Clinical Pathways for Individualized Management of Prostate Cancer: Addressing Disease Diversity with Emerging Therapies and Tailored Treatment

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Disclosures

NCCN Prostate Cancer Guidelines Panel Chair, Prostate Cancer Early Detection Panel member, honoraria only for lectures (usually annual meeting Guidelines update and occasional CME activity) or other activities (panel participation for Guidelines adaptation for other countries) on behalf of NCCN.

Neither Dr. Mohler nor his wife owns any stock in any company. His two adult children, to his knowledge, do not own any stock in any company in the biomedical sector.
Learning Objectives

• Outline the latest evidence-based guidelines for screening, stratifying, and treating prostate cancer (CaP) based on disease subtype and severity
• Discuss the mechanism of action, efficacy, safety, and indications of novel therapeutic options for the management of metastatic castration-recurrent/resistant CaP (mCRPC)
• Incorporate the latest guidelines and clinical trial results into strategies for the development of CaP clinical pathways that direct appropriate treatments to target patient populations
• Employ measures to improve guideline adherence and individualized care through the adoption of clinical pathways that optimize CaP treatment based on disease state
Outline

• CaP Early Detection and Treatment Guidelines
• New Treatments for mCRPC
• Pathway Construction and Adherence
The CaP Challenge

- Complex disease
- Many controversial aspects of management
- Lack of sound data to support most recommendations
- Several variables must be considered to tailor CaP therapy to an individual patient
- Guidelines provide a framework on which to base treatment decisions
CaP Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines – guideline-compliant staging, treatment, and follow-up
<table>
<thead>
<tr>
<th>Stage T1</th>
<th>T1a Tumor found in prostate tissue removed for reasons other than cancer; less than 5 percent of specimen is malignant</th>
<th>T1b Same as T1 but more than 5 percent of specimen contains cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic tumor confined to prostate gland; palpated gland feels normal</td>
<td>T1c Tumor found through biopsy done in response to an elevated PSA test or to an abnormal ultrasound exam; may be less extensive than a T1b tumor</td>
<td></td>
</tr>
</tbody>
</table>

TNM = tumor, node, metastasis
Urological Sciences Research Foundation [website].
## TNM Staging System

<table>
<thead>
<tr>
<th>Stage T2</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2a</td>
<td>Tumor confined to less than half of one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor affecting more than half of one lobe</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumor involving both lobes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage T3</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3a</td>
<td>Tumor that protrudes beyond the prostate</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor that has invaded the seminal vesicles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage T4</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>Tumor that is fixed and has pushed well beyond the prostate into adjacent structures</td>
</tr>
</tbody>
</table>
Biology: Summary

• Good = Low grade, low volume, slow PSA doubling time (40%)
• Bad = High grade, high volume, rapid PSA doubling time (20%)
• In between = Not good or bad (40%)
CaP Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines – guideline-compliant staging, treatment, and follow-up
Every 3 Minutes an American is Diagnosed with CaP

Every 20 Minutes an American Dies of CaP

US Annual Age-Adjusted Mortality Rates 1930 – 2009

CaP Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines – guideline-compliant staging, treatment, and follow-up
Since the Discovery of PSA, the Death Rate from CaP has:

a. Increased due to side effects from unnecessary treatments
b. Decreased 10%
c. Decreased 40%
d. Decreased 60%
Since the Discovery of PSA, the Death Rate from CaP has:

a. Increased due to side effects from unnecessary treatments
b. Decreased 10%
c. Decreased 40%
d. Decreased 60%
CaP Early Detection Recommendations

  - Routine screening not advocated especially >75
- American Urological Association (2009)
  - Annual PSA & DRE
    - From age 50 until LE <10 yrs
    - From age 40 if high risk (AA or family history)
- American Cancer Society (2010)
  - Annual PSA ± DRE
  - From age 50 until LE <10 yrs
  - From age 45 if high risk (AA or family history)
  - From age 40 if multiple family members
CaP Early Detection Recommendations

- **US Preventive Services Task Force (2011)**
  - Routine screening discouraged for everyone [D]

- **NCCN (the best recommendation) (2011)**
  - PSA and DRE at 40 (category 2B), if <1, at 45
  - PSA and DRE at 45, if <1, at 50
  - If high risk because AA, family history, taking 5ARI, or PSA >1, annual PSA and DRE at 40 (category 2B)
  - Routine screening less frequent in older men (65-75) and not advocated especially >75

- **American Urological Association (2013)**
  - Shared decision-making for 55-69, a target age group for whom benefits may outweigh harms
  - Outside this age range, PSA-based screening as a routine could not be recommended
CaP Early Detection Recommendations

• NCCN (current recommendation) (2016 V2)
  – PSA and ?DRE at 45-75, if <1, repeat testing in 2-4 years
  – PSA and ?DRE at 45-75, if ≥1, repeat testing in 1-2 years
  – PSA and ?DRE in selected men >75 (category 2B)
  – PSA >3, consider DRE and TRUS biopsy or PSA and DRE in 6-12 months or % free PSA, 4Kscore or PHI

• US Preventive Services Task Force (draft; May 2017)
  – Screening may be appropriate for men at higher risk [C]

• American College of Physicians; American Academy of Family Physicians
  – Counsel men 50-65 regarding risk vs benefit
Cancer Screening Costs

- Total cost of CaP screening/treatment: $17.6-$25.7 billion
- Cost per quality-adjusted life year gained
  - CABG: $7300-$62,900
  - CaP screening: $14,200-$51,267
  - Breast cancer screening: $20,000-$50,000
  - Colon cancer screening: $35,054
  - Liver transplant: $225,900

Screening Men with a Family History

- 2-3 fold increased risk if first-degree relative with CaP
- Younger age at presentation
- Comparable results with radical prostatectomy
- Begin screening at age 40

### CaP Incidence and Death Rates by Race and Ethnicity, 2001-2005*

<table>
<thead>
<tr>
<th></th>
<th>Caucasian American</th>
<th>African American</th>
<th>Asian American and Pacific Islander</th>
<th>American Indian and Alaska Native</th>
<th>Hispanic Latino</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>156.7</td>
<td>248.5</td>
<td>93.8</td>
<td>73.3</td>
<td>138</td>
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<tr>
<td>Mortality</td>
<td>24.6</td>
<td>59.4</td>
<td>11.0</td>
<td>21.1</td>
<td>20.6</td>
</tr>
</tbody>
</table>

* Per 100,000 population

Use of PSA for Early Detection is Most Appropriate for:

A. African Americans
B. Men with CaP in father or brother
C. Men with life expectancy $\geq 10$ yrs
D. Men with BRAC1 mutation
E. All of the above
Use of PSA for Early Detection is Most Appropriate for:

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D. Men with BRAC1 mutation
E. All of the above
CaP Basics

• Biology
• Incidence and mortality
• Early detection guidelines
• Treatment guidelines - guideline compliant staging, treatment, and follow-up
• Swedish RP vs Watchful Waiting
  - 44%, 35%, and 38% decline in CaP-specific mortality after 8.2, 10.8, and 12.8 years follow-up, respectively
  - Enrolled 1989 – 1999 and almost no PSA use
• Tyrol, Austria PSA-based screening study
  - 54% decline in CaP-specific mortality
  - 10 year PSA lead-time
  - Enrolled 1988 – 2005 and PSA since 1993

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L. J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O’Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

Need to Treat to Prevent 1 Death:

- 100 low-risk CaP, Canadian
- No survival benefit, American
- 48 PSA-detected CaP, European
- 12 PSA-detected CaP in Goteburg subset, Sweden
- 15 DRE-detected CaP; 7 if < age 65 years, Sweden
Active Surveillance?

- High prevalence of CaP upon autopsy
- High frequency of CaP upon biopsy even when PSA and prostate exam normal
- 29%-50% of screening-detected CaP overtreated
- Side effects avoided if don’t receive treatment that was unnecessary

Active Surveillance or Immediate Active Treatment?

• The **risks** include
  - Chance of missed opportunity for cure
  - Nerve-sparing may be more difficult
  - Anxiety

• The **benefits** include
  - Avoidance of treatment-related side effects from a treatment that was unnecessary
1. Separated Very Low Risk from Low Risk CaP

Low Risk CaP
- T1-T2a
- GS 2-6
- PSA<10

Very Low Risk CaP
- T1c
- GS 2-6
- PSA<10
- <3 cores positive
- <50% CaP in any core
- PSAD <0.15

2. Made AS the only recommendation for men with:
   a. Low Risk CaP and L Exp < 10 yrs
   b. Very Low Risk CaP and L Exp < 20 yrs

CaP Spreads While Patients Thinking!

- 645 Canadians who underwent RP 1987-1997
- 10 yr biochemical progression-free survival
  - RP < 3 mo  75%
  - RP ≥3 mo  61%
  - $P=.05$
- RP delay ≥ 3 mo associated with 46% increased chance of PSA progression after adjusting for grade, stage, and PSA at diagnosis

But Several Studies Show NO Harm from Treatment Delay

- BPFS not impacted by delay between diagnosis and RP of 3 mo, 6 mo, or even 2 yrs
- GS rarely changes between diagnosis and rebiopsy
  - 2.4% convert from low- to high-grade CaP at 7 yrs (SEER data)
  - change from <7 to some 4 or 5 after 1-6 yrs
  - 13% (n=90, Johns Hopkins)
  - 2.5% (n=206, Canadian)
  - 4% (n=331, Canadian)
- Klotz - “Need to treat an estimated 200 men with low-risk CaP in order to prevent 1 CaP death”

BPFS = biochemical progression-free survival; GS = Gleason score; SEER = Surveillance, Epidemiology, and End Results.
3. Active surveillance program clarified
   a. PSA as often as every 3 mo but at least every 6 mo
   b. DRE as often as every 6 mo but at least every 12 mo
   c. Needle biopsy may be repeated within 6 mo of diagnosis if initial biopsy was <10 cores; may be performed within 18 mo if initial biopsy >/= 10 cores
   d. Uncertain what the progression criteria should be to warrant treatment
Criteria for Progression

- Toronto: clinical or PSADT < 3 yrs
  - Neither PSA > 10 nor > 20 or PSAV > 2ng/mL/yr better
- Johns Hopkins: annual pbx grade group 4-5 or cores > 2 or core > 50%
  - Neither PSADT nor PSAV assoc w/ pbx progression
- No harm to period of AS
  - RP after AS has better PSA cure rate than RP
- Need biomarker for CaP aggressiveness

North American AS Experience

<table>
<thead>
<tr>
<th>Center</th>
<th>Toronto</th>
<th>Johns Hopkins</th>
<th>UCSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>450</td>
<td>603</td>
<td>531</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>F/U (mo, median)</td>
<td>82</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>OS</td>
<td>68%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>CSS</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment</td>
<td>30%</td>
<td>31%</td>
<td>24%</td>
</tr>
<tr>
<td>GS↑</td>
<td>8%</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td>PSA</td>
<td>14% (DT&lt;3 yrs)</td>
<td>-</td>
<td>16%</td>
</tr>
<tr>
<td>Nodule</td>
<td>1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

OS = overall survival rate; CSS = cause-specific survival; UCSF = University of California, San Francisco

HEY! Wait a Minute.....

Every 3 Minutes an American is Diagnosed with CaP

Every 20 Minutes an American Dies of CaP

Open Surgery
Laparoscopic Surgery
## Advantages of Robotic vs Open Radical Prostatectomy

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Yes</th>
<th>Maybe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better cancer control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less blood loss</td>
<td><img src="image" alt="Diamond" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved continence</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
<tr>
<td>Higher potency rate</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
<tr>
<td>Less postoperative pain</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
<tr>
<td>Shorter recovery</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
<tr>
<td>Cost</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
<tr>
<td>Total cost</td>
<td></td>
<td></td>
<td><a href="image">Diamond</a></td>
</tr>
</tbody>
</table>
Radiation Therapy

- Brachytherapy (interstitial radiation, “seeds”)
  - Iodine
  - Palladium
  - Cesium
- External radiation therapy
  - Electron, proton, or neutron
  - Conformal
  - IMRT
  - IGRT

IMRT = intensity-modulated radiation therapy; IGRT = image-guided radiation therapy.
Transperineal Technique
Implant/Dose Distribution
Dose Distribution: 3D Conformal
IMRT has the ability to deliver many “beamlets” of varying radiation intensity within one treatment field.

“Fluence” or Intensity Map

“Beamlets”
Treat Everyone... But Treatment Has Risks

- **Mortality**
  - RP 0.5%
  - RT 0.1%
- **Urinary incontinence**
  - RP 3% [5-60%]
  - RT 8%
- **Impotence**
  - RP 30% (≤65 yrs); 50% (>65 yrs) [12-56%]
  - RT 63-70%

RT = radiation therapy; RP = radical prostatectomy
Treatment Discussion

• Estimate Life Expectancy

• Risk stratify using stage, Gleason score, and PSA

• AS should be the first option discussed against which the benefits (potential and need for cure) and risks (mortality, urinary incontinence, and impotence) of treatment should be compared

• AS should be recommended for very-low and low-risk CaP when LExp is <20 and <10 yrs, respectively

LExp = life expectancy
Life Expectancy Estimation

- LExp can be estimated using the Minnesota Metropolitan Life Insurance Tables, Social Security Administration LExp Tables, or US Department of Health Trend Tables.
- LExp can be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.
  - LExp for 65-year-old African-American man = 16 yrs
  - If upper quartile of health, LExp = 24 yrs
  - If lower quartile of health, LExp = 8 yrs
- 2007 NCCN Guidelines, for the first time, included “Principles of Life Expectancy Estimation”

Time to CaP Death: Population-Based

- **Gleason score**
  - 2-6 favorable
  - 7-10 unfavorable
- **Tumor volume**
  - < 4 cc favorable
  - ≥ 4 cc unfavorable (nodule, PSA >12, >3 biopsies, >50% of biopsy)
- **Aggressiveness (Stanford criteria)**
  - Low if both favorable
  - High if both unfavorable
  - Intermediate if only 1 favorable
- **Time to symptomatic metastases (Sweden)**
  - Low 12 years
  - Intermediate 10 years
  - High 8 years
- **Time to death**
  - Time to symptoms + 3 years for ADT remission + 10 year PSA early detection lead time [if applicable]

ADT = androgen deprivation therapy
McNeal JE. *Hum Pathol.* 1992;23(3):258-266.
Time to CaP Death: PSADT-Based

• Calculate PSA doubling time
• Assume symptoms at PSA 100-200
• Add 5 yrs for ADT-induced remission
• Example
  – Average PSADT for clinically detected CaP = 4 yrs
  – Diagnosed at PSA = 6
  – PSA >100 after 4 doublings or 16 yrs
  – Death after 21 yrs
Time to Put into Practice!
Case 1

- A common presentation of clinically localized CaP
- Change patient’s health and use NCCN guidelines to estimate life expectancy
- Examine effect upon relationship between risk of death from CaP vs other causes
- Use NCCN guidelines to see how recommended treatment changes
Case 1 - Excellent

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is excellent. The best choice for treatment is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs

LExp by age = 16 yrs
- Excellent health = 24 yrs
- Average health = 16 yrs
- Poor health = 8 yrs

Chance of CaP death
- Excellent health = 50%
- Average health = 10%
- Poor health = 0%

Chance of cure of CaP by Partin Tables 83%

Chance of CaP death after RP
- Excellent health = 7%
- Average health = 2%
- Poor health = 0%

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is excellent. The best choice for treatment is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
Case 1 - Poor

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is poor. The best choice for treatment is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
• LExp by age = 16 yrs
  - Excellent health = 24 yrs
  - Average health = 16 yrs
  - Poor health = 8 yrs
• Chance of CaP death
  - Excellent health = 50%
  - Average health = 10%
  - Poor health = 0%
• Chance of cure of CaP by Partin Tables 83%
• Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
  - Poor health = 0%

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is poor. The best choice for treatment is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance (observation)
Case 1 - Average

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is average. The best choice for treatment is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
• LExp by age = 16.4 yrs
  - Excellent health = 24 yrs
  - Average health = 16 yrs
  - Poor health = 8 yrs
• Chance of CaP death
  - Excellent health = 50%
  - Average health = 10%
  - Poor health = 0%
• Chance of cure of CaP by Partin Tables 83%
• Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
  - Poor health = 0%

Case 1 - Average

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is average. The best choice for treatment prior to 2010 was

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
Case 1 - Average

65-year-old man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6. Prostate cancer in 10% of 1 of 12 biopsies. Health is average. The only treatment recommendation beginning 2010 is

1. IMRT
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• 5-yr OS worse when metastatic CaP diagnosed in younger men (≤ 55 yo) (27%) vs middle-aged (60%) vs elderly (55%)
• Nearly all CaP deaths from mCRPC; median OS < 2 yr
• Site of metastases predicts OS in CRPC
  - Lymph node-only metastases: 27 mo
  - Bone or bone + lymph node metastases: 20 mo
  - Visceral (lung, liver): 14 mo

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SYSTEMIC THERAPY FOR PROGRESSIVE CASTRATION-NAIVE DISEASE

**M0**
- **Orchiectomy**
- **LHRH agonist ± antiandrogen**
- **LHRH antagonist**
- **Observation**

**M1**
- **LHRH agonist + antiandrogen**
- **LHRH antagonist**
- Continuous ADT and docetaxel 75 mg/m² with or without prednisone for 5 cycles

Studies negative for distant metastases → See Systemic Therapy For M0 CRPC (PROS-10)

Progression* → See Systemic Therapy For M1 CRPC (PROS-11)

Studies positive for distant metastases → Consider biopsy if small cell suspected

Small cell → Cisplatin/etoposide or Carboplatin/etoposide or Docetaxel/carboplatin or Clinical trial

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*See Principles of Imaging (PROS-B).
See Principles of Androgen Deprivation Therapy (PROS-F).
*Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent.
See Principles of Active Surveillance and Observation (PROS-C).
*Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET. See Principles of Imaging (PROS-B).
*Continuous ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F).
*High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
*Assure castrate level of testosterone.
See Principles of Immunotherapy and Chemotherapy (PROS-G).
See NCCN Guidelines for Small Cell Lung Cancer.

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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How is ADT Like a Volkswagen?
VW Has Evolved...
### And So Has ADT!

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Drugs</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>DES parenteral</td>
<td></td>
</tr>
<tr>
<td>LHRH Agonists</td>
<td>leuprolide acetate, histrelin acetate, triptorelin pamoate</td>
<td></td>
</tr>
<tr>
<td>LHRH Antagonists</td>
<td>degarelix acetate</td>
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</tr>
<tr>
<td>Antiandrogens</td>
<td>flutamide, nilutamide, *apalutamide</td>
<td>bicalutamide, enzalutamide</td>
</tr>
<tr>
<td>5α-reductase inhibitors</td>
<td>finasteride</td>
<td>dutasteride</td>
</tr>
<tr>
<td>CYP17 inhibitors</td>
<td>ketoconazole, *orteronel</td>
<td>abiraterone acetate, *galeterone</td>
</tr>
</tbody>
</table>

* not FDA approved

DES = diethylstilbestrol
ADT for CaP Management

1. LHRH agonist or antagonist
2. LHRH agonist or CAB
3. Intermittent or continuous ADT
4. Docetaxel or abiraterone and ADT
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Shally isolates LHRH (Nobel Prize 1977)</td>
</tr>
<tr>
<td>1975</td>
<td>LHRH agonists developed</td>
</tr>
<tr>
<td>1985</td>
<td>LHRH agonists control advanced CaP</td>
</tr>
<tr>
<td>1992</td>
<td>LHRH antagonists developed</td>
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<tr>
<td>1998</td>
<td>LHRH antagonists control advanced CaP</td>
</tr>
<tr>
<td>2002</td>
<td>LHRH agonists and antagonists similar</td>
</tr>
<tr>
<td>2013</td>
<td>LHRH antagonist for LHRH agonist failure</td>
</tr>
<tr>
<td></td>
<td>• PSA response in 1 of 17²</td>
</tr>
</tbody>
</table>

LHRH = luteinizing hormone-releasing hormone
ADT for CaP Management

1. LHRH agonist or antagonist
2. LHRH agonist or CAB
3. Intermittent or continuous ADT
4. Docetaxel or abiraterone and ADT
1984: Flutamide and leuprolide cure advanced CaP
1989: Flutamide enhanced PFS and OS when added to leuprolide

Progression-free Survival (PFS)
(Two-Sided $P=0.039$)

Overall Survival
(Two-Sided $P=0.035$)

**Combined Androgen Blockade**

1998: Flutamide didn’t enhance PFS or OS when added to orchiectomy

1995-2016: Numerous RCTs and metanalyses demonstrate little if any benefit to CAB, which increases costs and side effects of ADT

**CAB = combined androgen blockade**

ADT for CaP Management

1. LHRH agonist or antagonist
2. LHRH agonist or CAB
3. Intermittent or continuous ADT
4. Docetaxel or abiraterone and ADT
Toxicities Associated with ADT

- Fatigue
- Hot flashes/hot flushes
- Loss of libido
- Osteoporosis
- Metabolic syndrome
  - Stroke
  - Myocardial infarction
  - Diabetes
Intermittent ADT

- Meta-analysis of 6 RCTs from 26 eligible (2996 men)
- Mortality similar for intermittent vs continuous ADT

- QoL better for intermittent vs continuous ADT (example, erectile dysfunction)

Can Intermittent ADT be Personalized using End-of-Induction PSA?

No response:
PSA > 10
survival 13 mo

Excellent response:
PSA 0.2 - <4.0
survival 4 yrs

Outstanding response:
PSA <0.2
survival 6 yrs

ADT for CaP Management

1. LHRH agonist or antagonist
2. LHRH agonist or CAB
3. Intermittent or continuous ADT
4. Docetaxel or abiraterone and ADT
Effect on Overall Survival of Adding Docetaxel to Standard of Care

- Systematic review identified 5 RCTs in M1 and 11 RCTs in M0
- Meta-analysis of 3206 M1 patients from 3 RCTs and 3978 M0 patients from 3 RCTs

**M1**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAARTED(^7)</td>
<td>136/393</td>
<td>101/397</td>
<td>0.61 (0.47–0.80)</td>
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<tr>
<td>GETUG-15(^8,^10)</td>
<td>NA/193</td>
<td>NA/192</td>
<td>0.90 (0.69–1.81)</td>
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<tr>
<td>STAMPEDE(^8) (SOC +/- Doc)</td>
<td>350/724</td>
<td>144/362</td>
<td>0.76 (0.62–0.93)</td>
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<tr>
<td>STAMPEDE(^8) (SOC + ZA +/- Doc)</td>
<td>170/366</td>
<td>158/365</td>
<td>0.85 (0.65–1.10)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.77 (0.68–0.87)</td>
</tr>
</tbody>
</table>

**M0**

<table>
<thead>
<tr>
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<th>Control</th>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-12(^2,^5)</td>
<td>49/206</td>
<td>42/207</td>
<td>0.94 (0.60–1.48)</td>
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<tr>
<td>RTOG 0521(^2,^8)</td>
<td>59/281</td>
<td>43/282</td>
<td>0.70 (0.47–1.04)</td>
</tr>
<tr>
<td>STAMPEDE(^8) (SOC +/- Doc)</td>
<td>65/460</td>
<td>31/230</td>
<td>0.95 (0.62–1.46)</td>
</tr>
<tr>
<td>STAMPEDE(^8) (SOC + ZA +/- Doc)</td>
<td>31/227</td>
<td>20/228</td>
<td>1.05 (0.57–1.95)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.87 (0.69–1.09)</td>
</tr>
</tbody>
</table>

LATITUDE Phase III Trial: ADT ± Abiraterone/Pred for Metastatic CaP

- 1199 men at 235 sites in 34 countries
- Planned interim analysis at median FU 30 mo/406 deaths
- Grade 3 hypertension and hypokalemia greater in tx arm
- Median OS was not reached in the tx arm vs 35 mo in the placebo group; medians for rPFS were 33 mo vs 15 mo

NCCN Recommendations for Metastatic CaP

- By disease-related symptoms
  - Asymptomatic
    - Intermittent ADT
    - Discuss possible decrease in OS
    - Trade off for improved QoL during off cycle
  - Symptomatic
    - Consider continuous ADT
    - If PSA falls to <4 and certainly <0.2, intermittent ADT reasonable

- By age and comorbidities
  - Younger and healthier - docetaxel or abiraterone + ADT
  - Older and/or unhealthier - ADT
Outline

- CaP Early Detection and Treatment Guidelines
- New Treatments for mCRPC
- Pathway Construction and Adherence
Definition of CRPC

• Increasing PSAs or progressive disease on imaging
• Castrate level of serum testosterone
  – T < 50 ng/dL most accepted
• Historical (but not accurate) terminology
  – Hormone refractory
  – Androgen independent

### Systemic Therapy for M1 Castration-Recurrent Prostate Cancer

**CRPC, studies positive for metastases**

- Maintain castrate levels of serum testosterone (<50 ng/dL)
- Consider bone anti-erosive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
- Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1 (category 1) (See PROS-G)\(^ {1b} \)
- Palliative RT for painful bony metastases
- Best supportive care

---

**Visceral metastases**

- Yes

**Progression\(^ {1b} \) after:****
- Abiraterone
g- Enzalutamide
d- Docetaxel

**No**

**Progression\(^ {1b} \) after all other therapies**

### Progression\(^ {1b} \) after all other therapies

- Abiraterone\(^ {1c} \) with prednisone (category 1)
- Docetaxel\(^ {1d} \) with prednisone (category 1)
- Enzalutamide\(^ {1a} \) (category 1)
- Radium-223 for symptomatic bone metastases (category 1)\(^ {1b} \)
- Clinical trial
- Secondary hormone therapy
- Antiandrogen
- Antiandrogen withdrawal
- Ketoconazole + hydrocortisone
- Corticosteroid
- DES or other estrogen\(^ {1a} \)

---

\(^ {1a} \)See Principles of Imaging (PROS-E).

\(^ {1b} \)See Principles of Androgen Deprivation Therapy (PROS-F).

\(^ {1c} \)Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET.

\(^ {1d} \)See Principles of Imaging (PROS-B).

\(^ {1a} \)See Principles of Immunotherapy and Chemotherapy (PROS-C).

\(^ {1b} \)DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.

\(^ {1c} \)Sipuleucel-T has not been studied in patients with visceral metastases.

---

For patients who are not candidates for docetaxel-based regimens.

Although most patients with no symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

---

Note: All recommendations are category 2A unless otherwise indicated.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Prostate Cancer

SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCERf

Prior therapy enzalutamide/abiraterone

- Docetaxel with prednisone (category 1)f
- Abiraterone with prednisone
- Enzalutamide
- Radium-223 for symptomatic bone metastases (category 1)
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole 1 hydrocortisone
  - Corticosteroid
  - DES or other estrogenf
- Best supportive care

No visceral metastases

- Enzalutamide (category 1)
- Abiraterone with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)
- Cabazitaxel with prednisone (category 1)f
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Docetaxel rechallengef
- Alternative chemotherapy (mitoxantrone with prednisone)f
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole 1 hydrocortisone
  - Corticosteroid
  - DES or other estrogenf
- Best supportive care

fSee Principles of Androgen Deprivation Therapy (PROS-F).
See Principles of Immunotherapy and Chemotherapy (PROS-Q).

Note: All recommendations are category 2 unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER

Prior therapy enzalutamide/abiraterone

- Docetaxel with prednisone (category 1)
- Clinical trial
- Abiraterone with prednisone
- Enzalutamide
- Other secondary hormone therapy
  - Antianдроген
  - Antianдроген withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

Prior therapy docetaxel

- Enzalutamide (category 1)
- Abiraterone with prednisone (category 1)
- Cabazitaxel with prednisone (category 1)
- Clinical trial
- Docetaxel rechallenge
- Alternative chemotherapy (mitoxantrone with prednisone)
- Other secondary hormone therapy
  - Antianдроген
  - Antianдроген withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

Note: All recommendations are category 3A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Asymptomatic or Minimally Symptomatic CRCP

1. Immunotherapy
2. Anti-androgen
3. Androgen synthesis inhibitor
Sipuleucel-T (Sip-T): Mechanism of Action

Antigen (PAP-GMCSF) is exposed to an antigen-presenting cell (APC).

APC takes up the antigen.

Antigen is processed and presented on surface of the APC.

Fully activated, the APC is now sipuleucel-T and is collected.

Sipuleucel-T activates T-cells in the body.

T-cells proliferate and attack cancer cells.
Sipuleucel-T: Logistics of Therapy

Day 1
Leukapheresis

Day 2-3
Sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center

Central Processing

Doctor’s Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4
Randomized Phase III Trial of Sip-T in CRPC (D9901)

Asymptomatic metastatic CRPC (N=127)

- Placebo q2wks x 3 (N=45)
- Sip-T q2wks x 3 (N=82)

Progression

- APC8015F q2wks x 3
- Long-term follow-up

Time to Disease Progression
(Primary Endpoint)

Log-rank $P = .052$

HR = 1.45, 95% CI, 0.99 to 2.11

- Sipuleucel-T ($n = 82$)
  Median: 11.7 weeks

- Placebo ($n = 45$)
  Median: 10.0 weeks

Overall Survival

Log-rank $P = .010$

HR = 1.71, 95% CI, 1.13 to 2.58

Median benefit: 4.5 months

Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (N = 512)

2:1

Sipuleucel-T Q 2 weeks x 3

Treated at physician discretion

Placebo Q 2 weeks x 3

Treated at physician discretion and/or salvage protocol

Primary endpoint: Overall survival
Secondary endpoint: Objective disease progression

IMPACT Overall Survival Final Analysis (349 events)

36.5 mo median f/u
HR = 0.759 (95% CI, 0.606, 0.951)
P = 0.017 (Cox model)
Median survival benefit = 4.1 months

Sipuleucel-T (n = 341)
Median survival: 25.8 mo.
36 mo. survival: 32.1%

Placebo (n = 171)
Median survival: 21.7 mo.
36 mo. survival: 23.0%

Asymptomatic or Minimally Symptomatic CRCP

1. Immunotherapy
2. Antiandrogen
3. Androgen synthesis inhibitor
AR Expression in CRPC

Androgen-Stimulated Benign Prostate

CRPC

AR Hypersensitized

- AR 10,000 times more sensitive in androgen-independent than androgen-sensitive CaP cell lines
- AR coactivators change from SRC-1 to TIF-2 in cell lines, xenografts, and clinical specimens
- AR phosphorylated by SRC or Ack1 tyrosine kinases

AR = androgen receptor
Enzalutamide

- 1199 men with CRPC after docetaxel
- 2:1 enzalutamide 160 mg qd vs placebo
- Stopped at interim analysis after 520 deaths
- Overall survival (primary endpoint)
  - Enzalutamide 18.4 mo
  - Placebo 13.6 mo
- All secondary endpoints met (ie, time to PSA progression)
  - Enzalutamide 8.3 mo
  - Placebo 3.0 mo
- Side effects
  - 0.6% seizures
  - Fatigue, diarrhea, hot flashes

Enzalutamide vs Bicalutamide

- International randomized, double-blind phase II study (TERRAIN)
- 375 men with metastatic castration-recurrent CaP enrolled March 2011 - July 2013
- 1:1 160 mg/d Enz or 50 mg/d Bic
- 1° endpoint: Progression-free survival
- Side effects
  - 1 seizure in each arm
  - Tx discontinued 8% Enz vs 5% Bic
  - Grade ≥3 9% Enz vs 8% Bic
- QoL
  - FACT-P improved at a higher rate in most domains for Enz vs Bic

FACT-P = Functional Assessment of Cancer Therapy-Prostate questionnaire
Enzalutamide vs Bicalutamide

PSA Waterfall Plot

Progression-Free Survival

Asymptomatic or Minimally Symptomatic CRCP

1. Immunotherapy
2. Antiandrogen
3. Androgen synthesis inhibitor
## Testicular Androgen Levels in Castration-Recurrent CaP

<table>
<thead>
<tr>
<th>Mass Spec</th>
<th>RIA</th>
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<tbody>
<tr>
<td>Titus 2005</td>
<td>Mohler 2004</td>
</tr>
<tr>
<td></td>
<td>T</td>
</tr>
<tr>
<td>AS-BP (n=18)</td>
<td>2.75</td>
</tr>
<tr>
<td>CR-CaP (n=18)</td>
<td>3.75</td>
</tr>
<tr>
<td>Montgomery 2008</td>
<td></td>
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<tr>
<td>AS-BP (n=6)</td>
<td>0.04</td>
</tr>
<tr>
<td>AS-CaP (n=4)</td>
<td>0.23</td>
</tr>
<tr>
<td>CR-Met CaP (n=8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Geller 1979</td>
<td></td>
</tr>
<tr>
<td>AS-BP (n=17)</td>
<td></td>
</tr>
<tr>
<td>CaP orch ± DES (n=9)</td>
<td></td>
</tr>
<tr>
<td>CaP DES 1 mg (n=6)</td>
<td>-</td>
</tr>
<tr>
<td>Labrie 1989</td>
<td></td>
</tr>
<tr>
<td>human CaP (n=?)</td>
<td></td>
</tr>
<tr>
<td>orch (n=5, 2-12m)</td>
<td></td>
</tr>
<tr>
<td>orch+fl (n=4, 2m)</td>
<td></td>
</tr>
</tbody>
</table>

Pathways to DHT Synthesis

Intact pathway

Adrenal androgen pathway

Cholesterol pathway

Backdoor pathway

CYP17A1 Inhibition

- Abiraterone
- Orteronel
- Galeterone

Pre-docetaxel: Abiraterone Extended OS by 3.4 Mo

Reported mechanisms for resistance based on in vitro studies include:

- Progesterone accumulation to overcome competitive inhibition by abiraterone\(^1,2\)
- CYP17A1 gene amplification\(^1\)
- Alternate pathways for DHT metabolism\(^2\)
- Development of AR mutants or splice variants\(^3\)

# Cross-Resistance: Abiraterone and Enzalutamide

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Prior Therapy</th>
<th>PSA&lt;sub&gt;50&lt;/sub&gt;, %</th>
<th>ORR, %</th>
<th>PFS, Mos</th>
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<tbody>
<tr>
<td>Noonan et al 2013</td>
<td>Abiraterone</td>
<td>Enzalutamide</td>
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<td>Loriot et al 2013</td>
<td>Abiraterone</td>
<td>Enzalutamide</td>
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<tr>
<td>Smith et al 2014</td>
<td>Enzalutamide</td>
<td>Abiraterone</td>
<td>–</td>
<td>–</td>
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<td>Schrader et al 2014</td>
<td>Enzalutamide</td>
<td>Abiraterone</td>
<td>46</td>
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<td>Badrising et al 2013</td>
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<td>Abiraterone</td>
<td>21</td>
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<td>Enzalutamide</td>
<td>Abiraterone</td>
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<td>Enzalutamide</td>
<td>Abiraterone</td>
<td>11</td>
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</tbody>
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Symptomatic CRPC

1. Enzalutamide
2. Abiraterone
3. Docetaxel
4. Enzalutamide/abiraterone for docetaxel failure
5. Cabazitaxel for docetaxel failure
6. Radiation
   • Radium-223
   • External beam for palliation
Docetaxel and Prednisone for mCRPC

- Standard-of-care first-line chemotherapy
- Most commonly used for treating rapidly progressing and/or symptomatic disease
- Often deferred in pts with no symptoms
- Toxicity: bone marrow suppression
- Uncertain duration (6, 10, or more cycles)
Docetaxel/Prednisone vs Mitoxantrone/Prednisone (TAX 327): OS

# TAX 327: Quality-of-Life Response

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel/Prednisone q3w</th>
<th>Docetaxel/Prednisone Weekly</th>
<th>Mitoxantrone/ Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable, n</td>
<td>278</td>
<td>270</td>
<td>267</td>
</tr>
<tr>
<td>Response,* %</td>
<td>22</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(17-27)</td>
<td>(18-28)</td>
<td>(9-18)</td>
</tr>
<tr>
<td>P value†</td>
<td>.009</td>
<td>.005</td>
<td></td>
</tr>
</tbody>
</table>

* ≥16 point improvement in FACT-P score compared to baseline
† Compared to mitoxantrone/prednisone

1. Enzalutamide
2. Abiraterone
3. Docetaxel
4. Enzalutamide/abiraterone for docetaxel failure
5. Cabazitaxel for docetaxel failure
6. Radiation
   • Radium-223
   • External beam for palliation
After Docetaxel: Abiraterone Improves Overall Survival

HR=0.646 (0.54-0.77)  P <0.0001

Abiraterone: 14.8 months (95% CI: 14.1, 15.4)

Placebo: 10.9 months (95% CI: 10.2, 12.0)

1 Prior Chemo OS: 15.4 months abiraterone vs 11.5 months placebo

Abiraterone

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>0</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
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<tr>
<td>797</td>
<td>728</td>
<td>631</td>
<td>475</td>
<td>204</td>
<td>25</td>
<td>0</td>
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</table>

Placebo

<table>
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<th>Days from Randomization</th>
<th>0</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
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<tr>
<td>398</td>
<td>352</td>
<td>296</td>
<td>180</td>
<td>69</td>
<td>8</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

AFFIRM: Phase III Registration Trial of Enzalutamide in mCRPC Post Docetaxel

Pts with mCRPC progressing on docetaxel (N=1199)

• Primary endpoint: OS

Randomized 2:1

Placebo daily PO
(n = 399)

Enzalutamide 160 mg/day PO
(n = 800)

OS (%)

Placebo: 13.6 mos (95% CI: 11.3-15.8)

Enzalutamide: 18.4 mos (95% CI: 17.3-NYR)

HR: 0.631 (95% CI: 0.529-0.752; P<.001)
37% reduction in risk of death

COU-AA-301: Phase III Study of Abiraterone Acetate in mCRPC

Pts with mCRPC progressing after 1-2 chemotherapy regimens, 1 of which contained docetaxel (N=1195)

Randomized 2:1

Abiraterone Acetate 1000 mg/day + Prednisone 5 mg BID (n=797)

Placebo + Prednisone 5 mg BID (n=398)

100
80
60
40
20
0

Mos

OS (%)

Abiraterone acetate:
14.8 mos (95% CI: 14.1-15.4)

Placebo:
10.9 mos (95% CI: 10.2-12.0)

HR: 0.65 (95% CI: 0.54-0.77; P<.001)

Symptomatic CRPC

1. Enzalutamide
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4. Enzalutamide/abiraterone for docetaxel failure
5. Cabazitaxel for docetaxel failure
6. Radiation
   • Radium-223
   • External beam for palliation
Cabazitaxel

New semi-synthetic taxane

- Selected to overcome the emergence of taxane resistance

Clinical data

- In phase I trials, dose-limiting toxicity (DLT) was neutropenia
- Antitumor activity in mCRPC in phase 1 trials that included docetaxel-resistant disease
TROPIC: Phase III Study

Primary endpoint: Overall survival
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Primary Endpoint: Overall Survival

Proportion of OS (%)

0  20  40  60  80  100

# at risk

MP  377  300  188  67  11  1
CBZ  378  321  231  90  28  4

<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>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59–0.83</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic CRPC

1. Enzalutamide
2. Abiraterone
3. Docetaxel
4. Enzalutamide/abiraterone for docetaxel failure
5. Cabazitaxel for docetaxel failure
6. Radiation
   • Radium-223
   • External beam for palliation
Radioisotope Therapy Options

• Symptomatic patients
  – Not candidates for chemotherapy, or
  – Already treated with chemotherapy
• Alpha emitter: radium 223
  – Survival benefit compared with BSC
  – Administer on outpatient basis
  – Treat every 4 wks x 6 (~ 6 mos total)
    • Unless other therapy initiated for progression of disease
  – Hematologic toxicity comparable to placebo
• Beta emitters: strontium-89, samarium-153
  – Approved for palliation of pain
  – Main toxicity on bone marrow
Relative Penetration of Different Radiation Wave Lengths
Phase III ALSYMPCA Study: Radium-223 Added to Best Standard of Care

Randomized 2:1 and stratified by total ALP (< vs ≥ 220 U/L), bisphosphonate use (yes vs no), and previous docetaxel (yes vs no)

Pts with:
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post docetaxel or unfit for docetaxel

(N = 921)

Radium-223 50 kBq/kg + Best Standard of Care

Placebo (saline) + Best Standard of Care

6 injections at 4-wk intervals

- Primary endpoint: OS
- Secondary endpoints included: time to first SRE, safety

Planned follow-up: 3 yrs

ALSYMPCA: Overall Survival

HR: 0.70 (95% CI: 0.58-0.83; \( P < .001 \))

Radium-223
(Median OS: 14.9 months)

Placebo
(Median OS: 11.3 months)

# Overview of Current Main Treatment Options for CRPC

<table>
<thead>
<tr>
<th>Nonmetastatic</th>
<th>Metastatic, asymptomatic/min sx</th>
<th>Metastatic chemotherapy naive</th>
<th>Metastatic, post docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-line hormonal therapy</strong></td>
<td>Abiraterone</td>
<td>Docetaxel</td>
<td>Abiraterone</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Radium-223</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td></td>
<td>Sipuleucel-T</td>
<td>Abiraterone</td>
<td>Cabazitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzalutamide</td>
<td>Radium-223</td>
</tr>
</tbody>
</table>

- **Strontium 89** extends survival time (level 1 evidence)
- **Samarium 153** pain palliation only (level 1 evidence)
- **Mitoxantrone** no level 1 evidence for outcome benefit

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Outline

- CaP Early Detection and Treatment Guidelines
- New Treatments for mCRPC
- Pathway Construction and Adherence
Why are Pathways Needed?

- Overdetection leads to overtreatment
- If it’s new, it’s better
- New CRPC agents are expensive and sequence of use remains uncertain
- MDs, hospitals, insurers, and government are rewarded when “more stuff is done to more patients”
Use of PSA: The Real World

- Men > 85 years old who have had PSA in last year
  - 25% in National Health Interview Study 2000 and 2005; 36% in US Dept of Veteran Affairs in 2002-2003
- Interventions
  - Stop including PSA in routine annual labs
  - Guidelines, pamphlets, internet, videos

• Where we were
  – 67% of men with NCCN low-risk CaP and Life Exp < 10 yrs were treated in SEER-Medicare analysis 2004-2007
  – US savings would be $1.32B annually if 80% were subjected to AS or observation

• Where we are
• Where we need to go
  – Simultaneous consultation vs linear consultation with urologist, radiation oncologist, and medical oncologist in 2009 in 3 Boston academic medical centers increased AS from 22% to 43% for men with NCCN low-risk CaP

Use of IMRT: The Real World

The ability to deliver many “beamlets” of varying radiation intensity, within one treatment field

“Fluence” or Intensity Map

“Beamlets”
Self Referral

IMRT
Brachy
Rad Px
ADT
AS
Other

Non-Self Referral

Self Referral

IMRT

Brachy

Rad Px

ADT

AS

Other

NCCN

Use of Robotic Surgery: The Real World
Management of Metastatic CaP

1. LHRH Agonist or Antagonist  
   - Doesn’t matter

2. LHRH Agonist or CAB  
   - Doesn’t matter

3. Intermittent or Continuous ADT  
   - Intermittent first because better QoL, less side effects, and survival same

4. Docetaxel or Abiraterone and ADT  
   - Extends survival

5. New agents for ADT for CRPC  
   - Yes but sequence unclear
How Much Do the New CRPC Agents Cost?
## Cost of Survival using New CRPC Agents: The Real World

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDA Approval</th>
<th>Cost</th>
<th>Added Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cycles of Docetaxel</td>
<td>05/19/2004</td>
<td>$78,000</td>
<td>2.4</td>
</tr>
<tr>
<td>1 course of Sipuleucel-T</td>
<td>04/26/2010</td>
<td>$110,000</td>
<td>4.1</td>
</tr>
<tr>
<td>8 mo Abiraterone</td>
<td>12/10/2012</td>
<td>$46,000</td>
<td>4.0</td>
</tr>
<tr>
<td>8 mo Enzalutamide</td>
<td>08/31/2012</td>
<td>$64,000</td>
<td>4.8</td>
</tr>
<tr>
<td>6 cycles of Cabazitaxel</td>
<td>06/17/2010</td>
<td>$168,000</td>
<td>2.4</td>
</tr>
<tr>
<td>1 course of Rad-223</td>
<td>05/15/2013</td>
<td>$66,000</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$532,000</strong></td>
<td><strong>23.3</strong></td>
</tr>
</tbody>
</table>

Assumptions: Drug stopped at mean time to progression, and patient realizes mean extension of survival reported in phase III trials, and patient completes the planned courses of Sipuleucel-T (2 treatments) and Rad-223 (6 treatments)
Toward Improved Use of New CRPC Agents

• “All treatment strategies greatly exceed a commonly assumed societal willingness-to-pay threshold of US$100,000 per life year saved (LYS).”

• Improvements in $LYS require price reduction and/or enhanced survival with better use of combinations or sequences of new agents.

• Clinical scenario, clinical trials regarding sequence, and biomarkers of response
  • Symptoms for chemotherapy vs immunotherapy?
  • Chemotherapy or abiraterone with initiation of ADT?
  • Abiraterone or enzalutamide first for CRPC?
  • AR-V7 for selection of chemotherapy vs androgen-directed therapy?
  • CTCs for treatment response assessment?
  • DNA repair gene mutation analysis for PARP inhibition?
  • Visceral vs skeletal metastasis for cis-platinum vs docetaxel?

Many publications have suggested that African Americans receive potentially curative therapies less often than Caucasian Americans for clinically-localized CaP.

Our group addressed this issue in the North Carolina-Louisiana Prostate Cancer Project (PCaP), the largest population-based study of CaP conducted to date.

No racial differences in the receipt of NCCN Guideline-concordant care were found after controlling for NCCN Risk Group in a carefully performed analysis of 777 NC participants in PCaP.

A different analysis of 804 NC participants in PCaP used precise quality metrics and showed that 66% of African Americans and 73% of Caucasian Americans received care that met all quality standards, a difference that was just significant ($P=.03$). Participants who were presented all treatment options suffered less decisional regret.

Pathway Development

- Academic-Community-Insurer Pathway
  - CaP early detection required 3 years
  - CaP treatment effort abandoned
- American College of Surgeons
- US Oncology-NCCN collaboration
  - Clear Value Plus by McKesson
- NCCN
  - Evinance Decision Support Platform
- VIA Oncology
- Oncology Suite by NantHealth
- eviCore Healthcare
Pathway Development

- Academic-Community-Insurer Pathway
- American College of Surgeons
- US Oncology-NCCN collaboration
- NCCN
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- Oncology Suite by NantHealth
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- Patients?
Why Guidelines and Pathways Matter: The Human Cost

- Financial burden is caused by co-pays for medications, nutritional supplements and alternative medications, travel for treatment, time lost from work by the patient and spouse/significant other/child(ren) caregivers.
- Financial burden is related to extent of disease and increases markedly as one receives expensive new agents for CRPC.
- The capacity for dealing with costs of care may be mitigated by socioeconomic status, household income and savings.
- Consequences of CaP treatment may include withdrawing savings, selling assets, foregoing recommended treatment or medication(s), decreasing work hours or changing to lower paying jobs (patient/spouse/significant other/child(ren)), loss of home, loss of retirement savings, taking out second mortgage or loans, or declaring bankruptcy.
- The end-of-life caregiving SUPPORT study indicated that 20% of family members stopped working, 31% of families lost all savings and 30% of families spend ≥10% of household income on care in an end-of-life situation.

Why Guidelines and Pathways Matter - The Human Cost

- The financial burden of CaP impacted survivors’ QoL more than any of 7 other cancers.
- Financial stress can impact the patient, the primary caregiver, and the family. The primary caregiver may suffer most when the caregiver is an adult child who has concomitant childcare and job duties.
- The primary caregiver can experience similar or greater anxiety than the patient, depression, and uncertainty, all of which may be remediated by education and training and communication with the healthcare provider.
Conclusions

- Right-sizing CaP early detection and treatment is challenging
- All appropriate treatment options (especially active surveillance) should be discussed
- Newer treatments (IMRT, robots, CRPC drugs) should be evaluated critically and compared carefully to older treatments
- Treatment recommendations should not be influenced by any business and/or personal interests of the care provider or health care system
- Treatment guidelines and care pathways provide opportunities to improve efficiency, quality, and outcomes while reducing costs and suffering from CaP
“... Or, if you elect *not* to have the surgery, the insurance company offers six days and seven nights in Barbados.”
Questions?