Prostate Cancer: Current Management and Future Directions

- Alan Koletsky, MD, Medical Oncology
- David Taub, MD, Urology
- Greg Goldin, MD, Radiation Oncology

- Lynn Cancer Institute
- Boca Raton, FL
Prostate Cancer: Current Management and Future Directions – An Overview

1. Review the Natural History of Prostate Cancer

2. Immunotherapeutic Treatment of Prostate Cancer

3. Discuss the Molecular Changes that Accompany the Transition from Hormone-Sensitive to Castration-Resistant Prostate Cancer (CRPC)

4. New Hormonal Therapies for Advanced Prostate Cancer

5. New and Novel Treatment Strategies
Prostate Cancer Progression

Patients typically progress within **18 to 24 months** of starting GnRH therapy. **10% to 20%** of men with prostate cancer will develop CRPC within **5 years** of initial diagnosis.

Castration-resistant disease: rising PSA value or radiographic progression despite castrate levels of testosterone (≤ 50 ng/dL) and despite androgen deprivation therapy.

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Definition of Castrate Resistant

• NCCN and PCWG2 define CRPC as:
  – Castrate level of testosterone (<50 ng/dL)
  – Disease progression despite ADT demonstrated by rising
  – PSA levels or radiographic evidence

• Term evolved from HRPC/AIPC based on new information on biology of resistance to androgen deprivation therapies
  – Many tumors remain sensitive to novel AR antagonists or androgen synthesis inhibitors
  – Amplifications and mutations in AR develop
  – Synthesis of androgenic precursors increases
  – Not truly hormone refractory

NCCN=National Comprehensive Cancer Network; PCWG2=Prostate Cancer Clinical Trials Working Group 2; HRPC=hormone-refractory prostate cancer; AIPC=androgen-independent prostate cancer; AR=androgen receptor.

Progression to mCRPC Is Rapid

- 46% of men with CRPC will develop metastases within 2 years

**Time to Onset of Metastases in Men With CRPC**

Data are from the placebo arm (n=331) of a randomized, controlled study to evaluate the effects of atrasentan on time to disease progression in men who had progressive CRPC and no radiographic evidence of bone metastases.

Even Patients With Low PSA or Longer PSADT Are at Significant Risk for Metastatic Disease

Data are from the placebo arm (n=201) of a randomized, double-blind, controlled study to evaluate the effects of zoledronic acid on time to first bone metastases in men with prostate cancer.

PSADT=prostate-specific antigen doubling time.

Metastatic Disease Is Often Occult

- Over 30% of men *thought* to have nonmetastatic CRPC were found to have metastatic disease when screened via imaging for a recent clinical trial.

<table>
<thead>
<tr>
<th>Leading Cause of Screening Failures</th>
<th>Patients (N=2577)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of metastatic disease</td>
<td>818 (32%)</td>
</tr>
</tbody>
</table>

Data represent screening failures of patients trying to enroll in the phase 3 study comparing zibotentan with placebo. Of the 2577 patients, 818 who were presumed to have nonmetastatic CRPC actually had metastatic disease and did not qualify for the study.

## Radiographic Methods* for the Identification of Prostate Cancer Metastases

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Sensitivity/Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI</strong></td>
<td>Provides an image of zonal anatomy. Useful in the detection of extracapsular extension or seminal vesicle invasion</td>
<td>Sensitivity 73% to 80% and high specificity for localized disease</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>May be useful in staging; however, smaller nodes occurring earlier in disease may not be detected</td>
<td>Broad variation in sensitivity and specificity reported</td>
</tr>
<tr>
<td>Bone scan (MDP-mTc(^{99}) scintigraphy)</td>
<td>Identifies bone metastases based on active osteoblastic activity and turnover</td>
<td>Sensitivity may range from 39% to 94%, specificity is as high as 89%. However, negative results do not necessarily always rule out bone metastases and newer modalities must be validated</td>
</tr>
<tr>
<td>(^{18})F-Sodium Fluoride PET/CT (NaF PET/CT)</td>
<td>NaF has a high affinity for osteoblastic activity</td>
<td>High sensitivity (100%) and specificity (100%) reported in one study; however, rigorously controlled prospective trials may be needed</td>
</tr>
</tbody>
</table>

*There are no definitive guidelines for methods of identifying CRPC.

Sequencing CRPC Therapy – 2010

- Metastatic, minimally symptomatic CRPC
  - Secondary hormonal Rx: not known
- Symptomatic or poor-prognosis CRPC
  - Docetaxel: 3 months
- Progression after docetaxel chemotherapy
  - Mitoxantrone: Best supportive care
    - Survival benefit: not known

Zoledronic acid with CRPC (metastatic disease)
Natural History of Prostate Cancer

- Typical patient presentation as they move through different stages

**Under UROLOGIST care**
- Androgen deprivation
- Therapies after LHRH agonists and antiandrogens

**Under ONCOLOGIST care**
- First-line therapy
- Burden of disease
- Death
- Salvage therapy

**Asymptomatic**
- Nonmetastatic
- Castrate sensitive

**Symptomatic**
- Metastatic
- Castrate resistant

Since 2010, 7 New Therapies Have Shown Clinical Benefit for Patients with mCRPC

- Sipuleucel-T: immunotherapy for men with asymptomatic to minimally symptomatic mCRPC (IMPACT)
- Cabazitaxel: second-line chemotherapy for mCRPC (TROPIC)
- Abiraterone acetate: in combination with prednisone in the pre- and postchemotherapy setting (COUGAR 302, COUGAR 301)
- Denosumab: for SRE prevention in mCRPC
- Enzalutamide: treatment of mCRPC in the pre- and postdocetaxel setting (AFFIRM, PREVAIL)
- Radium 223: treatment of CRPC with symptomatic bone metastases and no known visceral disease in the pre- and postdocetaxel setting (ALSYMPCA)
- Docetaxel: chemotherapy for treatment of mCRPC (TAX 327)

The Therapeutic Landscape of Prostate Cancer Today

*Abiraterone is FDA-approved across mCRPC.
†Radium 223 is indicated for patients with symptomatic bone metastases and no visceral metastases.
Chemotherapy – Historical Use in Metastatic Castration-Resistant Patients

Usually Reserved for CRPC Patients who were

Symptomatic

Rapidly Progressing

Had Visceral Disease

Now should be considered for patients with extensive disease at the initiation of androgen blockade
CHAARTED Trial: Is Earlier Use of Chemotherapy at Initiation of Androgen Blockade Beneficial for Patients With Extensive Disease?

**STRATIFICATION**

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

**Randomize**

**ARM A:**
- ADT + Docetaxel 75mg/m² every 21 days for maximum 6 cycles

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

**Evaluate**

- Every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks
- Every 12 weeks

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

**Chemotherapy at investigator’s discretion at progression**

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone
**Primary endpoint: Overall survival**

- **HR=0.61 (0.47-0.80) p=0.0003**
- **Median OS:**
  - ADT + D: 57.6 months
  - ADT alone: 44.0 months
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
Clinical interpretation

• 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy

• The benefit in patients with a high volume of metastases is clear and justifies the treatment burden
  – longer follow-up is required for patients with low volume metastatic disease
Immunotherapeutic Treatment of Prostate Cancer
The Immunotherapy Cell Cycle

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer cells by T cells
7. Killing of cancer cells

PD-L1 Blockade

References:
- Can Res 2010, 70: 6171
What Is Sipuleucel-T?

- An autologous cellular immunotherapy
- Derived from patient’s own cells, stimulated ex vivo with a fusion peptide of PAP and GM-CSF (adjuvant)
- Sipuleucel-T is administered approximately every 2 weeks for a total of 3 infusions, with dosing completed in about 1 month
- First FDA-approved immunotherapy for mCRPC
- Indicated for men with asymptomatic or minimally symptomatic mCRPC

PAP=prostatic acid phosphatase; GM-CSF=granulocyte-macrophage colony-stimulating factor.
Sipuleucel-T is personalized autologous cellular immunotherapy.

Leukapheresis → Sipuleucel-T dose manufactured → Personalized Sipuleucel-T dose

- Patient’s immature APCs collected (CD54+ cells)
- Antigen presentation to APC
- APC maturation and upregulation

APC=antigen-presenting cell.
Sipuleucel-T Activates Immune Cells to Stimulate a Response to Prostate Cancer

Personalized Dose Infused → Immune Response Activation → Immune Response Mobilization

Sipuleucel-T Activation of T Cells
Activated T Cell Proliferation
Activated T Cells Attack Prostate Cancer

IMPACT Trial Design

- Phase 3, randomized, double-blind, controlled study
- Primary endpoint—overall survival

64% of patients in the control group, following progression, crossed over to a nonrandomized, open-label protocol
  - They received investigational autologous immunotherapy made from cryopreserved cells
  - Treatment in the open-label protocol was at the physician’s discretion

*Sipuleucel-T Q2 Weeks x 3 (n=341)
*Treated at Physician Discretion (n=341)
†Open-label protocol: Immunotherapy from cryopreserved cells (n=109)
‡No immunotherapy (n=62)


*Control was nonactivated, autologous, peripheral blood mononuclear cells.
†Progression = radiographic evidence of disease progression.
‡Autologous, peripheral blood mononuclear cells that were cryopreserved at the time of control generation and subsequently activated.
Sipuleucel-T Extends Median Overall Survival (OS) Beyond 2 Years

- 64% of patients in the control group crossed over to receive an investigational autologous immunotherapy made from cryopreserved cells
- Consistent survival benefit observed both with and without censoring for docetaxel after sipuleucel-T

IMPACT: Survival Benefit Maintained Across Patient Subgroups Studied

Sipuleucel-T Subgroups of Interest

- **Age:** Above Median, Below Median
- **ECOG Performance Status:** =0, =1
- **Gleason Score:** ≤7, ≥8
- **No. of Bone Metastases:** 0–5, 6–10, >10
- **PSA:** Above Median, Below Median
- **Race:** All Patients, African American Patients

Hazard Ratio (95% Confidence Interval)

Favors PROVENGE  Favors Control
Patients in the 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>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
</tr>
<tr>
<td>Difference, months</td>
<td></td>
<td>13.0</td>
<td>7.1</td>
<td>5.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></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>
</tr>
</tbody>
</table>

- 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 (13.0 vs. 2.8 months median OS benefit, respectively).

PROSTVAC May Trigger a Progressively Expanding, Specific Immune Response Against Prostate Cancer

PROSTVAC (engineered poxvirus containing PSA and TRICOM) is injected subcutaneously.

PSA

TRICOM

Anti-PSA T cells attack prostate cancer cells...

...which are lysed...

...and release new tumor-associated antigens (TAAs)

...activating new T cells, generating a progressively expanding anti-cancer effect

Dendritic cells take up PROSTVAC...

...and activate anti-PSA T cells
PROSTVAC Monotherapy

Phase 2 Study

Survival (% of patients)

PROSTVAC 25.1 months

Placebo 16.6 months
PROSPECT Global Phase 3 Trial: Design (SPA) (US-CAN-AUS/WE/EE/Latin America)

- Non/Minimally symptomatic
- Metastatic Castration Resistant Prostate Cancer

PROSTVAC-(V)(F) TRICOM + low dose adjuvant GM-CSF

PROSTVAC-(V)(F) TRICOM Adjuvant placebo

Vector Placebo Adjuvant placebo

Standard of Care

No Cross Over

Primary Endpoint: Overall Survival
New Hormonal Therapies for Advanced Prostate Cancer
Prostate Cancer Remains Dependent on AR Signaling Throughout the Disease Continuum

Tn Treatment continuum based on historical data

AR signaling

Time

Castration sensitive

Castration resistant

Non-metastatic

Metastatic

\(^a\)The continuum is based on a historical paradigm and is not reflective of all currently available treatments.
ADT, androgen deprivation therapy; AR, androgen receptor.

The Transition From Hormone Sensitive to Castration Resistant Prostate Cancer Adaption Model and Selection Model

Adaptation model:
- Androgen-dependent prostate cancer cells
- Acquisition of genetic/epigenetic events
- Clonal expansion of resistant cells
- Castration-resistant prostate cancer

Selection model:
- Co-existing heterogeneous prostate cancer cells
- Killing of sensitive cancer cells
- Proliferation and differentiation of resistant cells
- Castration-resistant prostate cancer
The AR Signaling Pathway is a Key Driver of Prostate Cancer Growth and Proliferation
Continued AR Signaling in CRPC is Driven Through Aberrant Mechanisms

AR Overexpression

Result:
Overabundance of ARs, increasing the probability of androgen binding even at castrate levels of androgen

Androgen-Independent Activation

Result:
ARs remain constitutively active without the need for androgen or non-androgen ligands

AR Promiscuity

Result:
ARs are activated by non-androgen ligands (eg, estrogen, progesterone, prednisone)

Intratumoral Production of Androgen

Result:
Tumor produce androgens that can bind to ARs despite castrate levels of androgen

CRPC Tumors Produce their own Androgens that Bind to and Activate AR

Abiraterone Acetate: Androgen Biosynthesis Inhibitor

Cholesterol → Pregnenolone → 17OH-Pregnenolone → DHEA → Androstenedione → Testosterone → DHT

Abiraterone inhibits the conversion of cholesterol to pregnenolone, preventing the production of androgens.

Androgens
COU 301: Abiraterone Prolonged Overall Survival in CRPC Patients Who Received Prior Chemotherapy

2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo
1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo

Updated results: **4.6-month difference** in median survival with abiraterone acetate

COU 302: Abiraterone Acetate Phase III Trial in Chemo-naïve mCRPC

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

N = 1088
- Progressive chemo-naïve mCRPC patients
- Asymptomatic or mildly symptomatic

1:1

Abiraterone Acetate 1000 mg daily
Prednisone 5 mg bid
n = 546

Placebo daily
Prednisone 5 mg bid
n = 542

Primary Endpoints:
- Radiographic progression-free survival (rPFS) by central review
- OS

Secondary:
- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG PS deterioration
- Time to PSA progression

COU-AA-302, Final Overall Survival Analysis of a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy

- Median follow-up of 49.2 mos
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)
Patient reported outcomes favored AA + prednisone vs placebo + prednisone

Full data to be reported

*Pre-specified alpha level 0.0035
Note: All secondary end points remain significant after adjusting for multiplicity testing


<table>
<thead>
<tr>
<th>Outcome</th>
<th>AA + Prednisone Median (months)</th>
<th>Placebo + Prednisone Median (months)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rPFS</td>
<td>16.5</td>
<td>8.3</td>
<td>0.53 (0.45, 0.62)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>35.3</td>
<td>30.1</td>
<td>0.79 (0.66, 0.96)</td>
<td>0.0151 *</td>
</tr>
<tr>
<td>Time to opiate use (cancer related pain)</td>
<td>Not reached</td>
<td>23.7</td>
<td>0.71 (0.59, 0.85)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Time to chemotherapy initiation</td>
<td>26.5</td>
<td>16.8</td>
<td>0.61 (0.51, 0.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Time to ECOG PS deterioration</td>
<td>12.3</td>
<td>10.9</td>
<td>0.83 (0.72, 0.94)</td>
<td>0.0052</td>
</tr>
</tbody>
</table>
Enzalutamide – An Androgen Receptor Signal Inhibitor

• Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway

• No demonstrated agonist effects in pre-clinical models

AFFIRM Trial: Enzalutamide Prolonged Survival, Reducing Risk of Death in Patients Previously Treated with Chemotherapy


Median OS Δ: 4.8 months
37% reduction in risk of death

<table>
<thead>
<tr>
<th></th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Overall Survival (months)</td>
<td>18.4</td>
<td>13.6</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.53, 0.75</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td></td>
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PREVAIL Phase III Trial of Enzalutamide in Asymptomatic or Mildly Symptomatic mCRPC Pre Chemotherapy

PREVAIL: Phase III Trial of Ezalutamide in Asymptomatic or Mildly Symptomatic mCRPC Patients Pre-Chemotherapy -- OS

Hazard Ratio: 0.706 (95% CI: 0.60, 0.84)  
$P < 0.0001$

Median OS: Enzalutamide, 32.4 Months; Placebo, 30.2 months

Patients still alive at data cut off  
Enzalutamide: 72%; Placebo: 63%

Measuring Progression Can Be Problematic on Bone Scan

- MDP-mTc$^{99}$ images osteoblast activity, not prostate cancer directly
- Lesion healing may appear new or more intense over time, particularly with newer hormonal therapies (ie, abiraterone)
- New lesions are best measures of progression vs flare (within clinical context)
- Confirmation scans showing additional new lesions required
- Misclassification is common with older criteria

Thus, PCWG2 guidelines have redefined bone scan progression
  – Unknown if bone scan flare occurs with immunotherapy

Baseline: bone scan, PSA 200 ng/mL
Week 12: new lesion, PSA down to 2 ng/mL
Week 24: no new lesions, PSA still declining

Schematic Representation of CTCs Entering the Peripheral Circulation and Establishing a Metastatic Focus at a Distant Site

MA Goron Nature Reviews/Urology, November 2016
Potential Clinical Applications for Circulating Tumor Cell Analysis

1. Early cancer detection
2. Disease staging
3. Monitoring for recurrence
4. Prognostication
5. Aid in selection of therapy
   - Predict which CRPC patients are more likely to respond to androgen-receptor targeted therapies
Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

Howard I. Scher, MD; David Lu, PhD; Nicole A. Schreiber, BA; Jessica Louw, BS; Ryon P. Graf, PhD; Hebert A. Vargas, MD; Ann Johnson, MS; Adam Jendrisak, MBA; Richard Bambury, MB, BCh, BAO; Daniel Danila, MD; Brigit McLaughlin, BS; Justin Wahl, BS; Stephanie B. Greene, PhD; Glenn Heller, PhD; Dena Marrinucci, PhD; Martin Fleisher, PhD; Ryan Dittamore, MBA
AR-V7 Expression in CTCs and CRPC Outcomes – Key Results

- mCRPC patients with pre-androgen receptor signaling (ARS) inhibitor AR-V7-positive CTCs had
  - Resistant PSA responses
  - Shorter time on therapy
  - Shorter radiographic progression-free survival
  - Inferior overall survival
  - Shows significant interaction with taxane administration
Figure 4. Patients With Pretherapy AR-V7-Positive CTCs and Overall Survival on Taxanes and/or AR Signaling Inhibitors.

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment-Specific Hazards of Death (Overall Survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples (n = 191)</td>
<td>Favors Taxanes Favors AR Therapy</td>
</tr>
<tr>
<td>AR-V7-negative samples (n = 157)</td>
<td>[Graph showing hazard ratios for different sources]</td>
</tr>
<tr>
<td>AR-V7-positive samples (n = 34)</td>
<td>[Graph showing hazard ratios for different sources]</td>
</tr>
</tbody>
</table>
C Overall survival: pre-AR signaling inhibitor samples

- AR-V7 negative, n = 112
- AR-V7 positive, n = 16

**HR = 11.45 (95% CI: 5.67-23.82)**

**P < .001**

Median survival: 4.6 mo vs not reached

D Overall survival: pretaxane samples

- AR-V7 negative, n = 45
- AR-V7 positive, n = 18

**HR = 3.74 (95% CI: 1.95-7.20)**

**P = .001**

Median survival: 8.9 mo vs not reached
New and Novel Treatment Strategies
Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.
PARP Inhibition Enhances Tumor Response to Chemotherapy

1. Cancer
   - Chemo DNA Strand Break
   - Tumor Growth Inhibition

2. PARP Upregulation + BSI-201
   - DNA Repair
   - Enhance Tumor Response to Chemotherapy

3. Many commonly utilized cancer chemotherapy regimens target tumor cells via fatal DNA lesions.
   - Key DNA repair pathways (such as PARP) are upregulated in tumor cells - may lead to resistance.
   - Inhibiting PARP may potentiate chemotherapy or be used as monotherapy in conditions with pre-existing DNA repair defects (such as BRCA negative).
OVERALL SURVIVAL FOR OLAPARIB

- Biomarker-positive, median: 13.8 mo
- Biomarker-negative, median: 7.5 mo

No. at Risk:
- Biomarker-negative: 33 33 31 27 24 21 18 16 13 11 7 6 4 4 4 3 3 3 2 2
- Biomarker-positive: 16 16 16 16 15 15 14 13 10 6 5 5 4 3 2 2 1 0 0

No. of Events:
- Biomarker-negative: 0 2 4 2 3 3 1 2 1 1 1 2 0 0 0 0 0 1 0 0 0 1 0
- Biomarker-positive: 0 0 0 0 1 0 0 1 0 1 2 0 0 1 0 1 0 2 0 0

P < 0.05 by log-rank test.
Radiologic Evidence of Tumor Responses to Olaparib

J Mateo et al, NEJM (2015); 373: 1697-1708
TRITON 2: A Multicenter Phase 2 Study of the PARP Inhibitor Rucaparib in Patients with Metastatic CRPC Associated with Homologous Recombination Deficiency

**Figure 1. TRITON2 Study Design**

**Screening**
- Confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate
- Surgically or medically castrated, with testosterone levels of ≤50 ng/dL (1.73 nM)
- Disease progression after treatment with 1–2 prior next-generation AR-targeted therapies in the castration-resistant setting
- Disease progression after treatment with 1 prior taxane-based chemotherapy in the castration-resistant setting
- Disease progression after most recent therapy
- No prior PARP inhibitor treatment, mitoxantrone, cyclophosphamide, or any platinum-based chemotherapy

**Treatment**

Rucaparib 600 mg BID
28-day visits

**Cohort A** (~83 patients)
- BRCA1/2 or ATM mutation
- With measurable visceral and/or nodal disease

**Cohort B** (~54 patients)
- BRCA1/2 or ATM mutation
- Without measurable visceral and/or nodal disease

**Cohort C** (~20 patients)
- Deleterious mutation in another HR gene associated with sensitivity to PARP inhibition
- With or without measurable visceral and/or nodal disease

**Post-treatment**
- 28-day follow-up
- Patients receiving clinical benefit may be considered for continued treatment
- Long-term follow-up
  - Tumor assessments every 8–12 weeks for patients who discontinue for reason other than progression
  - All patients to be followed every 12 weeks for survival, subsequent therapies, and development of secondary malignancies

*Patients with known HRD mutations are required to submit archival tumor tissue. If available, however, enrollment is not contingent on analysis.

AR, androgen receptor; BID, twice daily; HR, homologous recombination; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.
PTEN Loss and Prognosis in mCRPC

- In abiraterone-treated patients with mCRPC, PTEN loss by IHC was associated with a shorter mOS\(^1\)
- Newly diagnosed, or surgically resected patients with PTEN loss or low expression demonstrated an increased risk for recurrence and death\(^1-6\)
- Paired intra-patient tumor samples from either archival hormone-sensitive prostate tissues or castration-resistant fresh biopsies demonstrated a high concordance in PTEN status by IHC (86\%)\(^1\)

![Graph showing overall survival](image-url)

**Overall Survival (95% CI)**
- PTEN negative 13.9 (9.5-18.2)
- PTEN positive 20.7 (13.8-26.6)

**HR** 1.75 (95% CI 1.19-2.55)
**P**=0.004
Clinical Trial of Abiraterone + Ipatasertib vs Aberaterone in mCRPC Patients
Revisiting anti-PD-1 Activity in Metastatic Castration-Resistant Prostate Cancer

- Prostate Cancer has a low mutation rate and limited infiltrating CD8 T-cells compared with melanoma and NSCLC where PD-1/PD-L blockade is effective.

- Phase 1 trials in patient’s with advanced prostate cancer have failed to show any objective responses to anti-PD-1 therapy.

- A recent Phase 2 study showed unexpected clinical activity when Pembrolizumab (an anti-PD-1 antibody was administered to patients who had progressed on Enzalutamide.

- Three of the first 10 patients treated had rapid PSA reductions to <0.2 ng/ml and 2 patients with measurable disease at study entry had partial responses.

- Biopsies obtained from these patients showed presence of CD8 tumor infiltration and PDL-1 expression.

Clinical Trial of Enzalutamide + Atezolizumab vs Enzalutanide in mCRPC

Metastatic CRPC after
- failure of an androgen synthesis inhibitor and
- failure of, ineligibility for, or refusal of a taxane regimen

Safety Run-in
n=10
Atezolizumab + Enzalutamide

Randomization
1:1
n=548

Atezolizumab + Enzalutamide

Enzalutamide
Conclusions

- New insights into the adaptive changes that occur in the transition from hormone sensitive to CRPC has led to the development of new and more effective therapies

- The optimal sequence of agents has yet to be determined

- ARV7 is a promising biomarker for sensitivities to enzalutamide and abiraterone

- Docetaxel chemotherapy for hormone sensitive patients should be offered to high disease volume patients

- Immune therapy should be given early in asymptomatic non visceral mCRPC patients

- PARP inhibition is a promising therapeutic target in patients with BRCA mutations
• Overall Survival 30% reduction in the risk of death (Hazard Ratio=0.70; 95% confidence interval, 0.59-0.83)

• Progression Free Survival: 81% reduction in risk of radiographic progression or death compared with placebo (Hazard Ratio=0.19; 95% confidence interval, 0.15-0.23).
Current Management Options for Men With mCRPC

- Maintenance of castrate levels of testosterone (GnRH agonist/antagonists)
- Antiandrogens
  - Nilutamide, bicalutamide, flutamide, enzalutamide
- Immunotherapy
  - Sipuleucel-T
- Androgen synthesis inhibitors
  - Ketoconazole, abiraterone acetate
- Estrogens
- Chemotherapy
  - Docetaxel, cabazitaxel
  - Mitoxantrone
- Radiopharmaceuticals
  - Radium 223
- Supportive care
  - Bone health: exercise, bisphosphonates, denosumab
  - Vitamin D and calcium

GnRH = gonadotropin-releasing hormone.
NCCN. Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology. V4.2013
## Prognostic Factors in CRPC

### Pre-treatment Prognostic Factors
- Performance status
- Gleason sum
- Visceral disease, number of sites of disease
- Anemia
- Alkaline phosphatase, urine NTx levels
- Pain
- PSA and PSA kinetics
- CTC count
- LDH, CRP levels
- Albumin
- Type of progression (bone, measurable disease, PSA only)
- Age
- VEGF, IL-6, chromogranin levels

### Post-treatment Prognostic Factors
- PSA declines
- Pain improvement
- Quality of life improvement
- Change in CTC count (>5 to <5)
- PSA and PFS
- Immune response parameters

CTC = circulating tumor cell; LDH = lactate dehydrogenase; CRP = C-reactive protein; VEGF = vascular endothelial growth factor; PFS = progression-free survival.

Role of Prognostic Models and Factors in the Clinic

• Nomograms may help guide discussions about expectations with patients and the need for more or less aggressive therapies

• Can identify men with asymptomatic or minimally symptomatic mCRPC who may benefit from immunotherapy

• May help identify men based on certain prognostic categories (pain, hepatic metastases, rapid disease progression) who are more appropriate for chemotherapy

IMPACT Trial Design

- Phase 3, randomized, double-blind, controlled study
- Primary endpoint—overall survival

64% of patients in the control group, following progression, crossed over to a nonrandomized, open-label protocol
  - They received investigational autologous immunotherapy made from cryopreserved cells
  - Treatment in the open-label protocol was at the physician’s discretion

*Control was nonactivated, autologous, peripheral blood mononuclear cells. †Progression=radiographic evidence of disease progression.
‡Autologous, peripheral blood mononuclear cells that were cryopreserved at the time of control generation and subsequently activated.

## IMPACT Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Sipuleucel-T (n=341)</th>
<th>Control (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, years (range)</td>
<td>72 (49-91)</td>
<td>70 (40-89)</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>89.4</td>
<td>91.2</td>
</tr>
<tr>
<td>ECOG status 0 (%)</td>
<td>82.1</td>
<td>81.3</td>
</tr>
<tr>
<td>Gleason sum ≤7 (%)</td>
<td>75.4</td>
<td>75.4</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>51.7</td>
<td>47.2</td>
</tr>
<tr>
<td>Disease localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only (%)</td>
<td>50.7</td>
<td>43.3</td>
</tr>
<tr>
<td>Soft tissue only (%)</td>
<td>7.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Bone and soft tissue (%)</td>
<td>41.9</td>
<td>48.5</td>
</tr>
<tr>
<td>&gt;10 bone metastases (%)</td>
<td>42.8</td>
<td>42.7</td>
</tr>
<tr>
<td>Bisphosphonate use (%)</td>
<td>48.1</td>
<td>48.0</td>
</tr>
<tr>
<td>Prior docetaxel (%)</td>
<td>15.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

ECOG=Eastern Cooperative Oncology Group.
Prostvac Vaccine

DNA plasmid

Mammalian cell

Vaccines:
(rV-PSA TRICOM)
(rF-PSA TRICOM)

Vaccinia (rV) or Fowlpox virus (rF)

Induction of PSA specific immune responses (T-cells)
Immunotherapy Work Differently to Change The Course of the Disease

![Graph comparing tumor burden over time with different therapies](image-url)
Following Treatment with Surgery or RT, Prostate Cancer Often Progresses

Local Disease → Biochemical Recurrence → CRPC → mCRPC

> One-third of men treated with surgery or radiation are not cured

Subsequent rise in PSA is an indicator of progression

Even after response to ADT, nearly all develop CRPC

> 80% will advance and develop metastases

CRPC = castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; ADT = androgen deprivation therapy.