Prostate Cancer

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Educational Objectives

By the end of this session, participants should be able to

Understand the treatment options for localized prostate cancer

Understand the treatment options for metastatic disease

Understand emerging data on treatment resistance
Presentation Outline

1. Prostate Cancer overview
2. Therapies for localized prostate cancer
3. Therapies for locally advanced disease
4. Systemic therapies for metastatic disease
   a. Androgen deprivation therapy (ADT)
   b. Chemotherapy
   c. Immunotherapy
      a. Radiopharmaceuticals
5. Mechanisms of Resistance
6. Future Directions
Prostate Cancer Clinical States

- Asymptomatic
- Symptoms
- Non-Metastatic
- Metastatic
- Castration Sensitive
- Castration Resistant

Tumor volume
Local Therapy
Castration
2nd-line Hormonal therapy
Abiraterone 2013 Enzalutamide 2014
Sipuleucel-T 2010
Docetaxel 2004
Cabazitaxel 2010
Abiraterone 2011 Enzalutamide 2012
Radium-223
Death
Epidemiology

- Most Common malignancy in men
- Lifetime risk of 1 in 6 men
- 2012 estimated new cases 241,740
- Estimated deaths 28,170
- 24% of men will die from their disease

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>241,740</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,470</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73,420</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>55,600</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>44,250</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,250</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,160</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>28,540</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>26,830</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,090</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>848,170</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Risks

Age
Family history
Genetic predisposition
  HPCG
  BRCA
  TMPRSS2-ETS
Environmental
Obesity
Race
Prevention in Prostate Cancer…
A cautionary Tale

• 5-α-reductase inhibitors
  – Finasteride
    • Selective inhibitor of type II enzyme
    • Decreases DHT by about 70%
    • *Prostate Cancer Prevention Trial*
  – Dutasteride
    • Inhibits type I and II enzymes
    • Decreases DHT by >90%
    • REDUCE trial (Reduction by Dutasteride of Prostate Cancer Events)

• SELECT Trial (Vitamin E and Selenium)
  • No protective effect
Screening – Digital Rectal Exam

Digital rectal examination

- Sensitivity 53% and specificity 83%
- More advanced disease are detected
Total PSA

At cutoff of 4.0ng/ml, sensitivity is 73% at 4 years and specificity is 91%

“The yield of screening in terms of cancer cases detected declines rapidly with repeated annual testing. If screening were to reduce deaths, PSA screening as infrequently as every 4 years could yield as much of a benefit as annual screening” - USPSTF
Incidence versus Mortality
Prostate cancer in the USA

Incidence vs. Mortality
Prostate Cancer in the U.S.

(G. Welch, “Should I Be Tested for Cancer?”, 2004)
Gleason Grading

Primary Grade
Greater 50%

Secondary Grade
<50% but ≥5%
## Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
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<tbody>
<tr>
<td>I (A)</td>
<td>T1a (incidental)</td>
<td>Localized</td>
</tr>
<tr>
<td>II (B)</td>
<td>T1b, $T1c$, T2a,b,c (within prostate)</td>
<td></td>
</tr>
</tbody>
</table>
| III (C)| T3a (through capsule)  
        | T3b (seminal vesicles)                  | Locally Advanced    |
| IV (D)| T4 (fixed, invades)                      |                     |
|       | N1, M1                                   | Metastatic          |
Principles Guiding Therapy of Localized Prostate Cancer

Patients with a life expectancy of at least 10 are more likely to benefit.

Patients older than 75 years have other competing causes of mortality.

Eradication of the cancer is the goal of therapy.

Low grade/stage tumors may just require active surveillance.
Watchful Waiting

Observation with palliative treatment for symptoms

No biochemical monitoring

Ideal for patients with poor life expectancy who are likely to die from causes other than prostate cancer
Active Surveillance

Periodic biochemical (PSA) monitoring

Annual Biopsy may be part of active surveillance

Conversion to active treatment when signs of disease progression develop
Who is the Ideal Candidate for Watchful Waiting/Active Surveillance?

The probability of prostate cancer mortality is low with:
- Lower Gleason score
- Advanced age

![Graph showing survival rates by age, Gleason score, and years following diagnosis.](image)
Randomized Trial Comparing Surgery and Watchful Waiting

Early stage prostate cancer (n=695)
Deaths at median 8.2 years of follow-up
Following prostate cancer surgery 83 died, 30 from prostate cancer
Also less metastasis
Caveats:
  - More advanced clinically then current US patients
    - Only 5% of men had screen detected PC
  - Advantage largely in men <65 y.o.
Surgery Complications

Incontinence
Erectile Dysfunction
Infection
Complications associated with anesthesia
Radiation Therapy-External Beam

The principle is to deliver therapeutic dose of radiation to the tumor but minimize damage to adjacent structures.

Modalities of external beam radiotherapy:
- 3-dimensional conformal radiation therapy (3D-CRT)
- Intensity modulated radiation therapy (IMRT)
- Image-guided radiation therapy (IGRT)
- Proton-beam radiation therapy
Radiation Therapy - Brachytherapy

Direct implantation of radiation seeds
Maximizes radiotherapy to the tumor
limits damage to the surrounding structures
One time treatment
Radiation Therapy-Complications

Gastrointestinal
  Less common with brachytherapy

Genitourinary
  Incidence of erectile dysfunction varies widely

Secondary malignancies
  Slight increase risk with bladder and to a lesser extent with rectal cancer
Primary Androgen Deprivation Therapy

May be used in men who refused or are not candidates for definitive local therapy

EORTC Trial 30891 randomized 985 men with localized or locally advanced prostate cancer to

Immediate ADT vs. deferred ADT

Overall survival HR 1.25, in favor of immediate ADT

Prostate cancer-specific survival not different

Time to hormone refractoriness not different
Management of Locally Advanced Prostate Cancer

- Surgery with ADT
  - Neoadjuvant or adjuvant
- Surgery with adjuvant RT
- Radiotherapy with ADT
Neoadjuvant ADT with Surgery

149 men with T2bNxFM0 prostate cancer were randomized to RP vs. RP + 3 mths of neoadjuvant leuprolide/flutamide

Neoadjuvant ADT led to

- Less positive surgical margin (18% vs. 48%, p<0.001)
- 5-year biochemical recurrence-free survival
  - 64.8% vs. 67.6% (p=0.663)

Overall survival not reported
Adjuvant ADT with Surgery

98 men with localized node-positive prostate cancer randomized to immediate ADT or deferred ADT

At 11.9 years of follow-up, immediate ADT had

- Better overall survival (HR 1.84, p=0.04)
- Prostate-specific survival (HR 4.09, p=0.0004)
- Progression-free survival (HR 3.42, p<0.0001)

Caveat: Deferred ADT given for metastases/symptomatic recurrence, not for rising PSA
Adjuvant RT with Surgery

SWOG study of adjuvant RT vs. observation for \( T_3N_0 \) or positive margin (\( n=425 \))

70 in the observation group ultimately received RT

Endpoint – metastasis-free survival

Median follow-up 12.7 years

For metastasis-free survival RT = 14.7 whereas the observation = 12.9 years (\( p = 0.016 \))

For overall survival RT = 15.2 whereas the observation = 13.3 years (\( p = 0.023 \))
Radiotherapy with ADT

EORTC 22863 randomized 415 men with high grade locally advanced prostate cancer

EBRT ± goserelin for 3 years (cyproterone for 1 mth)

ADT group had better

10-yr disease free-survival (22.7 vs. 44.7%, p<0.0001)
10-yr overall survival (39.8 vs. 58.1%, p=0.0004)
10-yr disease-specific mortality (30.4 vs. 10.3%, p<0.0001)
Biochemical Recurrence after Initial Prostatectomy or RT

Rising PSA without local recurrence or metastasis

Treatment options include watchful waiting, prostatectomy, RT, and ADT
ADT: Intermittent vs. Continuous for Non-Metastatic Castration Sensitive Disease

Hazard ratio, 1.03 (95% CI, 0.87–1.22)
P=0.009
ADT: Intermittent vs. Continuous for Non-Metastatic Castration Sensitive Disease
Natural History of Prostate Cancer

No patients received hormonal therapy without clinically evident metastatic disease.

Median time from PSA elevation to metastatic disease was 8 years.

Median time to death after metastatic disease was 5 years. Prognostic factors predictive of outcome included the Gleason score in the surgical specimen, and PSA doubling time.
Metastatic Prostate Cancer

About 4% of prostate cancer have distant metastases at diagnosis

Bone metastases are most common

Metastatic disease are virtually incurable

The aim of therapy is to control the disease while maintaining quality of life
TAX327: Influence on Metastatic Site on Survival
ADT

Bilateral orchiectomy or surgical castration
LHRH agonist
  Leuprolide acetate, goserelin, buserelin
LHRH antagonist
  Abarelix, degarelix
Anti-androgens
  Bicalutamide, nilutamide
ADT

LHRH antagonists may produce an initial surge in testosterone (flare) before a decline in the levels.

Orchiectomy is preferred in patients who are unlikely to comply with medical therapy or due to cost.

Orchiectomy causes immediate fall in testosterone levels.

LHRH antagonist do not cause the “flare”.

Anti-androgen do not cause a decline in testosterone levels.
# Side Effects of ADT

<table>
<thead>
<tr>
<th>Sexual Side Effects</th>
<th>Physical changes</th>
<th>Metabolic Changes</th>
<th>Mental Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Libido</td>
<td>Hot Flashes</td>
<td>Lipid changes (may lead to heart disease)</td>
<td>Lack of Initiative</td>
</tr>
<tr>
<td></td>
<td>Weight Gain</td>
<td>Increased risk of Diabetes Mellitus</td>
<td>Emotional lability</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Fatigue</td>
<td>Anemia</td>
<td>Decreased memory</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia</td>
<td></td>
<td>Decreased cognitive function</td>
</tr>
<tr>
<td></td>
<td>Decreased muscle mass</td>
<td>Decrease size of penis / testis</td>
<td></td>
</tr>
</tbody>
</table>

Sharifi et al, JAMA 2005
Keating et al, JCO 2006
Metastatic Castration-Resistant Prostate Cancer (CRPC)

Disease state characterized by progression despite castrate levels of testosterone
1st Generation Anti-Androgens

Androgen Receptor Antagonists

- Nilutamide
- Flutamide
- Bicalutamide

Ketokonazole (off-label, likely non-specific cyp-17 inhibition)

Limited role in treatment of non-metastatic Castration Resistant Prostate Cancer (or to prevent flare with ADT)
Therapeutic Options in Metastatic CRPC that Improve Survival

FDA approved
Docetaxel
Sipuleucel-T
Abiraterone
Cabazitaxel (after docetaxel)
Enzalutamide
Radium-223
Docetaxel

In 1960s, crude extract of the bark of the Pacific yew tree, Taxus brevifolia, was shown to have suppressive activity in preclinical tumor models.

By 1971, paclitaxel was identified as the active constituent of the bark extract.

Taxanes exhibit antimicrotubule and antitumor activity

Emerging data suggests that taxanes inhibit AR translocation via microtubules
TAX327

A multicenter randomized phase II study of 3 weekly Docetaxel + Prednisone vs Weekly Docetaxel + Prednisone vs Mitoxantrone + Prednisone
TAX327: Overall Survival

- **Docetaxel 3 wkly**
  - Median survival (mos): 18.9
  - Hazard ratio: 0.76
  - P-value: 0.009

- **Docetaxel wkly**
  - Median survival (mos): 17.3
  - Hazard ratio: 0.91
  - P-value: 0.3

- **Mitoxantrone**
  - Median survival (mos): 16.4
Pain response was better with docetaxel containing regimens (35% and 31% vs. 22%)

Quality of life was better with docetaxel containing regimens (22% and 23% vs. 13%)

Is 2.5 month clinically significant?

   The control arm consisted of an active agent
   There was a cross-over which likely diminished the treatment effect
Docetaxel AEs

Central nervous system: Central nervous system toxicity (20% to 58%; severe: 6%; including neuropathy)

Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)

Endocrine & metabolic: Fluid retention (13% to 60%; severe: 7% to 9%; dose dependent)

Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)

Hematologic & oncologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 97%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (5% to 14%; dose dependent)

Hepatic: Increased serum transaminases (4% to 19%)

Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

Infection: Infection (1% to 34%; dose dependent)

Neuromuscular & skeletal: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%), neuromuscular reaction (16%)

Respiratory: Pulmonary reaction (41%)
Therapeutic Cancer Vaccine: Sipuleucel-T
**IMPACT**: Randomized Phase 3 Trial

**IMPACT: Randomized Phase 3 Trial**
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

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

Sipuleucel-T Q 2 weeks x 3

Treated at Physician discretion

Placebo Q 2 weeks x 3

Treated at Physician discretion and/or Salvage Protocol

2:1

Primary endpoint: Overall Survival

Secondary endpoint: Time to Objective Disease Progression

Kantoff PW et al. NEJM. 2010;363:411-22
Sipuleucel-T: IMPACT Overall Survival

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]

Median Survival Benefit = 4.1 Mos.
Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.
Sipuleucel-T AEs

chills, fatigue, fever, nausea, and headache

Cerebrovascular events were reported in 3.5 percent of patients treated with sipuleucel-T patients and 2.4 percent of patients who received placebo.
Rationale for Abiraterone in CRPC.

There is up-regulation of androgen biosynthesis enzymes in CRPC. Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue.
Abiraterone: COU-AA-301 Study Design

1195 prostate cancer patients were randomized and treated with Abiraterone acetate 1000 mg orally daily
Prednisone 5 mg orally twice daily n = 797 or
Placebo orally daily Prednisone 5 mg orally twice daily n = 398.

The primary endpoint was overall survival.
This study was conducted in 147 sites in 13 countries

Patients were enrolled from May 2008 through July 2009
Abiraterone: COU-AA-301 Trial

![Overall Survival Graph](image)

No. at Risk

<table>
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<tr>
<th>Treatment</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
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<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>797</td>
<td>736</td>
<td>657</td>
<td>520</td>
<td>282</td>
<td>68</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>398</td>
<td>355</td>
<td>306</td>
<td>210</td>
<td>105</td>
<td>30</td>
<td>3</td>
<td>0</td>
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</table>
**Abiraterone: COU-AA-301 Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abiraterone Acetate (N=797)</th>
<th>Placebo (N=398)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to PSA progression (mo)</td>
<td>10.2</td>
<td>6.6</td>
<td>0.58 (0.46–0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression-free survival according to radiographic evidence (mo)</td>
<td>5.6</td>
<td>3.6</td>
<td>0.67 (0.59–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA response rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>38.0</td>
<td>10.1</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Confirmed response on the basis of the PSA concentration</td>
<td>29.1</td>
<td>5.5</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Objective response on the basis of imaging studies</td>
<td>14.0</td>
<td>2.8</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Abiraterone AEs

Cardiovascular: Edema (25% to 27%), hypertension (9% to 22%; grades 3/4: 1% to 4%)

Central nervous system: Fatigue (39%), insomnia (14%)

Dermatologic: Bruise (13%)

Endocrine & metabolic: Increased serum triglycerides (63%), hyperglycemia (57%), hypernatremia (33%), hypokalemia (17% to 28%; grades 3/4: 3% to 5%), hypophosphatemia (24%; grades 3/4: 7%), hot flash (19% to 22%)

Gastrointestinal: Constipation (23%), diarrhea (18% to 22%), dyspepsia (6% to 11%)

Genitourinary: Urinary tract infection (12%)

Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

Hepatic: Increased serum ALT (11% to 42%; grades 3/4: 1% to 6%), increased serum AST (31% to 37%; grades 3/4: 2% to 3%)

Neuromuscular & skeletal: Joint swelling (30%, including joint discomfort), myalgia (26%)

Respiratory: Cough (11% to 17%), upper respiratory infection (5% to 13%), dyspnea (12%), nasopharyngitis (11%)
Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump
Methoxyl side chain instead of hydroxyl groups found in docetaxel
TROPIC: Randomized Phase III Study of Cabazitaxel vs Mitoxantrone in mCRPC after Progression on Docetaxel
TROPIC: Progression-Free Survival
TROPIC: Overall Survival
Cabazitaxel AEs

Central nervous system: Fatigue (37%), fever (12%)
Gastrointestinal: Diarrhea (47%; grades 3/4: 6%), nausea (34%), vomiting (22%), constipation (20%), abdominal pain (17%), anorexia (16%), taste alteration (11%)
Hematologic: Anemia (98%; grades 3/4: 11%), leukopenia (96%; grades 3/4: 69%), neutropenia (94%; grades 3/4: 82%; nadir: 12 days [range: 4-17 days]), thrombocytopenia (48%; grades 3/4: 4%)
Neuromuscular & skeletal: Weakness (20%), back pain (16%), peripheral neuropathy (13%; grades 3/4: <1%), arthralgia (11%)
Renal: Hematuria (17%)
Respiratory: Dyspnea (12%), cough (11%)
Enzalutamide

A small molecule AR antagonist
Affinity 30 folds of bicalutamide
Prevent nuclear translocation
Prevents co-activator recruitment

Enzalutamide vs. Bicalutamide

1. AR Binding Affinity
   - DHT: ~5nM
   - Bicalutamide: ~160 nM
   - MDV3100: ~35 nM

2. Nuclear Import
   - DHT: ++++
   - Bicalutamide: +++
   - MDV3100: ++

3. DNA Binding
   - DHT: ++++
   - Bicalutamide: ++
   - MDV3100: (-)

4. Coactivator recruitment
   - DHT: ++++
   - Bicalutamide: ++
   - MDV3100: (-)
AFFIRM:
Randomized phase III Study of MDV3100 vs Placebo in mCRPC after Progression on Docetaxel
**AFFIRM**: Phase III trial with 1199 patients with mCRPC. Previously treated with docetaxel. OS: 18/4 to 13.6 mos (HR: 0.63; P<0.001) TTP: 8.3 vs 2.9 mos (HR: 0.40; P <0.001) FDA approved on 8/31/2012.
PREVAIL: Randomized Phase III Study of Enzalutamide vs Placebo in mCRPC before chemotherapy
Enzalutamide AEs

Cardiovascular: Peripheral edema (15%)
Central nervous system: Fatigue (51%), headache (12%)
Endocrine & metabolic: Hot flashes (20%)
Gastrointestinal: Diarrhea (22%)
Hematologic: Neutropenia (15%; grades 3/4: 1%)
Neuromuscular & skeletal: Back pain (26%), arthralgia (21%), musculoskeletal pain (15%)
Respiratory: Upper respiratory tract infection (11%)
Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical
High energy alpha-particles with short range (<100µm) hence less bone marrow toxicity
ALSYMPCA: Randomized Phase III study of Radium-223 vs Placebo in mCRPC with bone metastases
ALSYMPCA survival curve

![Graph showing survival curves for Radium-223 and Placebo groups.](image)

- **Hazard ratio:** 0.70 (95% CI, 0.58–0.83)
- **P-value:** <0.001

**Overall Survival**

- **Radium-223**
  - Median overall survival: 14.9 months
- **Placebo**
  - Median overall survival: 11.3 months

**Months since Randomization**

**No. at Risk**

- **Radium-223**
  - 614
  - 578
  - 504
  - 369
  - 274
  - 178
  - 105
  - 60
  - 41
  - 18
  - 7
  - 1
  - 0
  - 0
- **Placebo**
  - 307
  - 288
  - 228
  - 157
  - 103
  - 67
  - 39
  - 24
  - 14
  - 7
  - 4
  - 2
  - 1
  - 0
Radium 223 AEs

Cardiovascular: Peripheral edema (13%)
Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)
Hematologic & oncologic: Anemia (93%; grades 3/4: 6%), lymphocytopenia (72%; grades 3/4: 20%), leukopenia (35%; grades 3/4: 3%), thrombocytopenia (31%; grades 3/4: 1% to 6%), neutropenia (18%; grades 3/4: 1% to 3%)
Prostate Cancer Clinical States

- Asymptomatic
  - Non-Metastatic
    - Castration Sensitive
  - Metastatic
    - Castration Resistant

- Symptoms

- Time

- Tumor volume

- Local Therapy

- Castration

- 2nd-line Hormonal therapy

- Abiraterone 2013
  - Enzalutamide 2014

- Sipuleucel-T 2010

- Docetaxel 2004

- Cabazitaxel 2010
  - Abiraterone 2011
  - Enzalutamide 2012

- Radium-223

- Death
E3805-CHAARTED Treatment

**STRATIFICATION**
- Extent of Mets: High vs Low
- Age: ≥70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB: > 30 days
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 months

**.getRandomize**

**ARM A:**
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles
- Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks
- Follow for time to progression and overall survival
- Chemotherapy at investigator’s discretion at progression

**ARM B:**
- ADT (androgen deprivation therapy alone)
- Evaluate every 12 weeks

**Presented by:** Christopher J. Sweeney, MBBS

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed.
- Standard dexamethasone premedication but no daily prednisone
E3805 - CHAARTED Treatment

**STRATIFICATION**
- Extent of Mets: High vs Low
- Age: ≥70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB > 30 days: Yes vs No
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 months

**RANDOMIZE**

**ARM A:**
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles
- Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

**ARM B:**
- ADT (androgen deprivation therapy alone)
- Evaluate every 12 weeks

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- Chemotherapy at investigator’s discretion at progression

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Metastatic Prostate Cancer

About 4% of prostate cancer have distant metastases at diagnosis

Bone metastases are most common

Metastatic disease are virtually incurable

The aim of therapy is to control the disease while maintaining quality of life
Primary endpoint: Overall survival

HR = 0.61 (0.47 - 0.80) p = 0.0003

Median OS:
- ADT + D: 57.6 months
- ADT alone: 44.0 months
OS by extent of metastatic disease at the start of ADT

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.

Presented by: Christopher J. Sweeney, MBBS
Future Directions

How to sequence the array of available and potential agents

Multimodality therapy

Understanding Mechanisms of Resistance
Docetaxel activity after abiraterone

Mezynski et al had 35 patients with a TTP of 4.6 months and 12.5 month overall survival

Schweizer et al had 24 patients with a TTP of 4.4 months

Aggarwal et al had 23 patients with a TTP of 4.3 months and 12.4 month overall survival
Docetaxel activity after abiraterone

Dahut et al had 13 patients with a TTP of 12.4 months
Mechanisms of resistance to docetaxel in metastatic prostate cancer

Seruga, B. et al. (2010) Drug resistance in metastatic castration-resistant prostate cancer
Drug resistance due to continued or upregulated signaling from the AR

Future Directions

How to sequence the array of available and potential agents
Multimodality therapy
Understanding Mechanisms of Resistance
Can some of these therapies be moved earlier to increase the cure rate?