Treatment of Metastatic Castration Resistant Prostate Cancer

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Center for Cancer Research, National Institutes of Health
What I will not talk about today

- Treatment of primary disease
- Treatment of non-metastatic biochemically recurrent disease
What I will not talk about today

• Treatment of primary disease
  - Surgery is curative for localized disease
  - Radiation is curative for localized disease (with androgen deprivation for high risk)

• Treatment of non-metastatic (biochemically recurrent) disease
  - Surveillance and androgen deprivation are both options
  - PSA doubling time is metric that can be used to evaluate pace of disease (retrospective data)
Prostate Cancer Clinical States
Castrate resistant prostate cancer

What is Castration Resistance Prostate Cancer?

- Progressive disease despite castration levels of testosterone (50 ng/dL)

- Progression could be PSA or Imaging

- The androgen receptor drives prostate cancer growth
  - Depriving the tumor of testosterone is the primary therapy for metastatic disease
Anti-androgen therapy

So why do we use Anti-Androgen therapy in CRPC?

Resistance Mechanisms:
- AR Amplification
- Secondary androgen production
- Ligand independent growth
- Intranuclear changes

Integrative clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer

Prostate cancer rules

Rules of the Game:
Prostate Cancer Working Group

- PSA is **NOT** the primary measure of progression in mCRPC
- Radiographic imaging is the primary objective measure
- Patient symptoms and treatment tolerability also paramount

Scher, HI et al J. Clin Oncol, 2008
Optimal treatment sequence

Optimal Treatment Sequence?

- No clear data for sequencing treatment in metastatic castration resistant prostate cancer (*mCRPC*)
- Ongoing trials will evaluate this question further
- In the absence of data I will provide *my opinion* on treatment selection
- Treatment decisions should be made with understanding of the following factors
  - Treatment side effects
  - Patient co-morbidities
  - Patient symptoms
  - Pace of disease
Prostate cancer menu

**Menu**

**Appetizer**
- Sipuleucel-T

**First Course**
- Enzalutamide
- Abiraterone

**Second Course**
- Docetaxel
- Radium-223

**Third Course**
- Cabazitaxel
  Options from 1st or 2nd Course
Prostate cancer appetizer

*MENU*

**Appetizer**
Sipuleucel-T
*early mCRPC*
*minimal symptoms, low volume, slow pace*

- First Course
  - Enzalutamide
  - Abiraterone

- Second Course
  - Docetaxel
  - Radium-223

- Third Course
  - Cabazitaxel

*Options from 1st or 2nd Course*
Therapeutic Cancer Vaccine: Sipuleucel-T

Day 1
Leukapheresis

Apheresis Center

Day 2-3
sipuleucel-T is manufactured

Company (Dendreon)

Day 3-4
Patient is infused

Doctor’s Office
**IMPACT:** Randomized Phase 3 Trial

**Primary endpoint:**
**Secondary endpoint:**

Overall Survival
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: IMPACT Overall Survival

No Change in PFS, Rare PSA Declines

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

Median Survival Benefit = 4.1 Mos.

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

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

Kantoff PW et al. NEJM. 2010
**PSA and Sipuleucel-T**

Patients with Lower PSA Had Greater OS Benefit After Sipuleucel-T

<table>
<thead>
<tr>
<th>Baseline PSA (ng/ml)</th>
<th>&lt;22 (n=188)</th>
<th>22-50 (n=128)</th>
<th>50-134 (n=128)</th>
<th>&gt;134</th>
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</thead>
<tbody>
<tr>
<td><strong>Median OS (mos)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference</td>
<td>13.0</td>
<td>7.0</td>
<td>5.4</td>
<td>2.8</td>
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<tr>
<td>HR</td>
<td>0.51</td>
<td>0.74</td>
<td>0.81</td>
<td>0.84</td>
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</tbody>
</table>

_Schellhammer PF et al. Urol. 2013_
Sipuleucel-T Toxicity

• 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.
Prostate cancer first course

**MENU**

Appetizer
Sipuleucel-T

First Course
minimal to moderate symptoms
Enzalutamide
minimal side effects, optimal in low volume, slow pace of disease
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Enzalutamide

**MENU**

*Appetizer*
Sipuleucel-T

**First Course**
minimal to moderate symptoms
Enzalutamide
Abiraterone
requires concomitant prednisone

**Second Course**
Docetaxel
Radium-223

**Third Course**
Cabazitaxel
Enzalutamide

A small molecule AR antagonist

Affinity 30 folds of bicalutamide

Prevent nuclear translocation

Prevents co-activator recruitment

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
AFFIRM

AFFIRM: Randomized Phase III Study of MDV3100 vs. Placebo in mCRPC after Progression on Docetaxel

Castration Resistant Prostate Cancer (N=1199)

Enzalutamide 160mg/day Corticosteroids allowed but not required

2:1

Placebo
**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 Toxicity

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%)
Abiraterone

MENU

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone
requires concomitant prednisone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Options from 1st or 2nd Course
Abiraterone rationale

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 study

Abiraterone: COU-AA-301 Study Design

- N = 1195
- Progressive, mCRPC
- Previous docetaxel
- ECOG 0 – 2
- Medical or surgical castration with serum testosterone < 50 ng/dL

Randomized 2:1

Abiraterone acetate
1000 mg orally daily
Prednisone
5 mg orally twice daily
n = 797

Placebo orally daily
Prednisone 5 mg orally twice daily
n = 398

Primary end point:
- Overall Survival (OS)

- This study was conducted in 147 sites in 13 countries
- Patients were enrolled from May 2008 through July 2009

De Bono J, et al. NEJM 2011
Abiraterone: COU-AA-301 Trial
### 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>
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<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>

Source: de Bono JS et al. NEJM 2011
COU-AA-302 (chemo-naïve)

Ryan CJ, Lancet Oncol, 2015
Abiraterone Toxicity

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%)
Cross resistance

**Evidence for cross-resistance**
- Enzalutamide
- Abiraterone

**First Course**
- Many patients may not benefit from sequential use

**Second Course**
- Docetaxel
- Radium-223

**Third Course**
- Cabazitaxel
- Options from 1st or 2nd Course
Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constitutently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.
- Thus sequential abiraterone and enzalutamide use may not have additive benefits

Docetaxel

**MENU**

**Appetizer**
- Sipuleucel-T

**First Course**
- Enzalutamide
- Abiraterone

**Second Course**
- Moderate to substantial symptoms
- **Docetaxel**
- Radium-223

**Third Course**
- Cabazitaxel
- Options from 1st or 2nd Course
For fast paced disease

MENU

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Moderate to substantial symptoms
Docetaxel

perhaps the best option for patients with substantial symptoms, fast paced disease
Radium-223

Third Course
Cabazitaxel

Options from 1st or 2nd Course
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*
Phase III study

TAX327: A Multicenter, Randomized Phase III Study of 3 weekly Docetaxel + Prednisone vs. Weekly Docetaxel + Prednisone vs. Mitoxantrone + Prednisone

Castration Resistant Prostate Cancer (N=1006)

- Docetaxel 75mg/m2 Q3wks + Prednisone 10mg daily
- Docetaxel 30mg/m2 Q1wk + Prednisone 10mg daily
- Mitoxantrone 12mg/m2 Q3wks + Prednisone 10mg daily

TAX327: Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (mos)</th>
<th>Hazard Ratio</th>
<th>P-value</th>
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<tr>
<td>Docetaxel 3 wkly</td>
<td>18.9</td>
<td>0.76</td>
<td>0.009</td>
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<tr>
<td>Docetaxel wkly</td>
<td>17.3</td>
<td>0.91</td>
<td>0.3</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>16.4</td>
<td></td>
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</table>
Docetaxel Toxicity

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%)
Radium

**MENU**

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Moderate to substantial symptoms
Docetaxel
Radium-223

symptomatic bone disease, no visceral disease; ideal patient population unknown

Third Course
Cabazitaxel

Options from 1st or 2nd Course
Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical
High energy alpha-particles with short range (<100μm) hence less bone marrow toxicity
Radium trial

ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases

CRPC
Symptomatic
≥2 bone mets
(N=922)

Ra-223 50kBq/kg q4wks x 6

2:1

Placebo
Phase III study of Radium-223

ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases

A Overall Survival

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. at Risk</th>
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<tr>
<td></td>
<td>Radium-223</td>
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<tr>
<td>0</td>
<td>614</td>
</tr>
<tr>
<td>3</td>
<td>578</td>
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<tr>
<td>6</td>
<td>504</td>
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<table>
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<td>36</td>
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<tr>
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Hazard ratio, 0.70 (95% CI, 0.58–0.83) P<0.001
Overall survival

TROPIC: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
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<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td></td>
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<tr>
<td>95% CI</td>
<td>0.59–0.83</td>
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</tr>
<tr>
<td>P-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

de Bono JS. et al. Lancet. 2010
Radium toxicity

Radium 223 AEs

- Cardiovascular: Peripheral edema (13%)
- Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)
- Hematologic: 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%)
Third course

**MENU**

**Appetizer**
Sipuleucel-T

**First Course**
Enzalutamide
Abiraterone

**Second Course**
Docetaxel
Radium-223

**Third Course**
Docetaxel refractory
Cabazitaxel

Options from 1st or 2nd Course
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 protocol

TROPIC: Randomized Phase III Study of Cabazitaxel vs. Mitoxantrone in mCRPC after Progression on Docetaxel

Castration Resistant Prostate Cancer (N=755)

1:1

Cabazitaxel 25mg/m2 Q3wks + Prednisone 10mg daily

Mitoxantrone 12mg/m2 Q3wks + Prednisone 10mg daily

de Bono JS. et al. Lancet. 2010
TROPIC: Progression-Free Survival

TROPIC: Progression-Free Survival

Proportion of PFS (%)

<table>
<thead>
<tr>
<th>Median PFS (months)</th>
<th>1.4</th>
<th>2.8</th>
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<tbody>
<tr>
<td>Hazard Ratio</td>
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<tr>
<td>95% CI</td>
<td>0.64–0.86</td>
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<tr>
<td>P-value</td>
<td>&lt;.0001</td>
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</table>

PFS composite endpoint: PSA progression, pain progression, tumor progression, symptom deterioration, or death.

Number at risk

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<td>168</td>
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<td>90</td>
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TROPIC: Overall Survival

Proportion of OS (%)

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Number at risk

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<td>378</td>
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<td>6 months</td>
<td>300</td>
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<td>12 months</td>
<td>188</td>
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<td>18 months</td>
<td>67</td>
<td>90</td>
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<tr>
<td>24 months</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>30 months</td>
<td>1</td>
<td>4</td>
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</table>
Cabazitaxel Toxicity

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%)
Cabazitaxel and ASCO

Cabazitaxel at ASCO 2016

• Cabazitaxel was not superior to docetaxel in front-line chemotherapy setting

• Cabazitaxel at 20 mg has same long term outcomes as Cabazitaxel at 25 mg
Third course

MENU

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Docetaxel refractory
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223

OS data post docetaxel
Complete menu

MENU

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223

Ultimate Goal: Use as many items on the menu while also maximizing quality of life
## Cost of Treatments

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approval Date</th>
<th>Large Group Commercial Rate ($)</th>
<th>Medicare Rate ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>2011</td>
<td>5,171.90</td>
<td>6,409.11</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>1995</td>
<td>Generic, 82; brand, 520</td>
<td>Generic, 28; brand, 527</td>
</tr>
<tr>
<td>Cabazitaxel†</td>
<td>2010</td>
<td>11,233.78</td>
<td>12,806.06</td>
</tr>
<tr>
<td>Degarelix</td>
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<td>536.75</td>
</tr>
<tr>
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<td>Brand (pregeneric), 3,006.19</td>
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<td>2012</td>
<td>†</td>
<td>7,906.34</td>
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<tr>
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<td>79.65</td>
<td>125.80</td>
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<td>596.00</td>
<td>210.32</td>
</tr>
<tr>
<td>Ketoconazole</td>
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<td>19.22</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>1998</td>
<td>356.00</td>
<td>202.84</td>
</tr>
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<td>Mitoxantrone†</td>
<td>1987</td>
<td>615.63</td>
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</tr>
<tr>
<td>Nilutamide</td>
<td>1996</td>
<td>464.13</td>
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<td>1974</td>
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<tr>
<td>Radium-223</td>
<td>2013</td>
<td>12,455.00†</td>
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</tr>
<tr>
<td>Sipuleucel-T−s</td>
<td>2010</td>
<td>40,670.42</td>
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*Bash et al, CJ et al. JCO. 2014*
Cost of treatments

### Cost of Treatments

**Table 3. Treatment Costs in Patients With CRPC for 30-Day Period (oral drugs) or One Infusion/Cycle (parenteral drugs)**

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*FDA-Approved for mCRPC*
**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

**ARM B:**
ADT (androgen deprivation therapy alone)

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

**Evaluate every 12 weeks**

**Follow for time to progression and overall survival**

Chemotherapy at investigator’s discretion at progression

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

Presented by: Christopher J. Sweeney, MBBS
Survival curve

Hazard ratio for death with ADT+docetaxel, 0.61 (95% CI, 0.47–0.80) P<0.001

ADT+docetaxel (median overall survival, 57.6 mo)

ADT alone (median overall survival, 44.0 mo)

Sweeney, CJ et al. NEJM. 2015
Prostate Cancer Clinical States

![Prostate Cancer Clinical States Diagram]

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

Key Events:
- Castration
- 2nd-line Hormonal therapy
- Sipuleucel-T 2010
- Abiraterone 2013 Enzalutamide 2014
- Docetaxel 2004
- Cabazitaxel 2010 Abiraterone 2011 Enzalutamide 2012 Radium-223
- Death
Docetaxel

CHAARTED/ E3805 supports docetaxel in metastatic castration-sensitive prostate cancer

Local Therapy not Curative

Castration

2nd-line Hormonal therapy

Asymptomatic

Symptoms

Metastatic

Castration Sensitive

Castration Resistant

Docetaxel 2004

Abiraterone 2013

Enzalutamide 2014

Cabazitaxel 2010

Abiraterone 2011

Enzalutamide 2012

Sipuleucel-T 2010

Radium-223 2013

Time →
CHAARTED: Subgroup analysis

Sweeney, CJ et al. NEJM. 2015
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.
Subgroup analysis

CHAARTED: Subgroup Analysis

Should Low Volume Patients be Treated with this Regimen?

1. HR= 0.60 and curves may continue to separate

2. Study was not powered to look at subgroups

3. Toxicity and thus risks of therapy appear limited

Sweeney, CJ et al. NEJM. 2015
### Table 3. Adverse Events of Grade 3 or Higher among the 390 Patients Who Received the Docetaxel-Containing Regimen and Had Follow-up Data Available.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of patients (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>7 (1.8)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (4.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy, motor</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy, sensory</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1 (0.3)</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (1.0)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (3.1)</td>
<td>35 (9.0)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15 (3.8)</td>
<td>9 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>5 (1.3)</td>
<td>4 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Any event</td>
<td>65 (16.7)</td>
<td>49 (12.6)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

### Cycles Administered

<table>
<thead>
<tr>
<th>Arm A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>ADT + Docetaxel (N=397)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Number of cycles</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Sweeney, CJ et al. NEJM. 2015
Future Directions

- How to sequence the array of available and potential agents
- Multimodality therapy
- Understanding Mechanisms of Resistance