NCCN Virtual Oncology Fellows Program:
New Horizons in Quality Cancer Care™

Wednesday, March 17, 2021
4:05 PM – 5:05 PM EDT

Multidisciplinary Treatment of Prostate Cancer

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Learning Objectives

- Provide an overview of the treatments used to treat patients with prostate cancer.
- Discuss the roles that genetics and diagnostic radiology professionals play in the optimal management of prostate cancer.
- Understand management strategies for supportive care issues in patients with prostate cancer.

Timing of Post-Operative Radiation Therapy

Anthony V. D'Amico, MD, PhD
Dana-Farber Cancer Institute

RCTs of Adjuvant RT (aRT) vs Salvage RT (sRT)

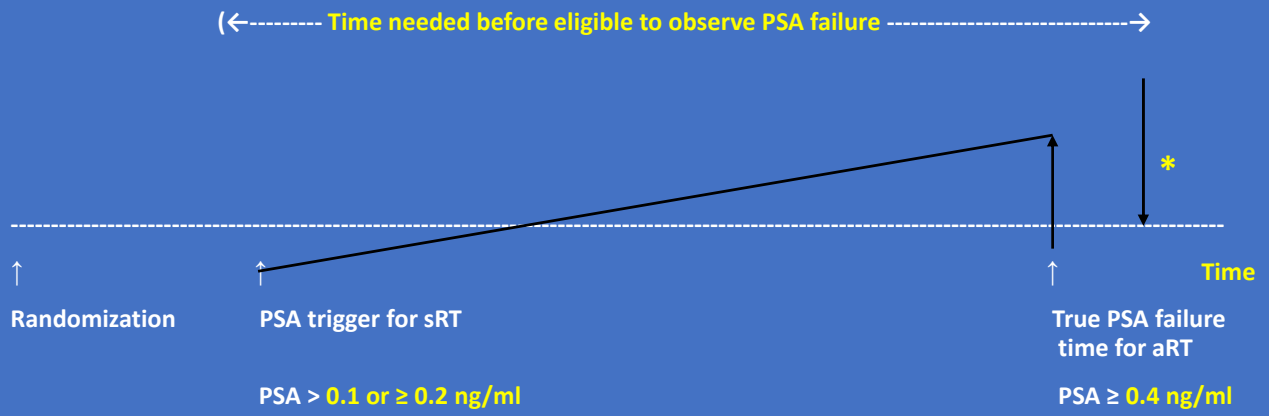
- **RADICALS-RT** (N = 1396) – Is Adjuvant superior to Salvage RT? [1]
  - Superiority, 1^0 end pt: DMFS
  - Median f/u = 5.0 years: PFS* 1.1 [0.81, 1.49]
- **RAVES** (N = 333)- Is Salvage non-inferior to Adjuvant RT? [2]
  - Non-inferiority: 5 yr FFBF (64 vs 74%; PSA > 0.4) (HR = 1.48)
  - Median f/u = 6.1 years: EFS: 1·12 [0·65–1·90]
    - Favored Salvage RT in pT3b and pGl 8 to 10
- **GETUG-AFU 17** (N = 424) - Is Adjuvant RT/ADT superior to Salvage RT/ADT? [3]
  - Superiority, 1^0 end point: PFS
  - Median f/u = 6.3 years: PFS* 0·81, 95% CI 0·48–1·36
    - ADT delays progression;
      - Rx: adjuvant (97%) > salvage (54%)

1. NCT00541047
2. NCT00860652
3. NCT00667069

DMFS, distant metastasis-free survival; FFBF, freedom from biochemical failure; EFS, event-free survival

*PFS driven by PSA failure

How can sRT "appear" superior to aRT?



- Men with pT3b or pGI 8-10 PC (9-17% of men on RCTs) can have short PSA DT
  - PSA reaches 0.4 before the PSA assessment time following sRT falsely prolongs the time to PSA failure* on the sRT verus aRT arm making sRT "appear" superior to aRT
  - Whether men with pT3b, GI 8 to 10 PC benefit from aRT remains to be discerned

PSA DT, PSA doubling time

Case 1

- 54 year old, fit with no PMH
  - PSA of 1.5 ng/mL (last year 0.5) on finasteride for hair loss
    - corrected PSA 3.0 last year 1.0
      - Testosterone: 547
  - DRE: nodule right mid to base (T2b)
  - 12 core TRUS bx: 4 cores of GS 4 + 3 - right mid and base post and lateral

What imaging should we consider?

(1) mpMRI and bone scan
(2) PET
(3) None

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance • Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-6

mpMRI and bone scan ordered

- Bone Scan (-)
- mpMRI: PIRADS 5 right anterior base prostate with possible bladder neck invasion and 0.9 cm left external iliac LN (equivocal)
- MR/TRUS fusion biopsy of PIRADS 5 lesion: Gleason 5 + 4

What would you discuss next?

(1) Radical prostatectomy and pelvic LND; possible need for post op RT/ADT

(2) External Beam RT (pelvic LNs and boost left ext iliac LN) and prostate/SV+ ADT/abiraterone x 2 years

(3) Additional imaging

SV, seminal vesicles

PET ordered

Pelvic LNs not PET avid, only intraprostatic uptake

- **Patients proceeds with RP with left NS and Pelvic LN sampling**
  - **pT3b (R SV) N0 (6 LN sampled) R1 (bladder neck), pGleason score 5 + 4**
- **Post op PSA at 4 weeks < 0.02, erectile dysfunction (ED) and stress urinary incontinence**
  - **Low-risk Decipher Score = 25**

According to the NCCN Guidelines for Prostate Cancer, what would be an appropriate next step?

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Oligometastatic prostate cancer:

Should SBRT be incorporated?
Supporting our patients on long-term ADT

Tanya Dorff, MD
Associate Clinical Professor of Medicine
Head of Genitourinary Cancer Program

Case history

- 45 year-old man presents with hematuria, PSA 36.7 ng/mL
  - Cystoscopy was negative, but prostate biopsy revealed Gleason 3+4 adenocarcinoma in all 8 cores
  - Staging CT and bone scan are negative for distant metastases or regional adenopathy

- Radical prostatectomy was performed: pGleason 4+4 adenocarcinoma, stage pT3aN0R0
  - Post-op PSA after 4 weeks is 0.5 ng/mL and a repeat 2 weeks later shows a rise to PSA 0.9 ng/mL
  - F-18 fluciclovine PET scan reveals a **2.3 cm sclerotic lesion in the left iliac bone and left posterior 8th rib**

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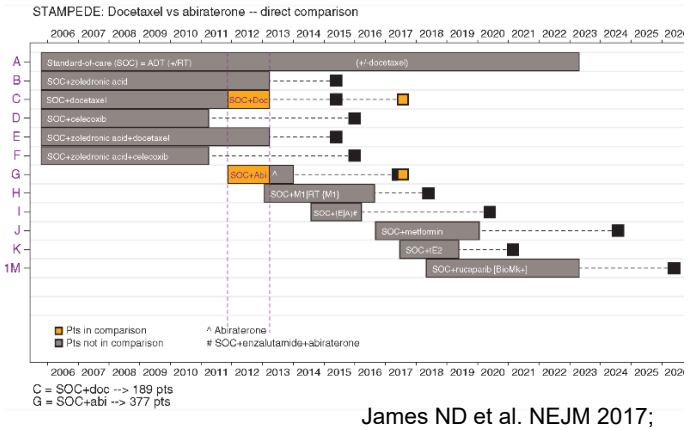
Intensified 1st line therapy improves survival in metastatic castration-naïve prostate cancer (mHSPC)

LATITUDE: abiraterone + pred 5
mHSPC with 2 of 3 high-risk features:
- Gleason 8-10
- 2+ bone metastases
- Visceral metastases

Fizazi K et al. NEJM 2017
DOI:10.1056/NEJMoa1704174

STAMPEDE arm C: docetaxel, arm G: abiraterone + pred 5
- Docetaxel benefit in CHAARTED in high volume only (≥4 bone mets, 1 outside axial skeleton OR visceral)



James ND et al. NEJM 2017;
DOI: 10.1056/NEJMoa1702900

ENZAMET, ARCHES: enzalutamide
TITAN: apalutamide

Davis ID et al. NEJM 2019; 381:121-31
Armstrong AJ et al. J Clin Oncol 2019; 37:2974
Chi KN et al. NEJM 2019; 381:13-24

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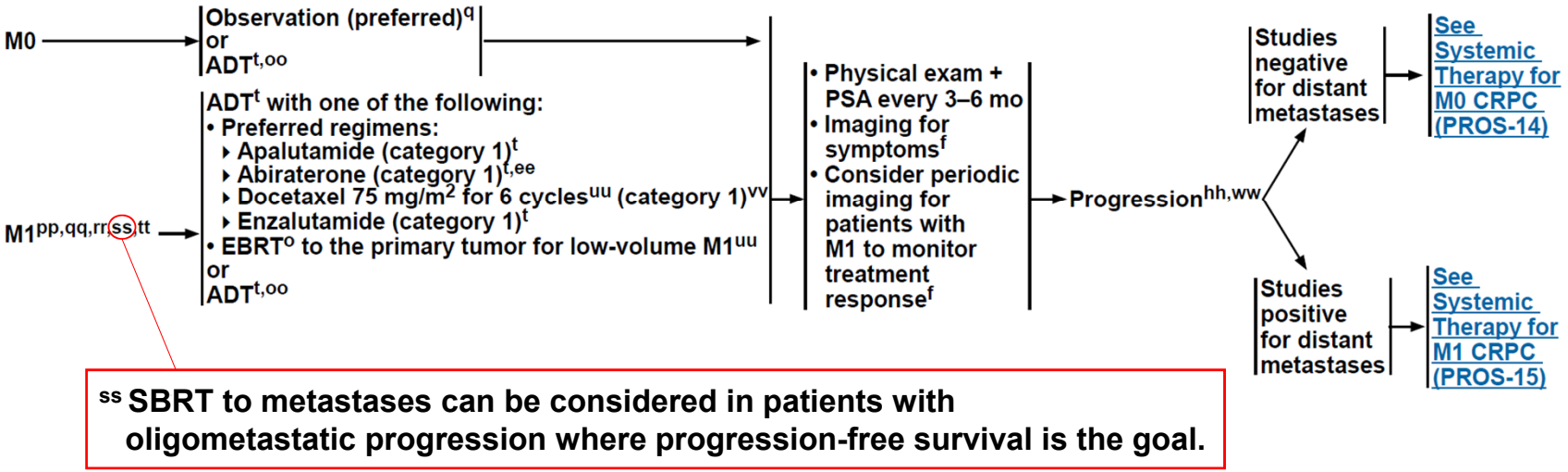
Prostate Cancer

SYSTEMIC THERAPY FOR CASTRATION-NAÏVE PROSTATE CANCER[nn]



[ss] **SBRT to metastases can be considered in patients with oligometastatic progression where progression-free survival is the goal.**

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

PROS-13

Should metastasis-directed therapy be added?

- **POPSTAR**[1] showed that SBRT is effective at eradicating the disease which is treated with hormone therapy
  - NaF PET, 30 pts, up to 3 mets
  - Bone: Local PFS 89%, distant PFS 39% @2 yrs
  - Pelvic Node: Local PFS 100%, distant PFS 42%
- **STOMP** showed SBRT alone delays time to ADT
  - Phase II, 119 pts with oligomet PC, SBRT to ≤ 3 mets, based on FDG or choline PET[2] – median DFS 27 mo
  - Randomized 62 pts, time to ADT 21 months w/SBRT vs 13 months surveillance[3]

1. Siva S et al. Eur Urol 2018; 74:455-62
2. Ost P et al. Eur Urol 2016;69:9-12
3. Ost P et al. JCO 2018; 36; 446-53

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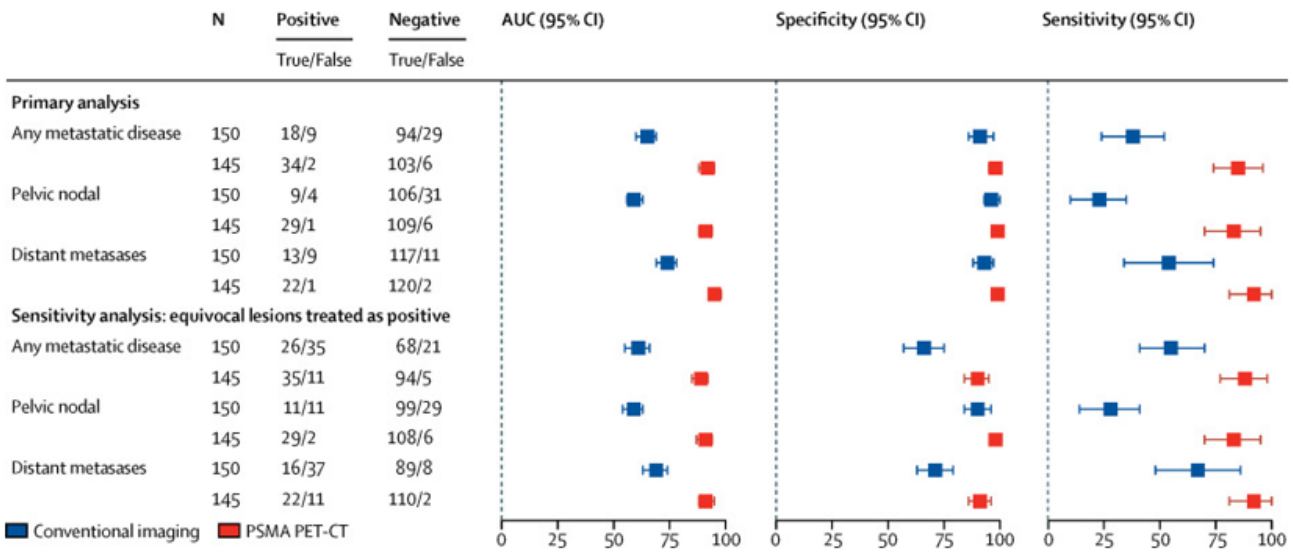
Defining oligometastatic depends on reliable imaging



Once PSMA imaging becomes available, the greater sensitivity will mean better selection of oligometastatic patients.

Hofman MS et al Lancet 2020; 395:1208-16

Case history (continued)

- He received ADT + abiraterone and SBRT to the 2 sites of bone metastases
  - PSA dropped to undetectable level
- Treatment was stopped due to unacceptable toxicity
  - PSA rising with testosterone recovery, now 0.52 ng/mL but F-18 fluciclovine PET shows no evidence of active metastatic disease

- Have we impacted this man's long-term cancer control?
- How can we support patients on long-term ADT?

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ADT: managing side effects

- Hot flashes (gabapentin[1], venlafaxine[2])
- Metabolic syndrome: diet/exercise, metformin[3], statins
- Cognitive changes (focus/attention): methylphenidate
- Emotional changes: SSRI
- Bone mineral density:
  - Bisphosphonates or denosumab 60 mg SQ q6 months[4]
  - DEXA scans
- Resistance and aerobic exercise can improve muscle mass, physical function[5]
- Toremifene also an option for hot flashes/bone density[6]

1. Loprinzi C et al. Ann Oncol 2009; 20:542
2. Irani J et al. Lancet Oncol 2010; 11:147
3. Nobes JP et al BJU Int 2012; 109:1495
4. Smith MR et al. NEJM 2009; 361:745
5. Kiwata/Dorff PCAN 2016; 19:323
6. Smith MR et al. JCO 2008; 26:1824

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Case #3

Edward Schaeffer, MD, PhD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Case 3

March 2019

- 59 year old presenting to Urologist with lower urinary tract symptoms (nocturia, slow stream, incomplete emptying)
- Exam markedly abnormal / PSA 1185 ng/mL
- PMHx: Male breast cancer s/p mastectomy and 6 cycles Chemotherapy (2013)
- FH Mother with Ovarian Ca. @ age 64

- Biopsy: all cores GG5 prostate cancer
- Imaging:
  - Bone Scan: Innumerable sclerotic lesions "super scan"
  - CT: Enlarged prostate with bladder invasion of the left wall. Liver lesions

- What are the next steps in the work-up?
  - Any additional tests…
- What initial treatment would you recommend?

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Prostate Cancer

Next Step in the workup -- Germline Testing

PRINCIPLES OF GENETICS

Germline Testing

- The panel recommends inquiring about family and personal history of cancer and family history for known germline variants at time of initial diagnosis. In cases when a patient says he was tested and had negative results, the clinician should inquire about the details of testing. Direct-to-consumer genetic tests do not test for all known relevant variants.
- Germline genetic 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
  - Family history of high-risk germline mutations (eg, ***BRCA1/2***, Lynch mutation)
  - A positive family history of cancer:
    - A strong family history of prostate cancer consists of: brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at <60 years of age or who died from prostate cancer
      OR
    - ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer
- Limited data suggest that prostate cancers with cribriform (ductal or intraductal) histology have increased genomic instability.
- Family history for known germline variants and genetic testing for germline variants should include ***MLH1, MSH2, MSH6,*** and ***PMS2*** (for Lynch syndrome) and homologous recombination genes ***BRCA1, BRCA2, ATM, PALB2,*** and ***CHEK2.***
  - Consider cancer predisposition next-generation sequencing (NGS) panel testing, which includes ***BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6,*** and ***PMS2.***
  - Additional genes may be appropriate depending on clinical context. For example, ***HOXB13*** is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease, but testing may be valuable for family counseling.
- Patient should be counseled to inform providers of any update to family history.
- Genetic testing in the absence of family history or clinical features (eg, high- or very-high-risk prostate cancer) may be of low yield.
- The prevalence of inherited (germline) DNA repair gene mutations in men with metastatic prostate cancer, unselected for family history (n = 692), was found to be 11.8% (***BRCA2*** 5.3%, ***ATM*** 1.6%, ***CHEK2*** 1.9%, ***BRCA1*** 0.9%, ***RAD51D*** 0.4%, and ***PALB2*** 0.4%). The prevalence was 6% in the localized high-risk population in the TCGA cohort (Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-1025; Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-453).
- Genetic counseling resources and support are critical and pre-test counseling is preferred when feasible, especially if family history is positive.
- Post-test genetic counseling is recommended if a germline mutation (pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in male and female relatives.
- If no pathogenic variant mutations or only germline variants of unknown significance (VUS) are identified but family history is positive, genetic counseling is recommended to discuss possible participation in family studies and variant reclassification studies.
- Resources are available to check the known pathologic effects of genomic variants (eg, https://brcaexchange.org/about/app; https://www.ncbi.nlm.nih.gov/clinvar/)
- Information regarding germline mutations in patients with metastatic disease can be used to inform future treatments or to determine eligibility for clinical trials.

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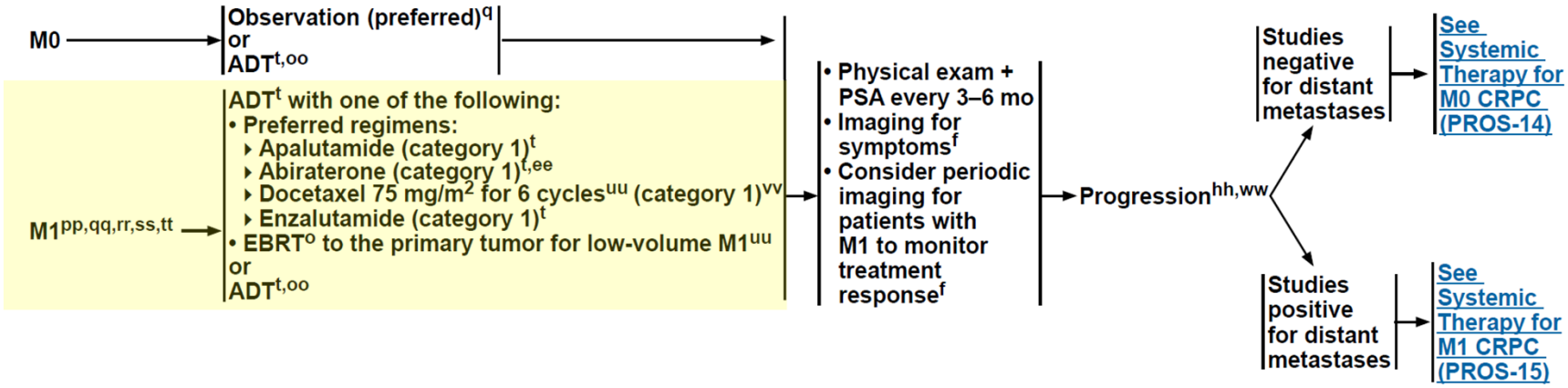
Prostate Cancer

Next Step in Treatment

SYSTEMIC THERAPY FOR CASTRATION-NAÏVE PROSTATE CANCER[nn]



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

PROS-13

Case 3

- Leuprolide + 6 cycles of docetaxel (last 8/2019)
  - PSA nadir to 5.17 ng/mL (9/19)
- Enzalutamide initiated in September 2019
  - PSA
    - 11/19 1.29 ng/mL
    - 2/20 1.29 ng/mL
    - 3/20 4.25 ng/mL

- What defines CRPC (castration-resistant prostate cancer)?
- What are the next steps for him?

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TRITON2

TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

Key eligibility criteria

- mCRPC
- Deleterious somatic or germline alteration in DDR gene
- Disease progression on AR-directed therapy (eg, abiraterone, enzalutamide, or apalutamide) for PC ***and*** 1 prior taxane-based chemotherapy for CRPC
- ECOG PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

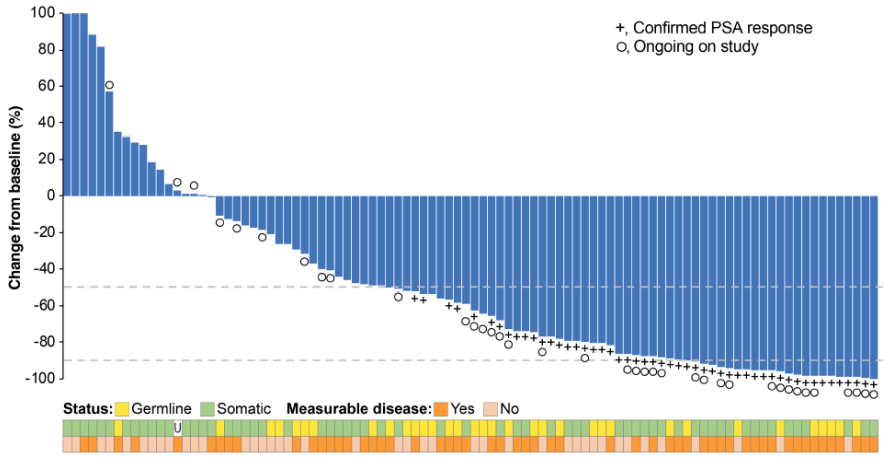
Treatment
28-day cycles

Rucaparib 600 mg BID

- Tumour assessments every 8 weeks for 24 weeks, then every 12 weeks
- PSA assessments every 4 weeks

Treatment until radiographic progression or discontinuation for other reason

Figure 4. Best Change from Baseline in PSA in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=96)



Abida W, et al. ESMO Congress, 2019.

PROfound STUDY DESIGN

Key eligibility criteria
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Stratification factors
- Previous taxane
- Measurable disease

Cohort A: *BRCA1, BRCA2* or *ATM* N=245
- Olaparib 300 mg bid n=162
- Physician's choice‡ n=83

2:1 randomization
Open-label

Upon BICR progression, physician's choice patients were allowed to cross over to olaparib

Cohort B: Other alterations N=142
- Olaparib 300 mg bid n=94
- Physician's choice‡ n=48

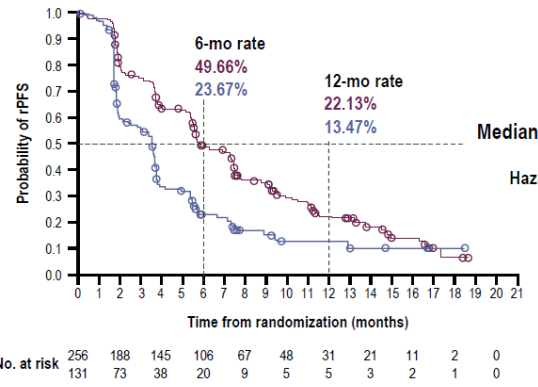
Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

*An investigational Clinical Trial Assay, based on the CDx next-generation sequencing test Developed and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

rPFS BY BICR IN THE OVERALL POPULATION (COHORTS A+B)



	Olaparib (N=256)	Physician's choice (N=131)
Events (%)	180 (70.3)	99 (75.6)
Median rPFS (months)	5.82	3.52
Hazard ratio (95% CI)	0.49 (0.38, 0.63) *P*<0.0001	

Hussain M, et al. ESMO Congress, 2019.

Case 3

- Germline testing revealed BRCA2-deficiency
- Enzalutamide discontinued and olaparib initiated 3/20
- PSA:
  - 4/20 0.45 ng/mL
  - 5/20 0.31 ng/mL
  - 6/20 0.24 ng/mL
  - 7/20 0.19 ng/mL
  - 10/20 0.19 ng/mL
  - 12/20 0.22 ng/mL
  - 1/20 0.30 ng/mL

What are the next steps for him?

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TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This can include *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
3. *Personal history of cancer*
   - Breast cancer with at least one of the following:
     - Diagnosed at age ≤45 y; or
     - Diagnosed at age 46–50 y with:
       - Unknown or limited family history;[e] or
       - A second breast cancer diagnosed at any age; or
       - ≥1 close blood relative[f] with breast, ovarian, pancreatic, or prostate cancer at any age
     - Diagnosed at age ≤60 y with triple-negative breast cancer;
     - Diagnosed at any age with:
       - Ashkenazi Jewish ancestry; or
       - ≥1 close blood relative[f] with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,[g] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer at any age; or
       - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[f]
     - Diagnosed at any age with male breast cancer
   - Epithelial ovarian cancer[h] (including fallopian tube cancer or peritoneal cancer) at any age
   - Exocrine pancreatic cancer at any age (See CRIT-3)
   - Prostate cancer at any age with:
     - Metastatic,[g] intraductal/cribriform histology, or high- or very-high-risk group (see NCCN Guidelines for Prostate Cancer);
     - Any NCCN risk group (see NCCN Guidelines for Prostate Cancer) with the following family history:
       - Ashkenazi Jewish ancestry; or
       - ≥1 close relative[f] with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,[g] or intraductal/cribriform prostate cancer at any age; or
       - ≥2 close relatives[f] with either breast or prostate cancer (any grade) at any age
   - A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
   - Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (see CRIT-4) or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria (see CRIT-5)
   - To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer[i]

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Footnotes on CRIT-2A

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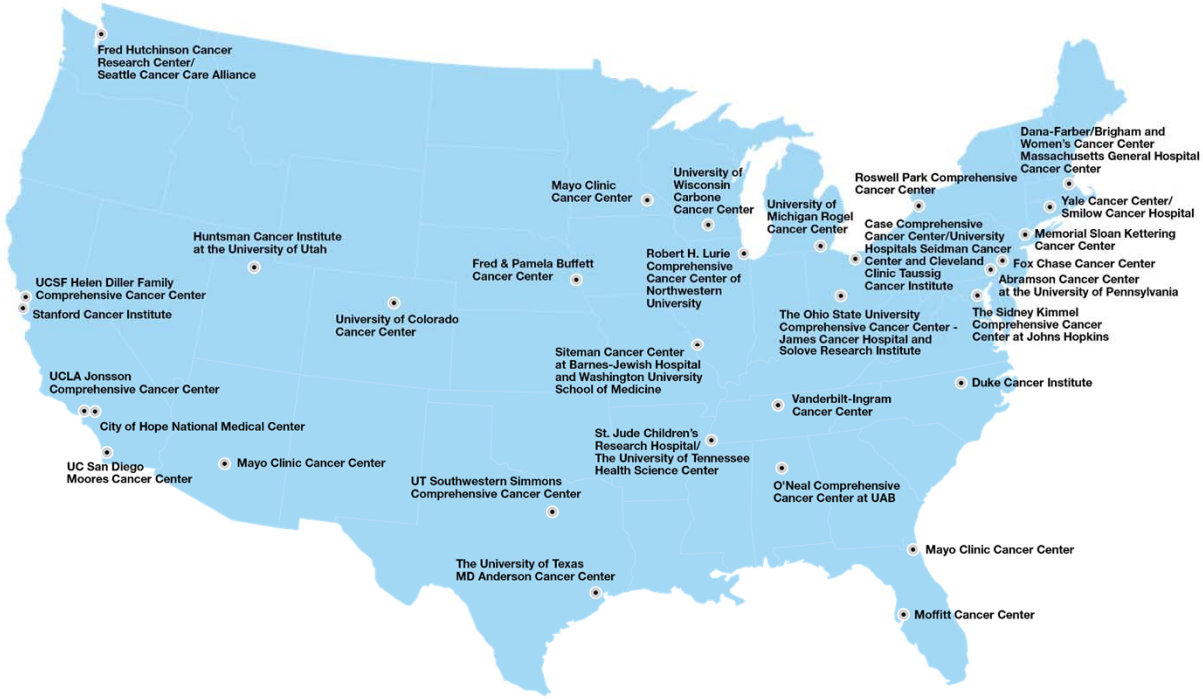
  An alliance of leading cancer centers devoted to patient care, research, and education
- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



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