Update On Treatment of Localized Prostate Cancer

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Incidence of CaP

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>956,850 (21%)</td>
<td>248,600 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>167,300 (4%)</td>
<td>168,470 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>76,800 (8%)</td>
<td>63,070 (8%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>56,500 (7%)</td>
<td>66,050 (7%)</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>48,070 (6%)</td>
<td>48,300 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,170 (5%)</td>
<td>32,410 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,000 (5%)</td>
<td>28,310 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; oropharynx</td>
<td>34,700 (4%)</td>
<td>26,050 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34,040 (4%)</td>
<td>24,400 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>28,410 (3%)</td>
<td>22,000 (3%)</td>
</tr>
<tr>
<td>ALL Sites</td>
<td>841,280 (100%)</td>
<td>343,209 (100%)</td>
</tr>
</tbody>
</table>

Mortality

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>68,300 (27%)</td>
<td>72,100 (26%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,125 (8%)</td>
<td>26,125 (8%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,025 (8%)</td>
<td>25,110 (8%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,490 (7%)</td>
<td>20,310 (7%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>18,200 (6%)</td>
<td>14,200 (6%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,100 (4%)</td>
<td>16,100 (4%)</td>
</tr>
<tr>
<td>Esophage</td>
<td>12,750 (4%)</td>
<td>16,010 (4%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,925 (4%)</td>
<td>8,550 (3%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,925 (4%)</td>
<td>8,560 (3%)</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,440 (3%)</td>
<td>8,670 (3%)</td>
</tr>
<tr>
<td>All Sites</td>
<td>314,250 (100%)</td>
<td>281,408 (100%)</td>
</tr>
</tbody>
</table>

Lifetime Risk of Dying from CaP

- Risk of dying from prostate cancer is ~3%
- Once metastatic disease develops there is no cure
- Prior to PSA screening only 25% of CaP were confined to prostate vs. 91% since
- 5 year CSS rates increased from ~70% to 100% (from 1980s to early 2000s)
Trends in Metastatic Breast and Prostate Cancer: Lessons in Cancer Dynamics

Initiation of widespread PSA screening

Prostate cancer

Breast cancer

Incidence of Metastatic Disease (per 100,000)


Initiation of widespread mammography screening

Natural History of Prostate Cancer

Hormone-Sensitive

Castration-Resistant

Surgery and Radiation

Therapies After GnRH Agonists and Antiandrogens

Immunotherapy

Death

Premetastatic

Asymptomatic

Radiographically Metastatic

Symptomatic
Management of Localized Prostate Cancer

• Early PSA era: screen and treat everyone
• Selective screening and treatment:
  − Patients health and life expectancy
  − Cancer risk
  − Biological potential
  − Patients and family wishes

Better Risk Stratification

A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score.

Table 4 – Histologic definition of new grading system

| Grade group 1 (Gleason score 3 + 3 = 6): | Only individual discrete well-formed glands |
| Grade group 2 (Gleason score 3 + 4 = 7): | Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands |
| Grade group 3 (Gleason score 4 + 3 = 7): | Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands |
| Grade group 4 (Gleason score 8): |
  - Only poorly formed/fused/cribriform glands or
  - Predominantly well-formed glands and lesser component lacking glands
  - Predominantly lacking glands and lesser component of well-formed glands |
| Grade group 5 (Gleason scores 9–10): | Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands |
Prostate Cancer: Indolent vs. Aggressive

<table>
<thead>
<tr>
<th></th>
<th>Very Low Risk</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/ml)</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>10-20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Stage</td>
<td>T1c</td>
<td>T1c, T2a</td>
<td>T2b-T2c</td>
<td>T3-T4</td>
</tr>
<tr>
<td>GS</td>
<td>≤ 6</td>
<td>≤ 6</td>
<td>7</td>
<td>8-10</td>
</tr>
<tr>
<td># of cores</td>
<td>≤ 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of cancer in any core</td>
<td>≤ 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA density (ng/mL/g)</td>
<td>&lt; 0.15</td>
<td></td>
<td></td>
<td></td>
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</table>

Biomarkers

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Tissue</th>
<th>Population studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>KI-67</td>
<td>IHC</td>
<td>Biopsy</td>
<td>Intermediate and high risk, EBRT</td>
<td>Mets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active surveillance</td>
<td>CSS</td>
</tr>
<tr>
<td>PTEN</td>
<td>IHC</td>
<td>TURP, biopsy</td>
<td>Adverse pathology</td>
<td>CSS</td>
</tr>
<tr>
<td>Decipher</td>
<td>FISH, IHC</td>
<td>Active surveillance</td>
<td>CSS</td>
<td></td>
</tr>
<tr>
<td>Oncomet</td>
<td>Quant-RT-PCR, 12 CaP genes and 5 controls</td>
<td>RP tissue</td>
<td>BCF</td>
<td>Mets, BCF</td>
</tr>
<tr>
<td>Decipher</td>
<td>Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls</td>
<td>Biopsy</td>
<td>low to intermediate risk RP</td>
<td>pT3 or GS 4 on RP</td>
</tr>
<tr>
<td>Prolaris</td>
<td>Quantitative RT-PCR</td>
<td>Biopsy</td>
<td>Active surveillance</td>
<td>CSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Localized CaP</td>
<td>BCF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy</td>
<td>BCF</td>
</tr>
<tr>
<td>ProMark</td>
<td>Multiplex immunofluorescent staining of 8 proteins</td>
<td>RP, N0</td>
<td>Localized Cap</td>
<td>BCF</td>
</tr>
</tbody>
</table>

PSA  Free PSA  PCA3  PHI  TMPRSS-ERG  4K score  EcoDx  PCA3  Confirm DX  Polaris  OncotypeDx  Decipher  Promark
Better Imaging

Multipartametric Prostate MRI

mpMRI guided biopsy

Treatment Options for Localized CaP

• Watchful waiting

Treatment Options for Localized CaP

• Watchful waiting
• Active surveillance
**Treatment Options for Localized CaP**

- Watchful waiting
- Active surveillance
- Ablation (Cryotherapy, HIFU, Laser…)
- Brachytherapy
- EBRT ± ADT
- Surgery
Active Surveillance

10,471 patients from 45 urologic practice (CaPSURE)
AS increased to 40.4% for low risk patients
76.2% of men >75 with low risk

ASCO

- PSA 3-6 months, annual DRE, confirmatory biopsy within 6-12 months and then every 2-5 years depending on results
- Genetic tests and MRI may be indicated in discordant clinical and pathologic findings
- MRI alone is not enough for follow up
- Patient who has higher grade or higher volume should consider therapy

AS long term results

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Toronto</th>
<th>Johns Hopkins</th>
<th>UCSF</th>
</tr>
</thead>
<tbody>
<tr>
<td># pts</td>
<td>993</td>
<td>1298</td>
<td>321</td>
</tr>
<tr>
<td>Med Age (Y)</td>
<td>68</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Med F/U (months)</td>
<td>77</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>10 Y OS</td>
<td>80%</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>CSS</td>
<td>98%</td>
<td>99.9%</td>
<td>100% (5Y)</td>
</tr>
<tr>
<td>Conversion to treatment</td>
<td>36.5%</td>
<td>50%</td>
<td>24% (3 y)</td>
</tr>
<tr>
<td>Gleason grade change</td>
<td>9.5%</td>
<td>15.1%</td>
<td>38%</td>
</tr>
<tr>
<td>PSA increase</td>
<td>11.7%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Positive lymph node</td>
<td>0.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal choice</td>
<td>1.6%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Chen JCO 2016
Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

- Swedish RTC of prostatectomy versus watchful waiting in disease detected mainly clinically (before PSA screening) continues to show a benefit for early prostatectomy.
- The number of men younger than 65 needed to treat to prevent one death is now four.
- Follow-up of 24 years

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

Death From Prostate Cancer, Men < 65 Years Of Age

Surgery

Robotic Radical Prostatectomy

- More than 90% robotic
- Less blood loss
- Less narcotic
- Faster recovery
- Similar oncologic outcome
- Similar Potency and continence (may be faster return)

Open vs Robotic Prostatectomy
**Prostate cancer Intervention Versus Observation Trial (PIVOT)**

- Randomized men ≤75yrs old to radical prostatectomy vs. expectant management with all-cause mortality as primary end-point
- 731 men studied
- Median f/up 10 years
- Different than Scandinavian trial
  ✓ looked at same thing, but now in PSA screening era

**Prostate cancer Intervention Versus Observation Trial (PIVOT)**

- Death From *Any Cause*
  - Observation
  - Radical Prostatectomy

**Prostate cancer Intervention Versus Observation Trial (PIVOT)**

- Death From *Prostate Cancer*
  - Observation
  - Radical Prostatectomy

**Focal therapy**
Focal therapy

- Focal Brachytherapy
- Cryotherapy
- HIFU

Focal therapy FDA

- FDA approved devices were approved for ablating tissue not for clinical effectiveness
- General consensus: current technologies are capable of selective ablation with reasonable accuracy but criteria for selecting patients, long term outcome remains to be established
- Concerns of excessive unnecessary use for patients with very low and low risk prostate cancer and inadequate treatment due to underestimation of the disease risk

Prospective Trial of HIFU Hemiablation for Localized CaP

- 50 patients unilateral low (60%) and intermediate risk (40%) CaP
- Median F/U 39.5 months
- Serial PSA
- 36% BCR (Pheonix definition)
- 5 years met free survival 93%
- 94% continent, 80% potent

R van Velthoven, Pros Can and Pros Dis (2016) 19, 79–83
Radiation Therapy

- Brachytherapy (including focal)
- EBRT
  - IMRT
  - Proton beam
  - Hypofractionation

### FRACTIONATION

- Standard fractionation (1.8-2.0 Gy/day)
- Hyperfractionation (1.0-1.2 Gy 2-3x/day)
  - more fractions, higher dose, same duration and late effects
- Accelerated fractionation (2-3x/day)
  - complete treatment in shorter duration, same or lower dose, equal late effects
- Hypofractionation: fewer fractions, more per fraction
  - Moderate Hypofractionation: 2.4 - 4 Gy/fraction
  - Extreme Hypofractionation: 6.5 - 10 Gy/fraction

### DATA FOR HYPOFRACTIONATION IN PROSTATE CANCER

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STD ARM</th>
<th>HFX ARM</th>
<th>Risk</th>
<th>PT #</th>
<th>EFFICACY</th>
<th>LATE TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0415</td>
<td>73.8 Gy/41 fx</td>
<td>70 Gy/28 fx</td>
<td>Low risk</td>
<td>1092</td>
<td>85% vs 86% DFS 5.4 yr</td>
<td>Mod &gt;Gr 2 GI and GU toxicity</td>
</tr>
<tr>
<td>CHHiP</td>
<td>74 Gy/37 fx</td>
<td>60 Gy/20 fx</td>
<td>Most intermediate</td>
<td>1000 each arm</td>
<td>BCF: HR for 60 Gy 0.83, 88.3 vs 90.5 vs 85.8%</td>
<td>&gt;acute GI Late Gr 2+ similar</td>
</tr>
<tr>
<td>PROFIT</td>
<td>78 Gy/39 fx</td>
<td>60 Gy/20 fx</td>
<td>Intermediate</td>
<td>1204</td>
<td>BCF 79% at 5 yr in both</td>
<td>Late Gr 3: trend better for short arm</td>
</tr>
<tr>
<td>HYPRO</td>
<td>78 Gy/39 fx</td>
<td>64.6 Gy/19 fx</td>
<td>Similar</td>
<td></td>
<td></td>
<td>&gt;GU</td>
</tr>
</tbody>
</table>
### Localized Prostate cancer

- Better screening and prognostication
- Active surveillance for appropriate patients
- Robotic surgery may offer some advantages
- Improved understanding of focal therapy and hypofractionation EBRT

### What to expect during your prostatectomy

### Urinary incontinence and impotence after different forms of treatment

### ADT and Chemotherapy for Advanced Prostate Cancer

Paul Monk, MD  
Associate Professor  
Internal Medicine  
College of Medicine  
The Ohio State University Wexner Medical Center
Case Discussion

- A 63-year-old engineer presents at a multidisciplinary clinic for evaluation of his prostate cancer.
  - PSA 1250 ng/mL, back pain, and decreased stream
- Patient has information that screening may result in over-diagnosis and lead to overtreatment.
- He undergoes a TRUS biopsy, which reveals GS 4+4 = 8 in 10/12 cores.
- Bone scan shows multiple lumbar metastases and CT indicates pelvic nodes 3–7cm.

Treatment options?

PSA = prostate-specific antigen; TRUS = transurethral ultrasound; GS = Gleason score; CT = computed tomography.

Advanced Prostate Cancer

Goals of Care in Advanced Prostate Cancer

- Locally advanced: cure, lengthening disease free period and optimal quality of life
- Advanced disease (incurable): longevity/disease control and optimal quality of Life
**Clinical Disease States: Prostate Cancer**

- **Clinical Disease States:**
  - Clinically Localized Disease
  - Rising PSA: Non-Castrate
  - Clinical Metastases: Non-Castrate
  - Rising PSA: Castrate
  - Clinical Metastases: Castrate
  - Death From Other Causes
  - Death From Disease

*Scher, H. I. et al. J Clin Oncol; 26:1148-1159 2008*

**Advanced Prostate Cancer Update - Take Home**

- **Progress**
  - Survival and palliation are improving
  - What was called “hormone refractory” is still driven by Androgen receptor signaling
  - Old drug learns new trick. Cytotoxic chemotherapy in new setting
  - Immunotherapy has an established role in advanced PrC

- **Keep an open mind to new data**
  - Screening every man is wrong
  - Screening no man is wrong

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**Androgen Deprivation Therapy**

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**“The quandary in prostate cancer: Is cure necessary in those for whom it is possible, and is cure possible in those for whom it is necessary?”**

Willet Whitmore
Charles Benton Huggins, M.D.

Huggins and Hodges

Studies on prostate cancer, I. The effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate.
Cancer Res. 1:293-297, 1941

Huggins, Stevens, and Hodges

Studies on prostate cancer, II. The effect of castration on advanced carcinoma of the prostate gland.
Arch. Surg. 43:209-223, 1941

Androgen Deprivation Therapy (Castration) for Metastatic Prostate Cancer

XRT + Adjuvant ADT well established
(Level 1 evidence)

Pituitary
Testis
Prostate Axis

Targets for Antiandrogen Therapy

Modified from Moyad and Pienta, 2000

Modified from Moyad and Pienta

Modified from Moyad & Pienta, 2000
Impact of Androgen Deprivation (ADT)

- Toxicity/QOL
  - Sexual dysfunction
  - Hot flashes
  - Gynecomastia and breast tenderness
  - Hepatotoxicity
  - Osteopenia
  - Anemia
  - Accelerated muscle loss (sarcopenia) - frailty
- Financial costs

Androgen Deprivation Therapy (Issues)

- Monotherapy vs Combined ADT
- Intermittent vs Continuous
- Early vs. Delayed ADT
- Adding chemotherapy and new agents

Androgen Deprivation Therapy (Issues)

- Monotherapy vs Combined ADT
- Intermittent vs Continuous
- Early vs. Delayed ADT
- Adding chemotherapy and new agents

E3805—CHAARTED: Treatment

- ARM A: ADT + docetaxel 75 mg/m² every 21 days for maximum 6 cycles
- ARM B: ADT (androgen deprivation therapy alone)

STRATIFICATION
- Extent of mets
  - High vs Low
- Age
  - ≥70 vs <70 years
- ECOG PS
  - 0–1 vs 2
- CAB
  - Yes vs No
- SRE Prevention
  - Yes vs No
- Prior adjuvant ADT
  - ≤12 vs >12 mos.

Randomize

Evaluate every 3 weeks while on docetaxel and at week 24, then every 12 weeks

Evaluate every 12 weeks

Follow for time to progression and OS survival

Chemotherapy at investigator’s discretion at progression

Mets = metastases; CAB = combined androgen blockade.

**E3805—CHAARTED: Study Endpoints**

- **Primary endpoint**
  - Overall survival
- **Secondary endpoints**
  - Rate of PSA <0.2 ng/mL at 6 months and 12 months
  - Time to biochemical, radiographic, or symptomatic progressive disease (PD)
  - Time to radiographic or symptomatic PD
  - Define AE profile and tolerability
  - Quality of life (FACT-P) until 12 months after randomization

*FACT-P = Functional Assessment of Cancer Therapy-Prostate*

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**E3805—CHAARTED**

**Primary Endpoint: OS**

<table>
<thead>
<tr>
<th></th>
<th>ADT + D (n = 397)</th>
<th>ADT (n = 393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>57.8 mos.</td>
<td>44.0 mos.</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.61 (0.47–0.80)</td>
<td></td>
</tr>
<tr>
<td><em>P</em>-value</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

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**E3805—CHAARTED**

**OS by Extent of Metastatic Disease at Start of ADT**

- In patients with high volume metastatic disease, there is a 17-month improvement in median overall survival, i.e., from 32.2 months to 49.2 months.
- We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
**Definition of Castration-Resistant Prostate Cancer (CRPC): HRPC, AIPC (non-metastatic and metastatic)**

- Castrate testosterone levels (<50 ng/dL)
- 3 × PSA rises 1 week apart (2 × levels 50% > nadir and >2 ng/mL)
- PSA progression despite consecutive HT±
- AA withdrawal for ≥4 weeks (flutamide) or ≥6 weeks (bicalutamide)

**CRPC**

- **CRPC** responds to secondary hormonal manipulation.
- True HRPC is resistant to all hormonal measures.

**HRPC = hormone-resistant PC; AIPC = androgen-independent PC; HT = hormone therapy; RECIST = Response Evaluation Criteria in Solid Tumors.**


**Development of CRPC**

**Hormone therapy**

- Mutation
- Gain of function
- Acetylation
- Overexpression
- Amplification

**CRPC**

Recrurred tumor development

**5 New Cancer Agents: What Are They?**

- **Immunotherapy**
  - Sipuleucel-T—autologous cell vaccine
- **Hormonal therapies**
  - Abiraterone—androgen biosynthesis inhibitor
  - Enzalutamide—androgen-receptor blocker
- **Chemotherapy**
  - Cabazitaxel—microtubule inhibitor
- **Radionuclide therapy**
  - Radium-223—alpha-emitter

**Sipuleucel-T**

**Indication**

Autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic mCRPC

**Dosing**

Leukapheresis followed by IV infusion 2–3 days later; 3 doses (60-minute IV infusions) every 2 weeks

**Warnings/precautions**

Most common AEs (incidence ≥15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache. Acute infusion reactions may occur. Syncope and hypotension have also been observed. Use with caution in patients with risk factors for thromboembolic events.

mCRPC = metastatic castration-resistant prostate cancer; IV = intravenous; AE = adverse event. Sipuleucel-T (Provenge®) prescribing information. Available at www.dendreon.com/prescribing-information.pdf
**IMPACT Trial Results**

- **Placebo** (n = 171)
  - Median OS (mos): 21.7
  - HR for death (95% CI): 0.78 (0.61–0.98)
  - P-value: 0.03

- **Sipuleucel-T** (n = 341)
  - Median OS (mos): 25.8

- **Survival (%)**
  - 0 25 50 75 100
  - 0 6 12 18 24 30 36 42 48 54 60 66

- **Survival (months)**
  - Placebo
  - Sipuleucel-T

- **Median OS**: 4.1 months
  - 22% reduction in risk of death

- **Optimal Timing for Treatment Of mCRPC**
  - Sequencing and Identifying Parameters of Early Progression With Sipuleucel-T: OS
  - Patients in lowest PSA quartile had greatest OS benefit with sipuleucel-T.

- **Baseline PSA, ng/mL**
  - ≤22.1 (n = 128)
  - >22.1 to 50.1 (n = 128)
  - >50.1 to 134.1 (n = 128)
  - >134.1 (n = 128)

- **Median OS, months**
  - Sipuleucel-T
  - Control

- **Difference, months**
  - 13.0

- **HR (95% CI)**
  - 0.51 (0.31–0.85)
  - 0.74 (0.47–1.17)
  - 0.81 (0.52–1.24)
  - 0.84 (0.55–1.29)

- **Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS.**

- **Optimal Timing for Treatment Of mCRPC**
  - Sequencing and Identifying Parameters of Early Progression With Sipuleucel-T: OS
  - Patients in lowest PSA quartile had greatest OS benefit with sipuleucel-T.

- **Baseline PSA, ng/mL**
  - ≤22.1 (n = 128)
  - >22.1 to 50.1 (n = 128)
  - >50.1 to 134.1 (n = 128)
  - >134.1 (n = 128)

- **Median OS, months**
  - Sipuleucel-T
  - Control

- **Difference, months**
  - 13.0

- **HR (95% CI)**
  - 0.51 (0.31–0.85)
  - 0.74 (0.47–1.17)
  - 0.81 (0.52–1.24)
  - 0.84 (0.55–1.29)

- **Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS.**

- **The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile; median 13.0 vs 2.8 months OS benefit, respectively.**

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**5 New Cancer Agents: What Are They?**

- **Immunotherapy**
  - Sipuleucel-T—autologous cell vaccine

- **Hormonal therapies**
  - Abiraterone—androgen biosynthesis inhibitor
  - Enzalutamide—androgen-receptor blocker

- **Chemotherapy**
  - Cabazitaxel—microtubule inhibitor

- **Radionuclide therapy**
  - Radium-223—alpha-emitter

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**OS = overall survival; HR = hazard ratio; CI = confidence interval.**
Abiraterone

**Hormonal therapy**

**Indication**

CYP17—androgen biosynthesis inhibitor indicated in combination with prednisone for treatment of patients with mCRPC

**Dosing**

1,000 mg (four 250 mg tablets) administered orally once daily on an empty stomach in combination with prednisone 5 mg administered orally twice daily

**Warnings/precautions**

Common AEs (≥10%) are fatigue, joint swelling or discomfort, edema, hot flushes, diarrhea, and vomiting. Common laboratory abnormalities (≥20%) include anemia, elevated alkaline phosphatase, and hypertriglyceridemia. Use with caution in patients with a history of CVD. Exposure (AUC) of abiraterone increases up to 10-fold when taken with meals. Due to effects on some CYP enzymes, check drug interactions.

**Abiraterone Acetate: Androgen Biosynthesis Inhibitor**

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnenolone</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>17OH-pregnenolone</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>DHEA</td>
<td>Androstenedione → Testosterone → DHT</td>
</tr>
</tbody>
</table>

DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone.


**COU 301: Overall Survival Post Chemotherapy**

Updated results:
- 2 prior chemo OS: 14.2 months (abiraterone acetate) vs. 10.4 months (placebo)
- 1 prior chemo OS: 17.1 months (abiraterone acetate) vs. 11.7 months (placebo)
- 4.6-month difference in median survival with abiraterone acetate

**5 New Cancer Agents: What Are They?**

- Immunotherapy
  - Sipuleucel-T—autologous cell vaccine
- Hormonal therapies
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- Radionuclide therapy
  - Radium-223—alpha-emitter

**Enzalutamide**

**Hormonal therapy**

**Indication**
An androgen-receptor inhibitor indicated for the treatment of patients with mCRPC

**Dosing**
- 160 mg (four 40 mg capsules) administered orally once daily
- Swallow capsules whole.
- Capsules can be taken with or without food.

**Warnings/precautions**
The most common AEs (≥10%) are asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, and diarrhea. Seizure occurred in 0.9% of patients receiving enzalutamide who previously received docetaxel and in 0.1% of patients who were chemotherapy-naïve.

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**Enzalutamide: Third-Generation Androgen-Receptor Inhibitor**

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding

DNA = deoxyribonucleic acid; T = testosterone.


---

**4.8-month Survival Advantage With Enzalutamide in PC After Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, mos.</td>
<td>18.4 (17.3–NYR)</td>
<td>13.6 (11.3–15.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.53–0.75)</td>
<td>0.19 (0.15–0.23)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Enzalutamide (Xtandi®) prescribing information. Available at www.astellas.us/docs/12A005-ENZ-WPI.PDF

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**Enzalutamide In mPC Before Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>rPFS, mos.</td>
<td>3.9 (3.7–5.4)</td>
<td>3.5 (3.7–5.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.19 (0.15–0.23)</td>
<td>0.19 (0.15–0.23)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


---

Enzalutamide (Xtandi®) prescribing information. Available at www.astellas.us/docs/12A005-ENZ-WPI.PDF
Enzalutamide in mPC Before Chemotherapy (continued)

Median time to chemotherapy by 17 months

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at risk</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>533</td>
<td>300</td>
<td>233</td>
</tr>
<tr>
<td>3</td>
<td>194</td>
<td>125</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>136</td>
<td>83</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>51</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>23</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>33</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.35 (0.30–0.40)
P-value: <0.001

With Enzalutamide: PSA Reduction

Abiraterone After Progression With Enzalutamide: PSA Reduction

Waterfall plot showing maximum PSA reduction prior enzalutamide and subsequent abiraterone acetate treatment in each patient

Androgen-Receptor Splice Variants

AR splice variants are associated with poor prognosis and treatment resistance.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Full-length AR</th>
<th>Ligand-binding domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

AR-V7

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>101</td>
<td>19–39%</td>
<td>50%</td>
</tr>
<tr>
<td>102</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of AR-V7 in mCRPC

<table>
<thead>
<tr>
<th>Pre-enzalutamide, pre-abiraterone</th>
<th>N = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-enzalutamide only</td>
<td>19–39%</td>
</tr>
<tr>
<td>Post-abiraterone only</td>
<td>50%</td>
</tr>
<tr>
<td>Post-abiraterone only</td>
<td>55%</td>
</tr>
</tbody>
</table>

Kaplan-Meier Analysis of PSA PFS and Clinical or Radiographic PFS According to AR-V7 Status


Enzalutamide-treated patients

Abiraterone-treated patients

• Immunotherapy
  - Sipuleucel-T—autologous cell vaccine
• Hormonal therapies
  - Abiraterone—androgen biosynthesis inhibitor
  - Enzalutamide—androgen-receptor blocker
• Chemotherapy
  - Cabazitaxel—microtubule inhibitor
  - Radionuclide therapy
  - Radium-223—alpha-emitter

5 New Cancer Agents: What Are They?

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  - Radium-223—alpha-emitter

Cabazitaxel

Indication
A microtubule inhibitor indicated in combination with prednisone for the treatment of patients with mCRPC previously treated with docetaxel

Dosing
25 mg/m² every 3 wks as 1-hour IV infusion in combination with oral prednisone 10 mg given daily during cabazitaxel therapy

Warnings/precautions
Most common all-grade AEs (≥10%) include neutropenia, anemia, leukopenia, thrombocytopenia, and diarrhea. Neutropenic deaths have been reported. Severe hypersensitivity (including generalized rash/erythema, hypotension, and bronchospasm) may occur. Renal failure, including fatal renal failure, has been reported. It should not be given to patients with hepatic impairment.

Cabazitaxel (Jevtana®) prescribing information. Available at http://products.sanofi.us/jevtana/jevtana.html

Cabazitaxel

Phase 3 Primary Endpoint—OS


Medicaid OS: 2.4 mo
30% reduction in risk of death
5 New Cancer Agents: What Are They?

- Immunotherapy
  - Sipuleucel-T—autologous cell vaccine
- Hormonal therapies
  - Abiraterone—androgen biosynthesis inhibitor
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- Chemotherapy
  - Cabazitaxel—microtubule inhibitor
- Radionuclide therapy
  - Radium-223—alpha-emitter

Radium-223

- Indication: An alpha particle-emitting radioactive therapeutic agent indicated for treatment of patients with CRPC with symptomatic bone metastases and no known visceral metastatic disease.
- Dosing: 50 kBq (1.35 microcurie) per kg body weight, given at 4-week intervals for 6 injections.
- Warnings/precautions: The most common AEs (≥10%) were nausea, diarrhea, vomiting, and peripheral edema; most common hematologic laboratory abnormalities (≥10%) were anemia, leukopenia, lymphocytopenia, thrombocytopenia, and neutropenia. Grade 3/4 anemia and thrombocytopenia each occur in 6%, and neutropenia in 2% (bone marrow suppression).

ALSYMPCA Phase III Study Design (ALpharadin in SYMptomatic Prostate CAncer)

- Patients: N = 921
  - Confirmed symptomatic CRPC
  - ≥2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel*

- Treatment phase: 2:1
  - Radium-223 dichloride (50 kBq/kg) + best standard of care†
  - Placebo (saline) + best standard of care†

- 6 injections at 4-week intervals
- >100 centers in 19 countries
- Planned follow-up is 3 years.

*Unfit for docetaxel includes patients who were ineligible for docetaxel (e.g., asymptomatic CRPC), or lived where docetaxel was unavailable.
†Best standard of care is defined as a routine standard of care at each center, e.g., local external beam radiotherapy, radium-223 dichloride, anti-androgens, estrogen (e.g., diethylstilbestrol), estramustine, or ketoconazole.

ALSYMPCA Updated Analysis: OS

- Median OS: 14.9 mos. vs 11.3 mos.
  - HR (95% CI): 0.70 (0.58–0.83)
  - P-value: <0.001

Median Δ: 3.6 months
30% reduction in risk of death
**ALSYMPCA: Safety Profile**

The number of patients who had AEs after they received the study drug was consistently lower in the radium-223 group than in the placebo group for all AEs.

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 (n = 600)</th>
<th>Placebo (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>558 (93%)</td>
<td>290 (96%)</td>
</tr>
<tr>
<td>Study drug d/c due to AEs</td>
<td>99 (16%)</td>
<td>62 (21%)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>339 (56%)</td>
<td>188 (62%)</td>
</tr>
<tr>
<td>Grade 3 febrile neutropenia</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>281 (47%)</td>
<td>181 (60%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>53%</td>
<td>44%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Spinal-cord compression</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Occurring in at least 5% of patients in either group.

---

**Phase III trials in CRPC with overall survival advantage**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Median survival benefit (months)</th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 327</td>
<td>Docetaxel/pred vs mitoxantrone/pred</td>
<td>1,006</td>
<td>2.4</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>IMPACT</td>
<td>sipuleucel-T vs placebo</td>
<td>314</td>
<td>4.1</td>
<td>0.75</td>
<td>0.002</td>
</tr>
<tr>
<td>TROPIC</td>
<td>Cabazitaxel/pred vs mitoxantrone/pred</td>
<td>765</td>
<td>2.4</td>
<td>0.70</td>
<td>0.0001</td>
</tr>
<tr>
<td>COU 301</td>
<td>Mitoxantrone/pred vs placebo/pred</td>
<td>1,193</td>
<td>3.9</td>
<td>0.80</td>
<td>0.0011</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>Abiraterone/pred vs placebo/pred</td>
<td>992</td>
<td>2.9</td>
<td>0.86</td>
<td>0.00181</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>MDV 3100/pred vs placebo/pred</td>
<td>1,119</td>
<td>4.8</td>
<td>0.82</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Phase II trials in Castrate Sensitive Metastatic PrC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Median survival benefit (months)</th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHART/STAMPEDE</td>
<td>Early + late chemo</td>
<td>790/2962</td>
<td>13.6-17/10.22</td>
<td>0.61/0.76</td>
<td>0.0012/0.003</td>
</tr>
</tbody>
</table>

---

**Advanced Prostate Cancer Update - Take Home**

- **Progress**
  - Survival and palliation are improving
  - What was called “hormone refractory” is still driven by Androgen receptor signaling
  - Old drug learns new trick. Cytotoxic chemotherapy in new setting
  - Immunotherapy has an established role in advanced PrC
- **Keep an open mind to new data**
  - Screening every man is wrong
  - Screening no man is wrong
<table>
<thead>
<tr>
<th>Role of PCP in the care of men with advanced Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary and secondary prevention of heart disease</td>
</tr>
<tr>
<td>• Bone health</td>
</tr>
<tr>
<td>• Frailty management/gerontology</td>
</tr>
<tr>
<td>• Sexual health</td>
</tr>
</tbody>
</table>