zoledronic q3w

- **Double-Blinded**
- **Open-label**

**Primary Endpoint:** First skeletal related event or death
Moving Forwards by Going Backwards

- Organ Confined Low Risk
- Clinically Localized - Risk of Mets
- Metastatic Disease
- Castration Resistant Prostate Cancer

Risk of cancer
- Rising PSA no mets
- Rising PSA no/min mets

Prostate Cancer
## The New Agents

<table>
<thead>
<tr>
<th>Trial/Agent Approved</th>
<th>Disease State</th>
<th>Comparator</th>
<th>Median Months Benefit</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX327 (Docetaxel+Pred) 2004</td>
<td>Pre-Docetaxel CRPC</td>
<td>Mitoxantrone Pred</td>
<td>2.5</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>IMPACT (Sipuleucel-T) 2010</td>
<td>Pre-Docetaxel mCRPC</td>
<td>Placebo</td>
<td>4.1</td>
<td>0.775</td>
<td>0.032</td>
</tr>
<tr>
<td>COU 302 (Abiraterone+Pred)</td>
<td>Pre-Docetaxel mCRPC</td>
<td>Pred</td>
<td>NR</td>
<td>0.75</td>
<td>0.0097</td>
</tr>
<tr>
<td>AFFIRM (Enzalutimide)</td>
<td>Post-Docetaxel CRPC</td>
<td>Placebo</td>
<td>4.8</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>Pre and Post-Docetaxel</td>
<td>Placebo</td>
<td>2.8</td>
<td>0.69</td>
<td>0.00185</td>
</tr>
<tr>
<td>TROPIC Cabazitaxel</td>
<td>Post-Chemotherapy</td>
<td>Mitoxantrone Pred</td>
<td>2.4</td>
<td>0.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COU 301 (Abiraterone+Pred) 2011</td>
<td>Post-Docetaxel CRPC</td>
<td>Pred</td>
<td>3.9</td>
<td>0.646</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Radiation Plus Adjuvant LHRH With or Without New Agent in High Risk Clinically Localized Prostate Cancer

Eligibility
- Patient group with projected OS at 8 years of 65%; DSS of 80% (based on Bolla 3-year arm and GI 8 in RTOG 28-months arm)
- Gleason ≥ 8 and GI 4+3 with tertiary 5
- PSA < 100 and T any

New Agent: Abiraterone, Enzalutamide, TAK700 – all drugs active in disease growing with low testosterone
ADT ± New Agent in Metastatic Prostate Cancer Commencing ADT

Eligibility
- Radiographically evident metastatic PCa
- No prior ADT except adjuvant therapy completed <24 months and completed >12 months prior to enrollment

N= Approximately 1,100

1:1

ADT (LHRH or surgical at investigator discretion)

Castration (surgical or LHRH) + New Agent

New Agent: Abiraterone, Enzalutamide, TAK700 – all drugs active in disease growing with low testosterone
Conclusions

• New science is starting to provide
  – More in depth information on who needs treatment versus not need treatment for localized disease
    • Old approach: can a doctor feel it and what do cells look like under microscope
    • New: identify genes driving bad cancer
  – Targets to direct drug development and lead to more effective killing of prostate cancer cells
    • Make testosterone suppression alone more effective by preventing resistance (more effective for metastatic disease and prevent relapse after surgery or radiation)