Update On Treatment of Localized Prostate Cancer

Ahmad Shabsigh, MD, FACS
Assistant Professor
Department of Urology
The Ohio State University Wexner Medical Center

Incidence of CaP

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>All Sites</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)

Mortality

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Esophagus</td>
</tr>
<tr>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>All Sites</td>
</tr>
</tbody>
</table>

Siegel, R.L., Miller, K.D., MPH2; Jemal, A. CA CANCER J CLIN 2016
Trends in Metastatic Breast and Prostate Cancer: Lessons in Cancer Dynamics

Initiation of widespread PSA screening

Incidence of Metastatic Disease (per 100,000)


Prostate cancer
Breast cancer

Natural History of Prostate Cancer

Hormone-Sensitive
Castration-Resistant

Androgen Deprivation
Therapies After GnRH Agonists and Antagonists
Chemotherapy
Immunotherapy
Postchemotherapy

Surgery and Radiation

Pre-metastatic Asymptomatic
Radiographically Metastatic Symptomatic

Time
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

### Table 4 – Histologic definition of new grading system

<table>
<thead>
<tr>
<th>Grade group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Gleason score 3 + 3 = 6)</td>
<td>Only individual discrete well-formed glands</td>
</tr>
<tr>
<td>2 (Gleason score 3 + 4 = 7)</td>
<td>Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands</td>
</tr>
<tr>
<td>3 (Gleason score 4 + 3 = 7)</td>
<td>Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands</td>
</tr>
<tr>
<td>4 (Gleason score 8)</td>
<td>Only poorly formed/fused/cribriform glands or Predominantly well-formed glands and lesser component lacking glands or Predominantly lacking glands and lesser component of well-formed glands</td>
</tr>
<tr>
<td>5 (Gleason scores 9–10)</td>
<td>Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands</td>
</tr>
</tbody>
</table>

---

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

![Graph showing probability of RP over years since surgery](image-url)
Prostate Cancer: Indolent vs. Aggressive

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>PSA (ng/ml)</th>
<th>Stage</th>
<th>GS</th>
<th># of cores</th>
<th>% of cancer in any core</th>
<th>PSA density (ng/mL/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low Risk</td>
<td>&lt; 10</td>
<td>T1c</td>
<td>≤ 6</td>
<td>&lt; 3</td>
<td>≤ 50%</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Low Risk</td>
<td>&lt; 10</td>
<td>T1c, T2a</td>
<td>≤ 6</td>
<td>3</td>
<td>&lt; 50%</td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>10-20</td>
<td>T2b-T2c</td>
<td>7</td>
<td>4-6</td>
<td>≤ 50%</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt;20</td>
<td>T3-T4</td>
<td>8-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biomarkers

<table>
<thead>
<tr>
<th>Who to biopsy</th>
<th>Who to rebiopsy</th>
<th>Who to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>PCA3</td>
<td>Polaris</td>
</tr>
<tr>
<td>Free PSA</td>
<td>Confirm DX</td>
<td>OncotypeDx</td>
</tr>
<tr>
<td>PHI</td>
<td></td>
<td>Decipher</td>
</tr>
<tr>
<td>TMPRSS-ERG</td>
<td></td>
<td>Promark</td>
</tr>
<tr>
<td>4K score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EcoDx</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4K score vs PHI

<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>FISH, IHC</td>
<td>FURP, biopsy</td>
<td>Active surveillance</td>
<td>CSS</td>
</tr>
<tr>
<td>Decipher</td>
<td>1.4M RNA expression oligonucleotide Microarray</td>
<td>RP tissue</td>
<td>adverse pathology</td>
<td>CSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adj EBRRT</td>
<td>Mets, BCP</td>
</tr>
<tr>
<td>OncotypeDx</td>
<td>Quant-RT-PCR, 12 CaP genes and 5 controls</td>
<td>Biopsy</td>
<td>low to interm-risk RP</td>
<td>pT3 or GG 4 on RP</td>
</tr>
<tr>
<td>ProLaris</td>
<td>Quantitative RT-PCR for 31 cell cycle-related genes and 16 housekeeping controls</td>
<td>TURP, biopsy</td>
<td>Active surveillance</td>
<td>CSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Localized CaP</td>
<td>BCP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy Interm-risk EBRT</td>
<td>BCP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RP N0</td>
<td>Localized Cap</td>
</tr>
<tr>
<td>ProMark</td>
<td>Multiplex immuno/fluorescent staining of 8 proteins</td>
<td>Biopsy</td>
<td>GS 3+3 or 3+4</td>
<td>pT3 or G2G4 on RP</td>
</tr>
</tbody>
</table>
Better Imaging

Multipartametric Prostate MRI

Better Imaging

mpMRI guided biopsy

Treatment Options for Localized CaP

• Watchful waiting

Treatment Options for Localized CaP

• Watchful waiting
• Active surveillance
<table>
<thead>
<tr>
<th>Treatment Options for Localized CaP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Watchful waiting</td>
</tr>
<tr>
<td>• Active surveillance</td>
</tr>
<tr>
<td>• Ablation (Cryotherapy, HIFU, Laser…)</td>
</tr>
<tr>
<td>• Brachytherapy</td>
</tr>
<tr>
<td>• EBRT ± ADT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Options for Localized CaP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Watchful waiting</td>
</tr>
<tr>
<td>• Active surveillance</td>
</tr>
<tr>
<td>• Ablation (Cryotherapy, HIFU, Laser…)</td>
</tr>
<tr>
<td>• Brachytherapy</td>
</tr>
<tr>
<td>• EBRT ± ADT</td>
</tr>
<tr>
<td>• Surgery</td>
</tr>
</tbody>
</table>
**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

---

**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>98%</td>
<td>99.9%</td>
<td>100% (5Y)</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></td>
<td>26%</td>
</tr>
<tr>
<td>Positive lymph node</td>
<td></td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>Personal choice</td>
<td>1.6%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

---

**ASCO**

- Recommended for most patients with low risk (GS≤6) prostate cancer
- Younger age, high volume, AA, family history should be taken into account
- Patients <55 with high volume low risk disease may need to be treated
- Patients with short life expectancy may be well with WW

---

- 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

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

Surgery

Robotic Radical Prostatectomy

Open vs Robotic Prostatectomy

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

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 (Phoenix 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 83.8% 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.

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**

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


---

**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

---

**“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

---

**Androgen Deprivation Therapy**
Charles Benton Huggins, M.D.

Huggins and Hedges

*Studies on prostate cancer, I. The effect of castration, of estrogen and of androgen injection on serum phosphastase in metastatic carcinoma of the prostate.*

Cancer Res. 1:293-297, 1941

Huggins, Stevens, and Hedges

*Studies on prostate cancer, II. The effect of castration on advanced carcinoma of the prostate gland.*

Arch. Surg. 43:209-223, 1941

Image courtesy of the American Urological Association, Inc. and the William P. Didusch Center for Urologic History.

Modified from Moyad & Pienta

**Androgen Deprivation Therapy (Castration) for Metastatic Prostate Cancer**

XRT + Adjuvant ADT well established (Level 1 evidence)

Modified from Moyad and Pienta
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

**Randomize**

- 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: Yes vs No
  - Prior adjuvant ADT: ≤12 vs >12 mos.

**Evaluate**

- ARM A: ADT + docetaxel 75 mg/m² every 21 days for maximum 6 cycles
  - Evaluate every 3 weeks while on docetaxel and at week 24, then every 12 weeks
- ARM B: ADT (androgen deprivation therapy alone)
  - 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

NCT00309985. Available at www.clinicaltrials.gov/ct2/show/NCT00309985?term=CHAARTED&rank=1

**E3805—CHAARTED Primary Endpoint: OS**

- Median OS 57.6 mos. vs 44.0 mos.
- HR (95% CI) 0.61 (0.47–0.80)
- P-value 0.0003

**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, ie, from 32.2 months to 49.2 months.
- We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.

**Castration Resistant Prostate Cancer**
Definition of Castration-Resistant Prostate Cancer (CRPC): HRPC, AIPC (non-metastatic and metastatic)

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

3 × PSA rises 1 week apart (2 × levels 50% > nadir and >2 ng/mL)
AA withdrawal for ≥ 4 weeks (flutamide) or ≥ 6 weeks (bicalutamide)

Castrate testosterone levels (<50 ng/dL)
PSA progression despite consecutive HTsa


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

Development of CRPC

- Selective pressure
- Adaptation
- Restored AR activity (rising PSA)
- CRPC

AC = acetylation; AR = androgen receptor; CoAct = coactivators; CoR = corepressors; GF = growth factor; P = phosphorylation; Sumo = sumoylation.

Alternative splicing
Aberrant modification
GF, cytokine pathways
Sumo
AC

Perturbation
CoAct gain
CoR loss/dismissal

Intracrine androgen synthesis

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

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

Immunotherapy

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.
**IMPACT Trial Results**

- Placebo (n = 171)
- Sipuleucel-T (n = 341)

<table>
<thead>
<tr>
<th>Median OS (mos)</th>
<th>Placebo</th>
<th>Sipuleucel-T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21.7</td>
<td>25.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR for death (95% CI)</th>
<th>Placebo</th>
<th>Sipuleucel-T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.78 (0.61–0.98)</td>
<td>0.78 (0.61–0.98)</td>
</tr>
</tbody>
</table>

**Survival (%)**

- Median OS: 4.1 months
- 12% 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.

<table>
<thead>
<tr>
<th>Baseline PSA, ng/mL</th>
<th>≤22.1 (n = 128)</th>
<th>&gt;22.1 to 50.1 (n = 128)</th>
<th>&gt;50.1 to 134.1 (n = 128)</th>
<th>&gt;134.1 (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference, months</td>
<td>13.0</td>
<td>7.1</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.51 (0.31–0.85)</td>
<td>0.74 (0.47–1.17)</td>
<td>0.81 (0.52–1.24)</td>
<td>0.84 (0.55–1.29)</td>
</tr>
</tbody>
</table>

**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

- 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.

**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
- 7.1
- 5.4
- 2.8

**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)

Abiraterone (Zytiga®, Zytiga®)

**Indication**
CYP17—an 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.

**Chemical Pathways**
- Cholesterol
  - Pregnenolone
  - Abiraterone
  - 17OHPregnenolone
  - Abiraterone
- DHEA
  - Androstenedione
  - Testosterone
  - DHT

**Hormonal therapy**
- CVD = cardiovascular disease; AUC = area under the curve; CYP = cytochrome P.

**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

**Results**
- 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

**COU 301: Overall Survival Post Chemotherapy**

<table>
<thead>
<tr>
<th>Days from randomization</th>
<th>Placebo</th>
<th>Abiraterone Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS: 3.9 months</td>
<td>14.8 mos.</td>
<td>10.9 mos.</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Abiraterone Acetate: Androgen Biosynthesis Inhibitor**

DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone.
Enzalutamide

**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-naive.

---

4.8-month Survival Advantage With Enzalutamide in PC After Chemotherapy

<table>
<thead>
<tr>
<th>Overall survival (%)</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 24 mos. (95% CI)</td>
<td>18.4 (17.3–NYR)</td>
<td>13.8 (13.6–NYR)</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>

No. at risk:
- Enzalutamide: 800 775 701 627 400 211 72 7 0
- Placebo: 399 376 317 263 167 81 33 3 0

NYR = not yet reached.


---

Enzalutamide: Third-Generation Androgen-Receptor Inhibitor

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

---

Enzalutamide In mPC Before Chemotherapy

<table>
<thead>
<tr>
<th>rPFS, mos. (95% CI)</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 24 mos. (95% CI)</td>
<td>3.9 (3.7–4.4)</td>
<td>0.19 (0.15–0.23)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.19 (0.15–0.23)</td>
<td>3.9 (3.7–4.4)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No. at risk:
- Enzalutamide: 832 514 256 128 34 5 1 0
- Placebo: 801 305 79 20 5 0 0 0


---

**Hormonal therapy**

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>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Enzalutamide
Placebo

Abiraterone After Progression With Enzalutamide: PSA Reduction

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

Maximum PSA Decline (%)

Prevalence of AR-V7 in mCRPC

N = 62

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

Androgen-Receptor Splice Variants

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

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Ligand-binding domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>AR-V7</td>
<td>1 2 3 6 4 6</td>
</tr>
<tr>
<td>1</td>
<td>3 6 4 6</td>
</tr>
</tbody>
</table>

Prevalence of AR-V7 in mCRPC


Androgen-Receptor Splice Variants

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


Enzalutamide-treated patients

Abiraterone-treated patients

No. at risk

AR-V7 negative 19 12 2 1 0
AR-V7 positive 12 1 0 0 0

No. at risk

AR-V7 negative 25 10 5 0
AR-V7 positive 6 1 0 0

Abiraterone—treatment with docetaxel

Chemotherapy

Phase 3 Primary Endpoint—OS


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

Cabazitaxel

Chemotherapy

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

Median OS 12.7 mos. 15.1 mos. HR (95% CI) 0.70 (0.59–0.83) P-value <0.0001

Median OS Δ: 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
  - Enzalutamide—androgen-receptor blocker
- Chemotherapy
  - Cabazitaxel—microtubule inhibitor
- Radioisotope 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**

- **Patients**
  - N = 921
  - Confirmed symptomatic CRPC
  - ≥2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel*
- **Stratification**
  - Total ALP: <220 U/L vs ≥220 U/L
  - Bisphosphonate use: Yes vs No
  - Prior docetaxel: Yes vs No
- **Treatment phase**
  - Radium-223 dichloride (50 kBq/kg) + best standard of care†
  - Placebo (saline) + best standard of care†
- **Planned follow-up** in 19 countries

**ALSYMPCA Updated Analysis: OS**

- **Patients**
  - Radium-223 dichloride (n = 614)
  - Placebo (n = 307)
- **Median OS**
  - Radium-223 14.9 mos.
  - Placebo 11.3 mos.
- **HR (95% CI)**
  - 0.70 (0.58–0.83)
- **P-value**
  - <0.001

*Unfit for docetaxel includes patients who were ineligible for docetaxel-based docetaxel, 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, anti-hormones, estrogen (e.g., diethylstilbestrol), estramustine, or ketoconazole.

ALP = alkaline phosphatase.
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>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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

Phase III trials in CRPC with overall survival advantage

<table>
<thead>
<tr>
<th>Trial 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 Docetaxel/pred vs mitoxantrone/pred</td>
<td>1,066</td>
<td>2.4</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>IMPACT Sipuleucel-T vs placebo</td>
<td>512</td>
<td>4.1</td>
<td>0.75</td>
<td>0.004</td>
</tr>
<tr>
<td>TROPIC Cabazitaxel/pred vs mitoxantrone/pred</td>
<td>705</td>
<td>2.4</td>
<td>0.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AFFIRM MDV 3100 /pred vs placebo/pred</td>
<td>1,119</td>
<td>4.8</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MOS-12 mo</td>
<td>922</td>
<td>2.8</td>
<td>0.695</td>
<td>0.00185</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
Role of PCP in the care of men with advanced Prostate Cancer

- Primary and secondary prevention of heart disease
- Bone health
- Frailty management/gerontology
- Sexual health