Integrating New Therapies into the Treatment of Advanced Prostate Cancer
Learning Objectives

- Evaluate current and emerging clinical trial data for therapies for prostate cancer
- Integrate novel therapies into the treatment of patients with advanced prostate cancer based on patient and disease factors, as well as efficacy and safety evidence
- Implement strategies to monitor and manage adverse events (AEs) of novel treatments for prostate cancer
Prostate Cancer in 2020

• In 2020:
  – ~192,000 new cases
  – ~33,000 deaths
• Incidence and mortality rates have declined
• 10-year OS: 98%
• Risk factors
  – Advancing age
  – African ancestry
  – Family history
  – Genetic mutations

Image: Histology slide showing prostate cancer. Courtesy of the National Cancer Institute. Photographer: Otis Brawley,
Advances in Treatment Approvals

- **2004**: Docetaxel (taxane)
- **2010**: Cabazitaxel (novel taxane)
- **2011**: Enzalutamide (2nd-generation hormone therapy)
- **2012**: Enzalutamide postdocetaxel
- **2013**: Radium-223 (radiopharmaceutical)
- **2014**: Abiraterone (2nd-generation hormone therapy)
- **2018**: Apalutamide (2nd-generation hormone therapy) for nmCRPC and mCSPC
- **2019**: Enzalutamide for mCSPC
- **2020**: Darolutamide (2nd-generation hormone therapy) for nmCRPC

**New Approaches**
- **2014**: Enzalutamide for nmCRPC
- **2020**: Olaparib and rucaparib (PARP inhibitors) for HRR-mutated mCRPC

**Key Genes and Malignancies**
- HRR = homologous recombination repair genes
- mCRPC = metastatic castrate-resistant prostate cancer
- mCSPC = metastatic castrate-sensitive prostate cancer
- nmCRPC = nonmetastatic castrate-resistant prostate cancer
- PARP = Poly (ADP-ribose) polymerase

- **Olaparib and rucaparib**
- **Ga 68 PSMA-11** for metastasis imaging

**Primary Sources**
Typical Progression

Localized/locally advanced prostate cancer → Definitive therapy → Biochemical recurrence

- Criterion 1: Rising PSA despite castrate levels of testosterone
- Criterion 2: Identification of metastases

Biochemical recurrence → mPC (de novo) → Rising PSA

mPC (de novo) → Identification of metastases → mCSPC

Rising PSA despite castrate levels of testosterone → Identification of metastases → mCRPC

Both criteria met → Start ADT

nmCRPC

ADT = androgen deprivation therapy; mPC = metastatic prostate cancer; PSA = prostate-specific antigen

Standard of Care for mHSPC: 4 Options Added to ADT

ASI = androgen signaling inhibitor; mHSPC = metastatic hormone-sensitive prostate cancer.
## Meta-Analysis: Combination Therapy Better Than ADT Alone

<table>
<thead>
<tr>
<th>OS</th>
<th>Failure-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors Combination</td>
<td>Favors ADT Alone</td>
</tr>
<tr>
<td>Doc+ADT</td>
<td>0.72 (0.60-0.86)</td>
</tr>
<tr>
<td>Abi+ADT</td>
<td>0.64 (0.53-0.80)</td>
</tr>
<tr>
<td>Enza+ADT</td>
<td>0.64 (0.46-0.88)</td>
</tr>
<tr>
<td>Apa+ADT</td>
<td>0.63 (0.43-0.92)</td>
</tr>
<tr>
<td>Bis+ADT</td>
<td>0.86 (0.72-1.00)</td>
</tr>
<tr>
<td>Bis+Doc+ADT</td>
<td>0.79 (0.58-1.10)</td>
</tr>
<tr>
<td>Cel+ADT</td>
<td>0.94 (0.67-1.30)</td>
</tr>
<tr>
<td>Bis+Cel+ADT</td>
<td>0.78 (0.56-1.10)</td>
</tr>
</tbody>
</table>

Abi = abiraterone; Apa = apalutamide; Bis = bisphosphonate; Cel = celecoxib; CI = confidence interval; Doc = docetaxel; Enza = enzalutamide; HR = hazard ratio.

Decision-Making Factors in First Line Choices for mCSPC

# Treatment Choice By Disease Stratification, Agent, and Patient Characteristics

*Strongly recommended in high volume disease, moderate recommendation in low-volume disease.*

HTN = hypertension; NYHA = New York Heart Association.


<table>
<thead>
<tr>
<th>Disease Stratification</th>
<th>Docetaxel</th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
<th>Apalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High/low volume*</td>
<td>• Neutropenia • Febrile neutropenia • Infections with neutropenia • Peripheral neuropathy</td>
<td>• Hypertension • Hepatotoxicity • Hyperglycemia • Hypokalemia</td>
<td>• Convulsions • Cognitive impairment • Hypertension • Fatigue • Loss of consciousness • Musculoskeletal events</td>
<td>• Rash • Fall • Fracture • Hypothyroidism • Seizure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent-Related AEs</th>
<th>Docetaxel</th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
<th>Apalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe/active cardiac disease • Prior peripheral neuropathy • Fragile patients</td>
<td>• Prednisone contraindication • Cardiac: NYHA ≥2, atrial fibrillation • Uncontrolled HTN • Hepatic, renal, or adrenal dysfunction</td>
<td>• History of seizure or any predisposing condition • Uncontrolled HTN</td>
<td>• History of seizure or any predisposing condition • Uncontrolled HTN • Ischemic cardiac disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of Not Fit Patients</th>
<th>Docetaxel</th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
<th>Apalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe/active cardiac disease • Prior peripheral neuropathy • Fragile patients</td>
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<td>• History of seizure or any predisposing condition • Uncontrolled HTN • Ischemic cardiac disease</td>
<td></td>
</tr>
</tbody>
</table>
One of the following (all category 1 recommendations):
- Docetaxel
  - Patients with high-volume disease derive greater benefit
- Abiraterone acetate + steroid
- Apalutamide
- Enzalutamide
Castrate-Resistant Prostate Cancer

- Disease progression despite castrate-level testosterone (<50 ng/mL)
- Heterogeneous—can be symptomatic or asymptomatic, with or without metastases
- Affects 10% to 20% within 5 years of prostate cancer diagnosis
  - Before recent therapeutic advances, ≥50% of these patients would have died within 3 years
- Progressive decline in health-related QoL
- Metastasis-free survival (MFS) is a new and reasonable endpoint

QoL = quality of life.
Nonmetastatic CRPC

- CRPC with no clinical or radiologic evidence of metastases
- New imaging techniques (eg, $^{18}$F-fluorocholine or PSMA-targeted PET)
  ‒ May reveal metastases earlier
- Recommend PSA testing every 4 to 6 months
- Treatment recommended when PSADT ≤10 months
  ‒ Memorial Sloan Kettering prostate cancer nomograms: PSADT
  ‒ Sunnybrook PSA calculator tool

PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
Case Study: Ben, 73 Years Old

- Mild COPD and hypertension
  - No family history of cancer
- Underwent radiotherapy for localized prostate cancer 5 years ago
- Experienced biochemical recurrence (increasing PSA)
- Not a surgical candidate because of previous radiotherapy
- Started on degarelix (ADT) 1 year ago
- He returns for a follow-up today
Case Study (cont’d): Ben’s Test Results

- PSA increased from 4 ng/mL to 14 ng/mL; PSADT = 9 months
  - Testosterone = 24 ng/dL
  - No evidence of metastases on CT or bone scan, no bone pain
  - No lymph node masses detected
- Now diagnosed with nmCRPC
SPARTAN, PROSPER, and ARAMIS: 2nd-Generation Hormone Therapy + ADT in nmCRPC

**PFS**

**SPARTAN (N = 1207)**

- **Placebo**
- **Apalutamide**

HR for metastasis or death,
0.28 (95% CI, 0.23-0.35) \( P < .001 \)

**PROSPER (N = 1401)**

- **Placebo**
- **Enzalutamide**

HR for metastasis or death,
0.29 (95% CI, 0.24-0.35) \( P < .001 \)

**ARAMIS (N = 1509)**

- **Placebo**
- **Darolutamide**

HR, 0.41 (95% CI, 0.34-0.55) \( P < .001 \)

**OS**

**SPARTAN (N = 1207)**

- **Placebo**
- **Apalutamide**

HR 0.75 (95% CI, 0.59-0.96) \( P = 0.0197 \)

**PROSPER (N = 1401)**

- **Placebo**
- **Enzalutamide**

HR 0.73 (95% CI, 0.61-0.89) \( P = 0.001 \)

**ARAMIS (N = 1509)**

- **Placebo**
- **Darolutamide**

HR for death, 0.69 (95% CI, 0.53-0.88) \( P = 0.003 \)

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**References**

Safety Considerations With Newest Agents

<table>
<thead>
<tr>
<th>Apalutamide</th>
<th>Enzalutamide</th>
<th>Darolutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most common AEs (≥10%):</td>
<td>• Most common AEs (≥10%):</td>
<td>• Most common AEs (≥2%):</td>
</tr>
<tr>
<td>– Fatigue</td>
<td>– Asthenia/fatigue</td>
<td>– Fatigue</td>
</tr>
<tr>
<td>– Arthralgia</td>
<td>– Back pain</td>
<td>– Pain in extremity</td>
</tr>
<tr>
<td>– Rash</td>
<td>– Hot flushes</td>
<td>– Rash</td>
</tr>
<tr>
<td>– Decreased appetite</td>
<td>– Constipation</td>
<td>• Embryo-fetal toxicity</td>
</tr>
<tr>
<td>– Fall/fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Decreased weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Hot flushes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cerebrovascular events, ischemic CVD, fractures, falls, seizure, embryo-fetal toxicity</td>
<td>• Seizures, PRES, hypersensitivity, ischemic CVD, falls and fractures, embryo-fetal toxicity</td>
<td></td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; PRES = posterior reversible encephalopathy syndrome.
2020 NCCN Guidelines for nmCRPC

Continue ADT to maintain castrate serum levels of testosterone (<50 ng/dL)

PSADT ≤10 months
- Apalutamide (category 1)
- Darolutamide (category 1)
- Enzalutamide (category 1), or
- Other secondary hormone therapy

PSADT >10 months
- Observation, or
- Other secondary hormone therapy

Case Conclusion

- Ben is taking darolutamide 600 mg twice daily and continuing ADT
- His bone health is being monitored closely
- PSA is now 2.9 ng/mL
- Will continue serial PSA monitoring
- Will undergo imaging only if new symptoms develop or PSA level increases
Metastatic Prostate Cancer

- 72% increase from 2004 to 2013, even as incidence of low-risk prostate cancer declined
- 5-year survival rate: ~30% vs nearly 100% for nonmetastatic disease
- 90% have bone metastases
- Treatment evolving rapidly
  - Novel therapies improve outcomes but increase treatment complexity
Case Study: Ted, 70 Years Old

- Ted has arterial hypertension and well-controlled diabetes
  - Family history: mother had breast cancer; uncle diagnosed with prostate cancer at age 48
- Diagnosed with *de novo* metastatic prostate cancer
  - PSA level of 38 ng/mL
- Metastases in multiple bone sites and lymph nodes; is considered low volume disease
ALL men with mPC should receive genetic testing. Testing should be considered in specific histologic/family history for localized disease or considered high risk of disease.

BRCA1 or BRCA2 and other DDR germline mutations associated with increased risk of prostate cancer.

11.8% of men with mPC have germline DNA-repair gene mutations irrespective of family history.

Somatic mutations in DNA repair pathways in 19% of localized and 23% of mCRPC tumors.

# NCCN 2020 Recommendations for Biomarker and Germline Testing

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Molecular Analysis of Tumor</th>
<th>Germline Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Not indicated</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Low</td>
<td>Consider if life expectancy ≥10 years</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Consider if life expectancy ≥10 years</td>
<td>If family history positive or intraductal/cribriform histology</td>
</tr>
<tr>
<td>High</td>
<td>Consider if life expectancy ≥10 years</td>
<td>Recommended</td>
</tr>
<tr>
<td>Very High</td>
<td>Not routinely recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Regional</td>
<td>Consider for homologous recombination gene mutation (HRRm)*, microsatellite instability (MSI) or mismatch repair deficiency (dMMR)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Recommend for HRRm and consider for MSI or dMMR</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

*Genes include: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2.*

Inquire about family and personal history at time of initial diagnosis

Germline testing is recommended for patients with prostate cancer and any of the following:

- High-risk, very high-risk, regional, or metastatic prostate cancer
- Ashkenazi Jewish ancestry
- Intraductal histology
- Family history of high-risk germline mutations (e.g., BRCA1/2, Lynch mutation)
- A positive family history of cancer:
  - Brother/father or multiple family members diagnosed at <60 years or who died from PC;
  - ≥3 cancers on same side of family, especially diagnoses at ≤50 years: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer

A framework based on the Philadelphia Prostate Cancer Consensus Conference has recently been published

Suggested Genes:
- ATM
- BRCA1
- BRCA2
- CHEK2
- HOXB13
- MLH1
- MSH2
- MSH6
- PALB2
- PMS2

Role of Genetic and Molecular Biomarker Testing

• Germline genetic testing
  – Evaluate all patients with prostate cancer for family/personal history for risk of germline variants
  – If indicated, germline genetic testing and genetic counseling
• Somatic tumor testing recommended in metastatic prostate cancer
  – Somatic homologous recombination gene mutations (BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2)
  – MSI or dMMR
  – Multigene molecular testing assays
  – DNA repair gene mutations (eg, BRCA1/BRCA2) in 25% of patients with mCRPC

Case Study (cont’d): Ted’s Initial Treatment

• Molecular diagnostics revealed germline BRCA2 mutation
• Started on ADT and enzalutamide 160 mg once daily
• His PSA level became undetectable but began to increase 6 months ago
• Presents with asymptomatic metastatic CRPC
  – Reports no pain
  – Imaging unchanged
Treatment Options: Immunotherapy

Sipuleucel-T

- OS benefit, even without PSA response
  - Patient education
- Most beneficial in less advanced disease → early use recommended
- AEs: chills, fatigue, pyrexia, nausea

Day 1
Leukapheresis

Days 2-3
Sipuleucel-T is manufactured

Days 3-4
Patient receives infusion

Apheresis Center
Central Processing
Clinician’s Office

COMPLETE COURSE OF THERAPY
Weeks 0, 2, 4

Phase 3 Trials in Chemotherapy-naïve mCRPC

**COU-302: Abiraterone + Prednisone**

- **OS (%)**
  - Abiraterone + prednisone
  - Placebo + prednisone
  - HR, 0.81 (95% CI, 0.70-0.93)
  - \( P = .0033 \)

- **PFS (%)**
  - Abiraterone + prednisone
  - Placebo + prednisone
  - HR, 0.53 (95% CI, 0.45-0.93)
  - \( P = .0033 \)

**PREVAIL: Enzalutamide**

- **OS (%)**
  - Enzalutamide
  - Placebo
  - HR, 0.71 (95% CI, 0.60-0.84)
  - \( P < .001 \)

- **PFS (%)**
  - Enzalutamide
  - Placebo
  - HR, 0.19 (95% CI, 0.15-0.23)
  - \( P < .001 \)

Men with mild or no symptoms
Primary endpoints:
- OS, rPFS
- No prior ketoconazole
- Men with liver metastases eligible in PREVAIL

rPFS = radiographic progression-free survival.
COU-AA-301: Phase 3 Trial of Post-Chemo 2nd-line Abiraterone in mCRPC

- Abiraterone vs placebo: 1195 patients with mCRPC progressing after docetaxel
  - 2 prior chemo
    - OS: 14.0 months abiraterone vs 10.3 months placebo
  - 1 prior chemo
    - OS: 15.4 months abiraterone vs 11.5 months placebo
- Most common AEs, grade ≥3:
  - Fatigue (<9% vs 10%)
  - Anemia (7% vs 8%)
  - Back pain (<7% vs <10%)

AFFIRM: Phase 3 Trial of Post-Chemo, 2nd-line Enzalutamide in mCRPC

Enzalutamide vs placebo for 1199 men with mCRPC after chemotherapy

Most common grade ≥3 AEs: fatigue (6% vs 7%), diarrhea (1% vs <1%), cardiac disorder (1% vs 2%)

# Treatment Options for mCRPC: 2nd-Generation Hormone Therapy

- Both drugs are approved for use with or without prior docetaxel

<table>
<thead>
<tr>
<th><strong>Abiraterone</strong></th>
<th><strong>Enzalutamide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inhibits CYP17, enzyme needed for androgen synthesis</td>
<td>• AR antagonist; binds competitively to ligand-binding domain of AR</td>
</tr>
<tr>
<td>• Administered with steroids</td>
<td>• Concomitant steroids not required</td>
</tr>
</tbody>
</table>

AR = androgen receptor; CYP = cytochrome.
## Abiraterone and Enzalutamide: Drug Characteristics and Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>1000 mg/day orally</td>
<td>160 mg/day orally</td>
</tr>
<tr>
<td><strong>Empty stomach required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prednisone required</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug interactions (CYP)</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lowers seizure threshold</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Potential liver toxicity</strong></td>
<td>Yes</td>
<td>Less likely</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>Yes</td>
<td>More likely</td>
</tr>
<tr>
<td><strong>Cardiac toxicity</strong></td>
<td>More likely</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Risk of hypertension is increased by required coadministration of prednisone.

Treatment Options: Radiopharmaceuticals—Radium-223

Unlike beta-emitting radioisotopes (eg, samarium-153), the alpha-emitting isotope radium-223 delivers less radiation to bone marrow → fewer effects of marrow suppression

**ALSYPPCA: Symptomatic mCRPC with bone metastases**

**OS**

- **Placebo** (median OS, 11.3 months)
- **Radium-223** (median OS, 14.9 months)

**Median Time to First Symptomatic Skeletal Event**

- **Placebo** (9.8 months)
- **Radium-223** (15.6 months)

- **Most common AEs**: bone pain, nausea, anemia (no between-group differences)
- Phase 2 open-label studies: Radium-233 + enzalutamide or abiraterone decreased bone pain and increased QoL in patients with mCRPC and bone metastasis

Treatment Options: Chemotherapy

- **Docetaxel (first-generation taxane)**
  - Until 2010, only approved drug to improve OS for mCRPC
  - Appropriate for castrate-sensitive disease
- **Cabazitaxel (next-generation taxane)**
  - Improves OS in docetaxel-pretreated mCRPC
  - Improves QoL; reduces pain through 10 treatment cycles
  - Approved at lower dosage (20 mg/m²) in 2017 for patients with mCRPC previously treated with docetaxel

### AE Profile With Reduced-dose Cabazitaxel

<table>
<thead>
<tr>
<th>Grade ≥3 AE</th>
<th>20 mg/m²</th>
<th>25 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9.9%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28.9%</td>
<td>59.5%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41.8%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.6%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

**CARD Trial: Randomized, Open-label Study of Cabazitaxel vs Abiraterone or Enzalutamide in mCRPC**

N = 255 men with mCRPC that progressed ≤12 months on prior alternative 2nd-generation hormone therapy (before or after docetaxel)

<table>
<thead>
<tr>
<th></th>
<th>Cabazitaxel</th>
<th>Abiraterone/Enzalutamide</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain progression</td>
<td>NE (NE-NE)</td>
<td>8.5 (4.9-NE)</td>
<td>0.55 (0.32-0.97)</td>
</tr>
<tr>
<td>Symptomatic skeletal events</td>
<td>NE (20.0-NE)</td>
<td>16.7 (10.8-NE)</td>
<td>0.59 (0.35-1.01)</td>
</tr>
</tbody>
</table>

ARSI = androgen receptor signaling inhibitor; NE = not evaluated.
Molecular Targeted Therapy

**Pembrolizumab: PD-1 Inhibitor**

- For the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment or have no satisfactory alternative treatment options.
- For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutation/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and have no satisfactory alternative treatment options.

PD-1 = programmed cell death protein 1.
Molecular Targeted Therapy

**Olaparib: PARP inhibitor**
- For the treatment of adults with deleterious or suspected deleterious *germline or somatic HRR gene-mutated mCRPC* who have progressed following treatment with enzalutamide or abiraterone
- Patients selected based on FDA- approved companion diagnostic

**Rucaparib: PARP inhibitor**
- For the treatment of adults with a deleterious *BRCA mutation (germline or somatic)-associated mCRPC* previously treated with AR- directed therapy and a taxane-based chemotherapy
- Patients selected based on FDA- approved companion diagnostic

PROfound: Randomized Open-label Trial of Olaparib vs Abiraterone or Enzalutamide

N = 378 men with mCRPC who progressed on abiraterone or enzalutamide and had alteration in one of 15 prespecified HRR genes

**PFS**

- Median value at 6 mo: Olaparib = 0.49, Control = 0.70
- Value at 12 mo: Olaparib = 0.13, Control = 0.22

**OS**

- HR for death, 0.79 (95% CI 0.61-1.03)
- Median OS (95% CI) months: Olaparib = 17.3 (15.5-18.6), Control = 14.0 (11.5-17.1)

**Graphs:**

- Graph showing PFS and OS with detailed data points and survival curves.

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TRITON2: Rucaparib in mCRPC With DNA Damage Repair Mutations

- Confirmed PSA response 54.8% (95% CI, 38.1%; 64.1%)
- ORRs similar between BRCA1 and BRCA2; germline and somatic alterations

<table>
<thead>
<tr>
<th></th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>43.5 (31.0; 56.7)</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>33.3 (7.5; 70.1)</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>45.3 (31.6; 59.6)</td>
</tr>
<tr>
<td>Germline</td>
<td>42.9 (21.8; 66.0)</td>
</tr>
<tr>
<td>Somatic</td>
<td>43.9 (28.5; 60.3)</td>
</tr>
</tbody>
</table>

rPFS in BRCA-altered mCRPC (n = 115)

## Toxicities with PARP Inhibitors

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib (n = 256)</th>
<th>Rucaparib (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>ALT/AST increased</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dizziness</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported.

# 2020 NCCN Guidelines for mCRPC: First- and Second-line

## First-line Treatment
- Abiraterone
- Docetaxel
- Enzalutamide
- Sipuleucel-T

**Useful in certain circumstances:**
- Radium-223
- Mitoxantrone

**Other recommended:**
- Fine particle abiraterone
- Secondary hormone therapy

## First-line Treatment
- Docetaxel
- Sipuleucel-T

**Useful in certain circumstances:**
- Olaparib
- Rucaparib
- Pembrolizumab
- Radium-223

**Other recommended:**
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Fine particle abiraterone
- Secondary hormone therapy

## Second-line Treatment
### First-line Abiraterone/Enzalutamide
- Docetaxel
- Sipuleucel-T

**Useful in certain circumstances:**
- Olaparib
- Rucaparib
- Pembrolizumab
- Radium-223

**Other recommended:**
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Fine particle abiraterone
- Secondary hormone therapy

## Second-line Treatment
- Abiraterone
- Cabazitaxel
- Enzalutamide

**Useful in certain circumstances:**
- Mitoxantrone
- Olaparib
- Rucaparib
- Pembrolizumab
- Radium-223

**Other recommended:**
- Consider docetaxel rechallenge
- Sipuleucel-T
- Fine particle abiraterone
- Secondary hormone therapy

---

### 2020 NCCN Guidelines for mCRPC: Subsequent Treatment

**Subsequent Treatment**

- Abiraterone
- Docetaxel rechallenge
- Cabazitaxel
- Enzalutamide

*Useful in certain circumstances:*

- Olaparib
- Rucaparib
- Pembrolizumab
- Mitoxantrone
- Radium-223

*Other recommended:*

- Fine particle abiraterone
- Secondary hormone therapy

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*Patients may also require antiresorptive bone therapy: zoledronic acid or denosumab*
Example of Therapy Sequencing for mCRPC

- Optimal sequencing not established (sample shown)
- Treatment pathway is unique for each patient
- Cross-resistance between abiraterone and enzalutamide
- Need to identify molecular subtypes for more rational sequencing

*All treatment options should include ADT (surgical/medical orchiectomy); †In patients with BRCA-mutated mCRPC (rucaparib) or alterations in homologous recombination repair genes (olaparib).

Factors to Consider When Selecting Therapies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preferences</td>
<td>• Metastatic?</td>
<td>• Toxicity profile</td>
</tr>
<tr>
<td>• Medical history, comorbidities, medications</td>
<td>– To bone?</td>
<td>• Possible drug-drug interactions</td>
</tr>
<tr>
<td>• Treatment and response history</td>
<td>– Visceral?</td>
<td>• Effects on pain, QoL</td>
</tr>
<tr>
<td>• Symptoms</td>
<td>• Disease volume</td>
<td>• Practitioner experience and preference</td>
</tr>
<tr>
<td>• Overall condition and performance status</td>
<td>– Low or high?</td>
<td></td>
</tr>
</tbody>
</table>

Lifestyle Modifications for Men with PC

- Improvements in diet:
  - ↓ saturated fat intake, dairy products
  - Limit alcohol (2 drinks/day)
  - ↑ fiber and lycopene-containing foods (tomatoes)
- Increased physical activity (150 min/week):
  - ↑ psychological well-being
  - ↓ depression
  - ↑ energy levels, improved fitness level
- Manage comorbid conditions: diabetes, hyperlipidemia, hypertension, cardiovascular
- Assess and treat: urinary, bowel, sexual dysfunction; anxiety; stress

| Risk Factors of Advanced or Lethal Prostate Cancer |
|---------------------------------|------------------|
| Increased risk                  | Decreased risk   |
| • Lipid levels                  | • Physical activity |
| • Obesity                       | • Vitamin D       |
| • Smoking                       | • Statins         |
| • Dairy, calcium                | • Balanced diet-low in animal fat |

**Shared Decision-Making**

- Patients and clinicians collaborate on treatment selection
- May enhance adherence to therapies → better treatment responses
- Discuss potential barriers: AEs, costs

- **S**eek patient’s participation
- **H**elp patients explore and compare treatment options
- **A**ssess patient’s values and preferences
- **R**each a decision with your patient
- **E**valuate your patient’s decision

Case Conclusion

- Ted receives olaparib 300 mg orally twice daily
- His blood glucose and CBC are monitored regularly
- After 3 months of treatment:
  - PSA has decreased to 6 ng/mL
  - He reports decreased pain but does notice fatigue; you recommend he try to increase his physical activity
  - Bone scans show stable lesions and no new lesions
  - Blood glucose managed by intensifying diabetes medications
  - CBC is stable

CBC = complete blood count.
For patients with mCSPC, consider adding docetaxel (± prednisone), abiraterone + steroid, apalutamide, or enzalutamide to ADT.

Consider early use of approved agents for nonmetastatic CRPC to improve MFS and OS.

Consider germline genetic testing and counseling for all patients with prostate cancer and somatic tumor testing in patients with metastatic prostate cancer.

Implement shared decision-making to optimize treatment outcomes.

PCE Promotes Practice Change