Prostate Cancer

AUA Annual Review Course
June 2025

Kristen R. Scarpato, MD, FACS
Associate Professor of Urology
Vanderbilt University Medical Center
Kristen.r.scarpato@vumc.org

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Disclosures

- Photocure
- Cxbladder
- UroGen

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Resources *(Guidelines)*

Prostate Cancer: Advanced
(Published 2020; Amended 2023)

Prostate Cancer: Early Detection
(2023)

Prostate Cancer: Hypofractionated Radiotherapy
(2018)

Prostate Cancer: Localized
(2022)

Salvage Therapy for Prostate Cancer
(2024)

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Resources *(Core Curriculum)*

Prostate Cancer Screening, Diagnosis and Risk Stratification

Prostate Cancer Localized and Locally Advanced Treatment

Prostate Cancer: Advanced Disease

Cancer Survivorship

Genetics and Genomics of Urologic Malignancy

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AUA *University*

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Outline

- Epidemiology and Risk Factors
- Screening and Diagnosis
  - PSA, Biomarkers, MRI, Risk Stratification
- Treatment of Localized Cancer
  - Surveillance, Radiation, Surgery, ADT

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Outline

- Treatment Failure/Recurrence
- Advanced Prostate Cancer
  - Hormone sensitive metastatic
  - Castration resistant metastatic and nonmetastatic
  - Genetic testing

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EPIDEMIOLOGY

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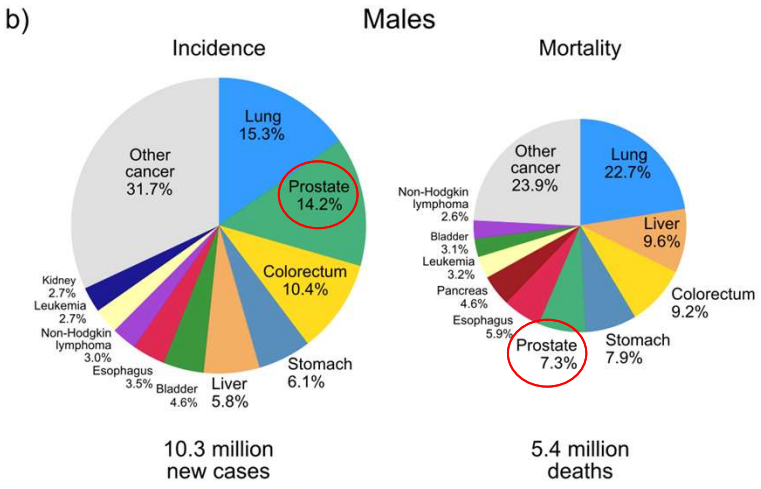
Epidemiology *(Global)*



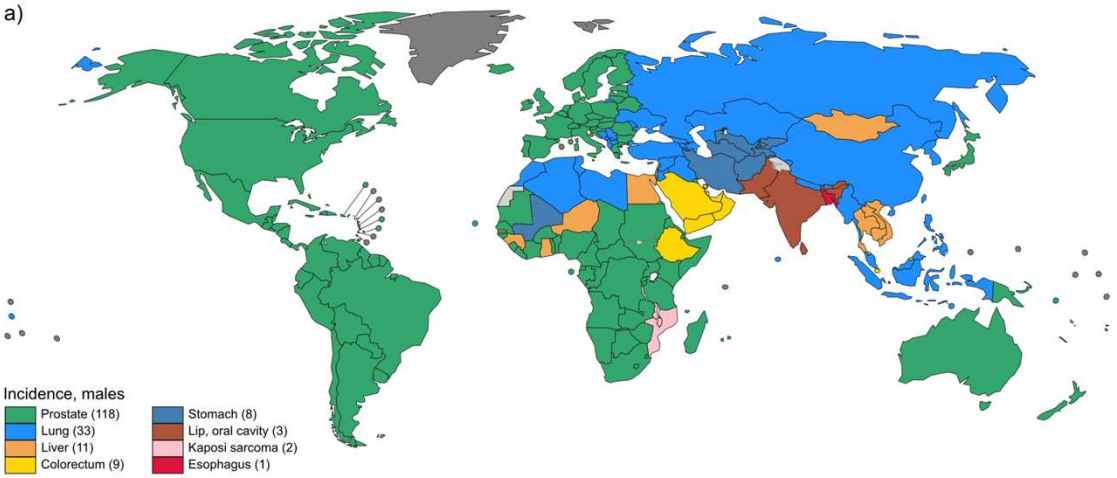
1.5 Million/year incident

- 2nd in males behind lung but most frequent in 118/185 countries

400 K/year deaths

- 5th in males
- Leading cancer death in 52/185 countries (Caribbean, sub-Saharan Africa, Central & South America)

CA CANCER J CLIN 2024;71:209–249



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CA Cancer J Clin. 2024;74:229–263.

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Epidemiology *(U.S.)*

Estimated New Cases

Male		
Prostate	313,780	30%
Lung & bronchus	110,680	11%
Colon & rectum	82,460	8%
Urinary bladder	65,080	6%
Melanoma of the skin	60,550	6%
Kidney & renal pelvis	52,410	5%
Non-Hodgkin lymphoma	45,140	4%
Oral cavity & pharynx	42,500	4%
Leukemia	38,720	4%
Pancreas	34,950	3%
All sites	**1,053,250**	

Estimated Deaths

Male		
Lung & bronchus	64,190	20%
Prostate	35,770	11%
Colon & rectum	28,900	9%
Pancreas	27,050	8%
Liver & intrahepatic bile duct	19,250	6%
Leukemia	13,500	4%
Esophagus	12,940	4%
Urinary bladder	12,640	4%
Non-Hodgkin lymphoma	11,060	3%
Brain & other nervous system	10,170	3%
All sites	**323,900**	

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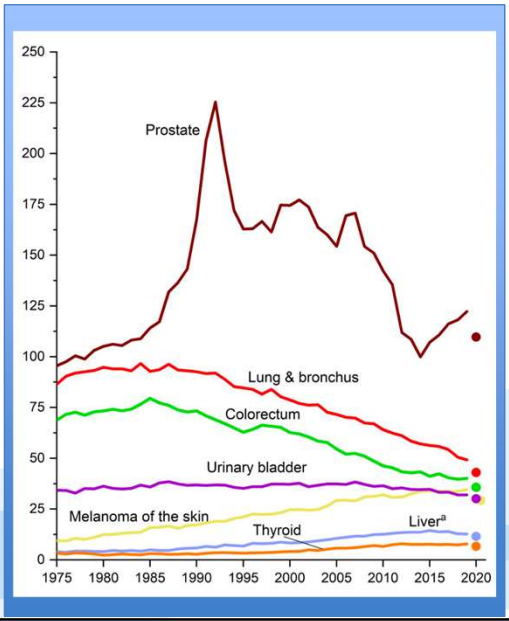
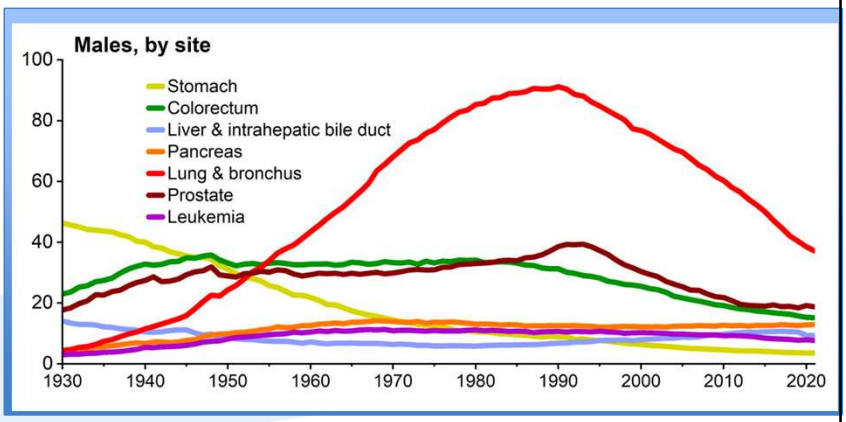
CA Cancer J Clin. 2025;75:10-45

Epidemiology *(u.s.)*





CA Cancer J Clin. 2025;75:10-45

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Risk Factors

- Gender
- Advancing age
- Ethnicity
  - Black or African American
- Family History
  - First degree (male) relatives
- Chronic inflammation
- Smoking
  - Recurrence, PCa death
- Obesity
  - high-grade disease, higher treatment failure rates and mortality

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Table 1: Risk factors for prostate cancer

Risk factor	Relative risk of prostate cancer
1st degree relative diagnosed <60 years	2.1-2.8
Above germline mutations	2-8
African ancestry	1.6

SCREENING AND DIAGNOSIS

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What is PSA?

- Glyco**protein** produced by epithelial cells of prostate gland
- Trauma, infection, inflammation, malignancy results in a larger amount of PSA in serum
  - Therefore, serves as a marker for prostate disease
- Serum measurements for prostate cancer became widespread in ~ 1988

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Randomized Screening Trials

- **PLCO** – no difference in prostate cancer specific mortality with yearly PSA screening
- **ERSPC** – significant survival benefit from regular PSA screening
- **CAP** – no difference in mortality with a single PSA screen (*but… recent update)

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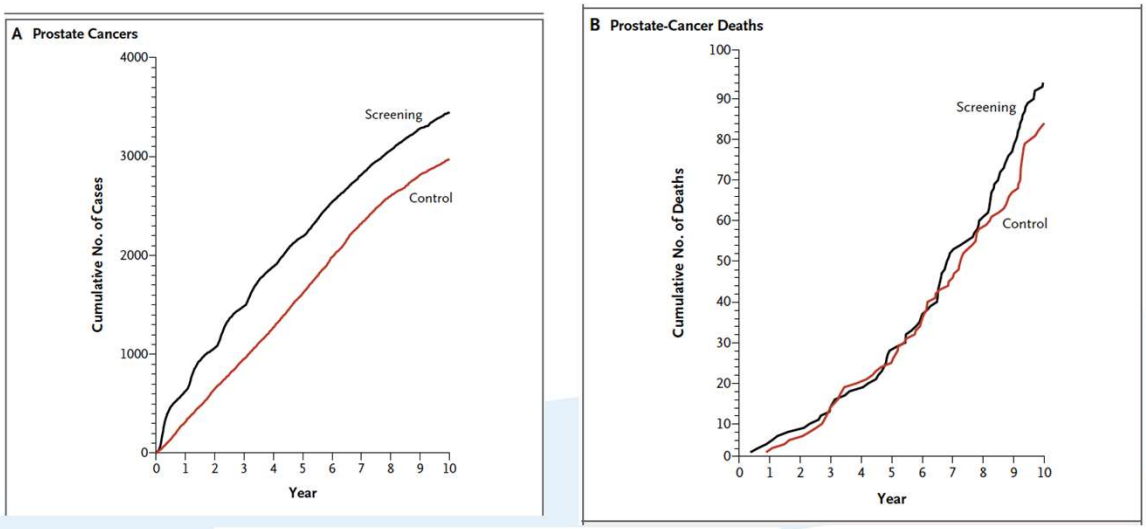
PLCO



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CONCLUSIONS
After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. (ClinicalTrials.gov number, NCT00002540.)

N Engl J Med 2009;360:1310-9.

PLCO Criticism

- **"Contamination"**
  - Degree of screening in the control arm; both before and during the study
    - 10% with baseline screening test before trial entry
    - 80% of control group reported having undergone PSA test during trial

85% screened in intervention arm
90% screened in control arm

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Shoag et al, NEJM, 374:1795, 2016

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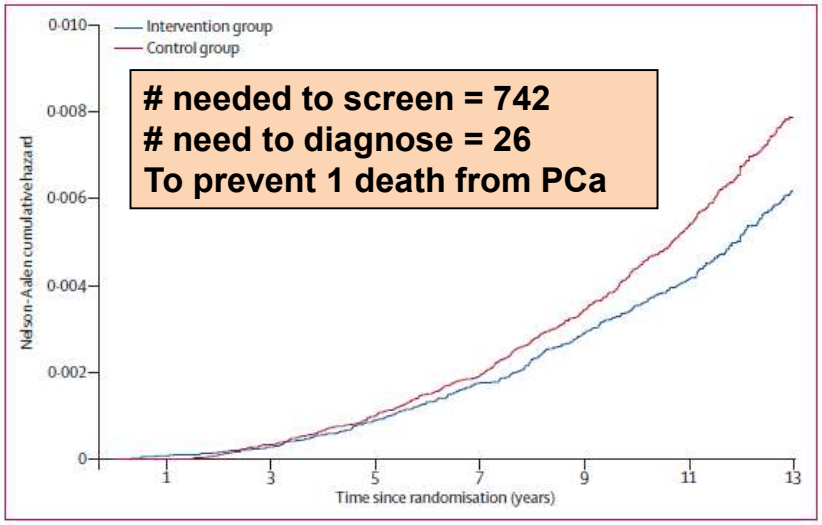
ERSPC



 # needed to screen = 742
 # need to diagnose = 26
To prevent 1 death from PCa

13-year follow up

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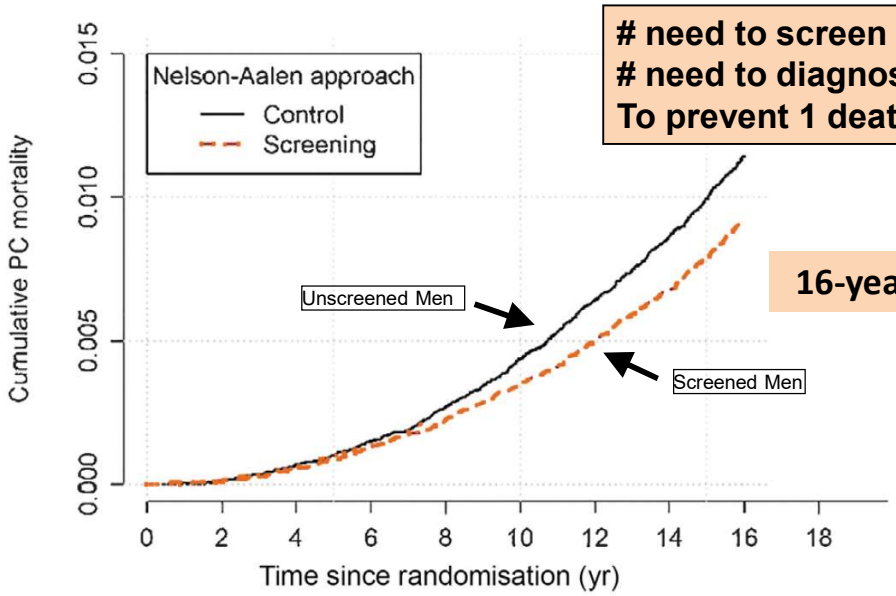
Relative risk for prostate cancer death = 0.79
(95% CI, 0.69-0.91; p = 0.001)

Schroder et al Lancet , 384:2027-35, 2014

ERSPC



 # need to screen = 570
 # need to diagnose = 18
To prevent 1 death from PCa

16-year follow up

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Relative risk for prostate cancer death of 0.80
(95% CI, 0.72–0.89, p < 0.001)

Hugosson et al, Eur Urol , 2019

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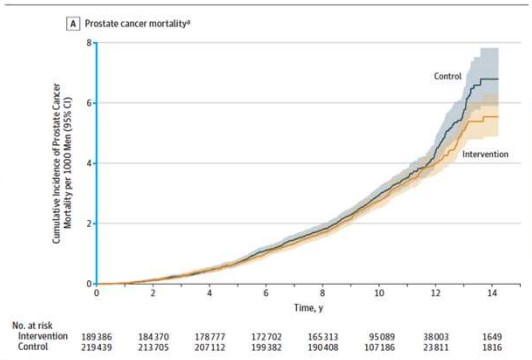
Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

- ProtecT
- 415,357 randomized men to a single PSA vs no PSA
- 50-69 years of age
- At 10 years
  - More cancer in the intervention arm
  - Cancer mortality – ***no difference***
  - Survival – ***no difference***



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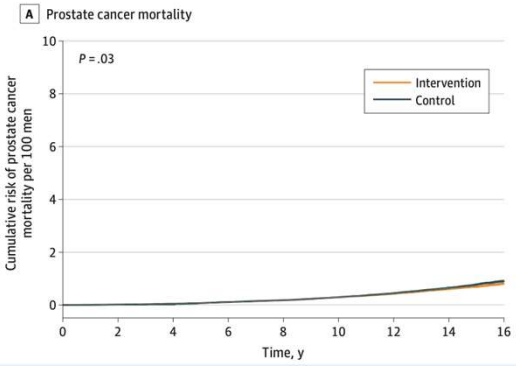
Single PSA test not recommended for population screening

JAMA March 6, 2018 Volume 319, Number 9

Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial



Absolute reduction in Pca mortality of 0.09% after a median follow-up of 15 yrs

JAMA 2024; April 6

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Conclusions and relevance: In this secondary analysis of a randomized clinical trial, a single invitation for PSA screening compared with standard practice without routine screening reduced prostate cancer deaths at a median follow-up of 15 years. However, the absolute reduction in deaths was small.

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USPSTF Recommendations

- **2008:** recommended against routine use of PSA testing (Grade D) in men **ages 75 and older**
- **2012:** recommended against routine use of PSA testing (Grade D) in **all men** due to growing concerns regarding overdiagnosis and overtreatment
- **2018:** issued a draft statement revising its recommendation for men **aged 55-69 years** to informed decision making (Grade C)

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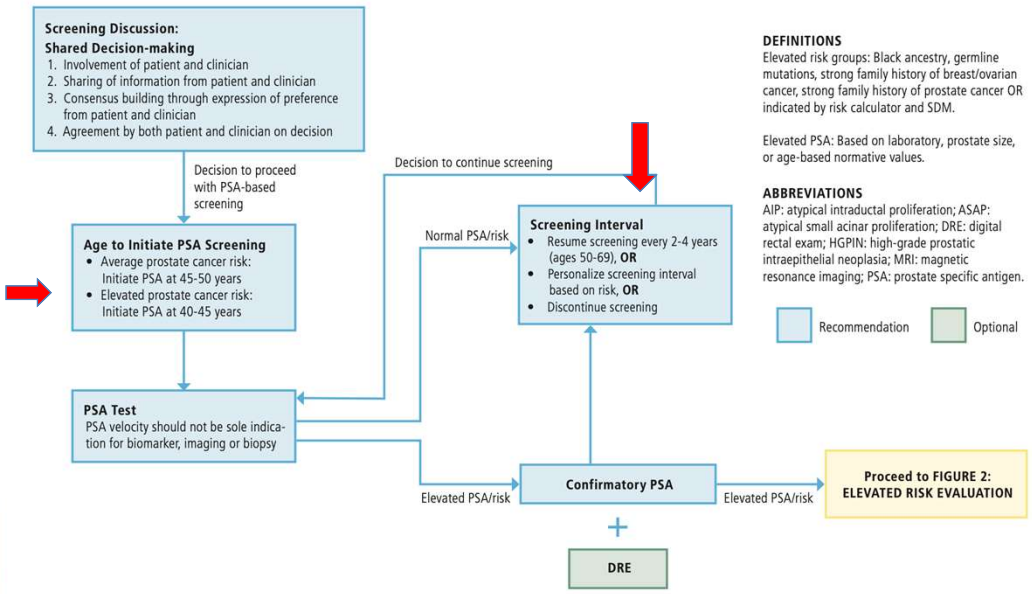
AUA Guideline Statement

FIGURE 1: INITIAL SCREENING FOR PROSTATE CANCER



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Non-PSA Biomarkers in Screening and Diagnosis

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Biomarkers

- Decrease number of unnecessary biopsies
- Limiting overdiagnosis, improve specificity
- Imperfect
  - Will miss some cancers (including aggressive cancers)
- **Not yet recommended as first line screening tests**

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Biomarkers

Urine-Based

- PCA3
- SelectMDx
- MiPS

Serum-Based

- PHI
- 4K

Tissue-Based

- OncotypeDx
- ConfirmMDx
- Prolaris
- Decipher

MRI…

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Biomarkers

- **PCA3**
  - PCA3 Score = Ratio of mRNA PCA3/PSA x10^3
  - Higher value = Higher risk of significant Pca
- **PHI**
  - Combines three isoforms of PSA (total PSA, free PSA, p2PSA)
  - Higher value = Higher risk of significant Pca
- **4KScore**
  - Combines PSA derivatives (total PSA, free PSA, intact PSA) + hK2
  - Incorporates clinical variables (age, DRE, prior biopsy)
  - Higher value = Higher risk of significant PCa

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Test	Biomarker Component	Clinical Variable	Biopsy Population
Serum			
4Kscore[175, 183, 187, 188]	PSA, fPSA, iPSA, hK2	Age, prior biopsy status, DRE (optional)	Initial biopsy[175, 183, 187] Repeat biopsy[188]
IsoPSA*[189]	All PSA isoforms	None	Not specified[189]
Proclarix[190]	THBS1, CTSD, PSA, fPSA	Age, prostate volume (optional)	Mixed[190]
PHI[169-171, 173, 183, 191-193]	p2PSA, fPSA, PSA	None	Initial biopsy[169-171, 173, 183] Repeat biopsy[191-193]
STHLM-3[20, 22, 25]	232 genetic polymorphisms (SNPs), PSA, fPSA, iPSA, hK2, MSMB, MIC1	Age, family history, previous biopsy, DRE (optional)	Mixed[20, 25]
Post-DRE Urine			
PCA3[170, 174, 176, 185, 194-197]	PCA3	Some studies add age, PSA, prostate volume	Initial biopsy[170, 174, 176, 185, 194, 195] Repeat biopsy[196, 197]
MPS[179, 195, 198, 199]	PCA3, TMPRSS2:ERG, PSA	None	Initial biopsy[179, 195, 198, 199] Repeat biopsy[198]
SelectMDx[180, 200]	HOXC6, DLX1 mRNA	Age, PSA, prostate volume, DRE	Initial biopsy[180, 200]
TMPRSS2:ERG[195]	TMPRSS2:ERG	None	Initial biopsy[195]
Urine			
ExoDx Prostate Intelliscore[181, 182, 184, 201]	PCA3, ERG, SPDEF mRNA	None	Initial biopsy[181, 182, 184] Repeat biopsy[201]
MiR Sentinel[202]	Small non-coding RNAs	None	Mixed[202]
Tissue			
Confirm MDx[203, 204]	Hypermethylation of GSTP1, APC, RASSF1	None	Repeat biopsy[203, 204]

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Multiparametric MRI

- A screening tool - useful at multiple points in **diagnosis, evaluation**, and **surveillance** of prostate cancer
- Multiple sequences (PIRADs v.2)
  - T1- and T2-weighted images
    - Water content – tumors are water poor/dark on T2W
  - Diffusion-weighted images (DWI)
    - Water diffusion – tumors are dense/dark
  - Dynamic contrast enhanced images (DCE)
    - Contrast flow – vascularity, tumors are bright

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Note: BIPARAMETRIC MRI (PRIME study EAU 2024) is non-inferior

BMJ Open 2023;**13**

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PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2

EUROPEAN UROLOGY 69 (2016) 16–40

PIRADS Score	Risk
1	Very Low
2	Low
3	Intermediate
4	High
5	Very High

Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2

EUROPEAN UROLOGY 76 (2019) 340–351

- Prostate Cancer Detection
  - Sensitivity - 0.89 (95% CI 0.86–0.92)
  - Specificity - 0.73 (95% CI 0.60–0.83)

Woo et al, European Urology, 72: 177 – 188, 2017

Table 5: Prevalence of Prostate Cancer Detection based on PI-RADS Score*

PI-RADS Score	Any Prostate Cancer (% (95%CI))	Clinically Significant Prostate Cancer (% (95%CI))
1 or 2	15% (95%CI: 8% to 22%)	7% (95%CI: 4% to 11%)
3	25% (95%CI: 22% to 29%)	11% (95%CI: 8% to 14%)
4	58% (95%CI: 53% to 63%)	37% (95%CI: 33% to 40%)
5	85% (95%CI: 80% to 90%)	70% (95%CI: 62% to 79%)

*Detection prevalence for both any prostate cancer and clinically significant prostate cancer based on the PI-RADS score when 23 identified studies were pooled using a random-effects inverse-variance method.[116-138] Due to the paucity of data using only PI-RADS version 2.1, pooled studies used version 1.0 through version 2.1.

Comparison of MR/Ultrasound Fusion–Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer

- 1003 patients
- 30% more high grade cancers
- 17% fewer low grade cancers

Table 2. Performance of Different Biopsy Approaches in the Detection of Intermediate- to High-Risk Prostate Cancer on Whole-Gland Prostatectomy Specimen

	Targeted MR/Ultrasound Fusion Biopsy	Standard Extended-Sextant Biopsy	Combined Biopsy
Sensitivity, % (95% CI)	77 (67-84)	53 (43-63)	85 (76-91)
Specificity, % (95% CI)	68 (57-78)	66 (54-76)	49 (37-60)
Negative predictive value, % (95% CI)	70 (58-80)	53 (43-63)	73 (58-84)
Positive predictive value, % (95% CI)	75 (65-83)	66 (54-76)	67 (58-75)
Accuracy, % (95% CI)	73 (70-76)	59 (55-63)	69 (65-72)
AUC (95% CI)	0.73 (0.66-0.79)	0.59 (0.52-0.67)	0.67 (0.60-0.74)
P value of comparison with targeted MR/ultrasound biopsy		.005	.04

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JAMA. 2015 Jan 27;313(4):390-7

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PROMIS Trial

- 576 Men
- MRI, TRUS-bx and Saturation transperineal bx
- **Avoid 27% of the biopsies** if negative MRI
- MRI guidance - 18% more cases of significant cancers

	MP-MRI, % (95% CI)	TRUS-biopsy, % [95% CI]	Test ratio* [95% CI]	p value
Any Gleason score 7 (≥3+4), prevalence of clinically significant cancer 308 (53%, 49–58%)				
Sensitivity test	88 (84–91)	48 (43–54)	0·55 (0·49–0·62)	p<0·0001
Specificity test	45 (39–51)	99 (97–100)	2·22 (1·94–2·53)	p<0·0001
PPV	65 (60–69)	99 (95–100)	40·8 (10·2–162·8)	p<0·0001
NPV	76 (69–82)	63 (58–67)	0·53 (0·38–0·73)	p<0·0001

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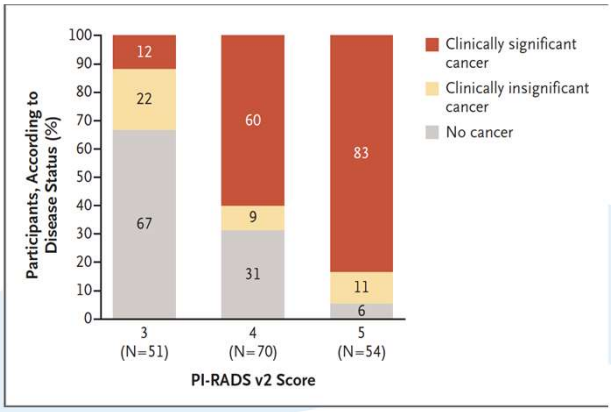
Ahmed et al, Lancet 2017; 389: 815–22

PRECISION Trial

- 500 men, randomized
  - MRI directed v. standard biopsy (10-12 cores)
- Clinically Significant Cancer (GS ≥ 3+4)
  - 95 (38%) in the MRI targeted group
  - 64 (26%) in the standard biopsy group
- Clinically Indolent Cancer
  - 23 (9%) in the MRI groups
  - 55 (22%) in the standard biopsy group
- 71 **(28%)** in MRI group could **avoid a biopsy**



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V Kasivisvanathan et al. N Engl J Med 2018;378:1767-1777.

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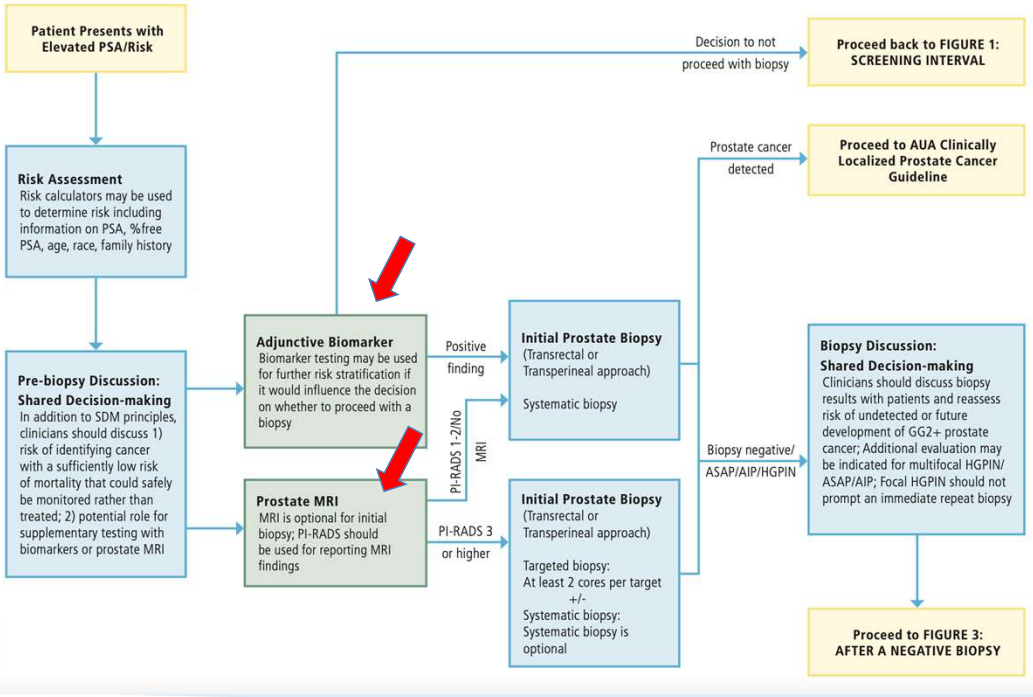
FIGURE 2: ELEVATED RISK EVALUATION



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Biopsy Techniques

- Transrectal
  - Sextant, 12-core, saturation; Risk of infection
- Transperineal
  - Very low infection risk; ? higher bleeding risk; similar cancer detection
- MRI-Guided
  - Cognitive fusion, in-bore, **MRI-US Fusion**

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Biopsy

Initial Prostate Biopsy
(Transrectal or Transperineal approach)

Systematic biopsy

Initial Prostate Biopsy
(Transrectal or Transperineal approach)

Targeted biopsy:
At least 2 cores per target
+/-
Systematic biopsy:
Systematic biopsy is optional

Repeat Prostate Biopsy
(Transrectal or Transperineal approach)

Systematic biopsy is optional in patients with prior negative biopsy and negative MRI

Repeat Prostate Biopsy
(Transrectal or Transperineal approach)

Targeted biopsy:
At least 2 cores per target
+/-
Systematic biopsy:
Systematic biopsy is optional

For biopsy-naïve patients who have a suspicious lesion on MRI, clinicians should perform targeted biopsies of the suspicious lesion and may also perform a systematic template biopsy. (*Moderate Recommendation [targeted biopsies]/Conditional Recommendation [systematic template biopsy]; Evidence Level: Grade C*)

For patients with both an absence of suspicious findings on MRI and an elevated risk for GG2+ prostate cancer, clinicians should proceed with a systematic biopsy. (*Moderate Recommendation; Evidence Level: Grade C*)

Clinicians may use either a transrectal or transperineal biopsy route when performing a biopsy. (*Conditional Recommendation; Evidence Level: Grade C*)

Risk Assessment

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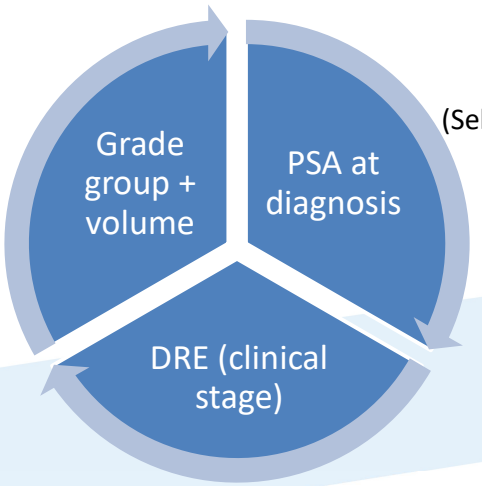
Risk Assessment



(Selective use of tissue based genomic biomarkers; PSA density)

(mpMRI)

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Gleason Grading

- **Biopsy** - Grading by individual needle core
  - Most common histologic patterns
  - Length of core; % involved
- **Surgery** – Grading for entire gland
  - Most common histologic patterns
  - Report a tertiary pattern
  - Volume of cancer, Margin status, EPE
  - Upgrade or downgrade biopsy data due to better sample

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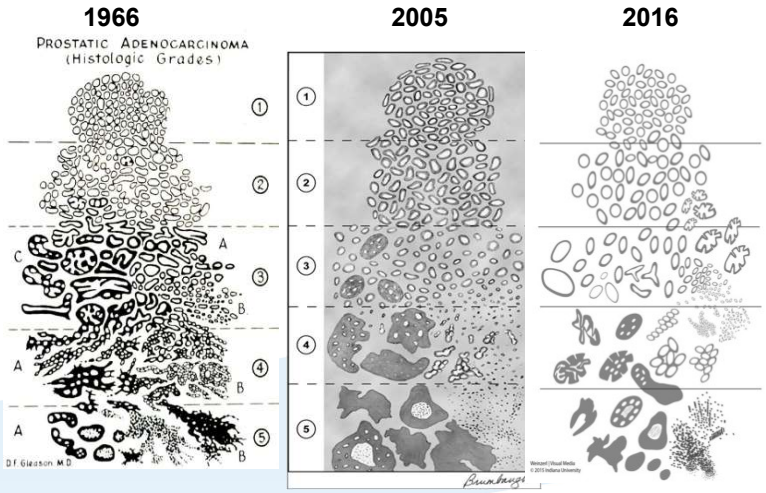
Gleason Grading – Pattern Based



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Grade Group System

- Renaming Grade Group 1 Prostate "Cancer" From a Pathology Perspective: A Call for Multidisciplinary Discussion → ?

Gladell P. Paner, MD,† Ming Zhou, MD, PhD,‡ Jeffry P. Simko, MD, PhD,§ Scott E. Eggener, MD,† and Theodorus van der Kwast, MD, PhD‖*

- Gleason 3+4 — Group 2
- Gleason 4+3 — Group 3
- Gleason 8 — Group 4
- Gleason 9-10 — Group 5

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Risk Stratification

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Table 2: Prostate Cancer Risk Stratification

	AUA Risk Category	NCCN Risk Category
Very Low	—	PSA ≤ 10 ng/mL, Gleason score ≤ 6, clinical stageT1c, < 3 positive biopsy cores, ≤ 50% in each core, and PSA density < 0.15 ng/mL/g
Low	PSA ≤ 10 ng/mL, Gleason score ≤ 6, and clinical stageT1c or T2a	PSA < 10 ng/mL, Gleason score ≤ 6, and clinical stageT1-T2a
Intermediate	PSA > 10-20ng/mL or Gleason score 7, or clinical stage T2b	PSA 10-20 ng/mL, Gleason score 7, or clinical stageT2b-T2c
High	PSA > 20ng/mL or Gleason score 8-10, or clinical stage ≥T2c	PSA > 20ng/mL or Gleason score 8-10, or clinical stage T3a
Very High	—	Clinical stage T3b-T4

View Image

Heterogeneity exists between risk schema

Don't forget about risk calculators and nomograms

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Table 4: Select Risk Calculators with Risk Factors and Risk Factors Evaluated

	PCPT V2 (https://riskcalc.org/PCPTRC/)	Chun (There is no publicly available online calculator for Chun)	ERSPC (https://www.prostatecancer-riskcalculator.com)	PBCG (https://riskcalc.org/PBCG/)
Race	x			x
Family history of prostate cancer	x			x
Age	x	x	x	x
PSA	x	x	x	x
Free PSA %	x	x		
DRE	x	x	x	x
Prior biopsy	x		x	x
Urinary PCA3	x	x		
TMPRSS2:ERG fusion	x			
Prostate volume		x	x	
Sampling density		x		
MRI – PI-RADS score			x	

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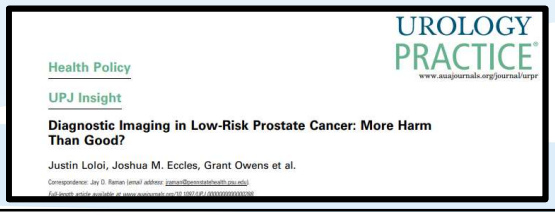
Risk Stratification - Imaging

- Very low, low risk – not indicated
- Intermediate risk – Bone scan if PSA > 10 + cT2; pelvic/abdominal if predicted LNs >10%
- High risk – Bone scan; pelvic/abdominal if predicted LNs > 10%
  - **NM PET imaging**


UROLOGY PRACTICE
www.auajournals.org/journal/urpr
Health Policy
UPJ Insight
Diagnostic Imaging in Low-Risk Prostate Cancer: More Harm Than Good?
Justin Loloi, Joshua M. Eccles, Grant Owens et al.

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Risk Stratification - Genomic Testing

- **Prolaris**
  - Cell cycle progression signature (31 genes)
- **Oncotype Dx**
  - Multipathway signatures (17 genes)
- **Decipher**
  - 22 gene panel; score range 0 - 1

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TABLE 4: Indications for Germline Testing in Patients with Localized Prostate Cancer*	
Strong family history of prostate cancer	Examples: first-degree relative or multiple second-degree relatives diagnosed with Grade Group 2 or higher prostate cancer, particularly at early age (< 60 years), particularly if metastatic or lethal
Strong personal or family history of related cancers	Examples: breast, colorectal, ovarian, pancreatic, upper tract urothelial carcinoma
Known family history of familial cancer risk mutation	Examples: *BRCA1, BRCA2, ATM*, Lynch-syndrome associated genes
Ashkenazi Jewish ancestry	Particularly in patients with Grade Group 2 or higher disease
Adverse tumor characteristics	Examples: High-risk disease; intermediate-risk disease with intraductal or cribriform morphology
*The Panel recognizes that this list is not exhaustive.	

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TREATMENT OF LOCALIZED CANCER
(RISK-BASED MANAGEMENT)

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Clinically Localized Prostate Cancer: AUA/ASTRO Guideline

Limited Life-Expectancy	Low risk	Favorable intermediate risk	Unfavorable intermediate risk	High risk
No symptoms: Watchful waiting Symptoms: Palliative ADT	Active Surveillance	Active surveillance Radiation Radical prostatectomy	Radiation + ADT Radical prostatectomy	Radiation + ADT Radical prostatectomy NOT ablation

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J Urol. 2022;208(1):10-33.

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Who to treat and with what?

- Patient Factors + Disease Parameters + Treatment Side Effects
- ***Treatment prevents local progression, metastasis and prostate cancer death in intermediate and high-risk disease***

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PRINCIPLES OF MANAGEMENT

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Watchful Waiting

- Asymptomatic patients with limited life expectancy
- Limited follow-up
- Palliative therapy for symptoms/advanced disease
- No plan for definitive therapy

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Competing Risk Analysis

SEER Connecticut Registry

- 767 men diagnosed with localized disease
  - 138/767 (18%) Grade I
  - 549/767 (72%) Grade II
  - 77/767 (10%) Grade III
- Age 55-74
- Analyzed cohort for cumulative mortality from prostate cancer and other causes

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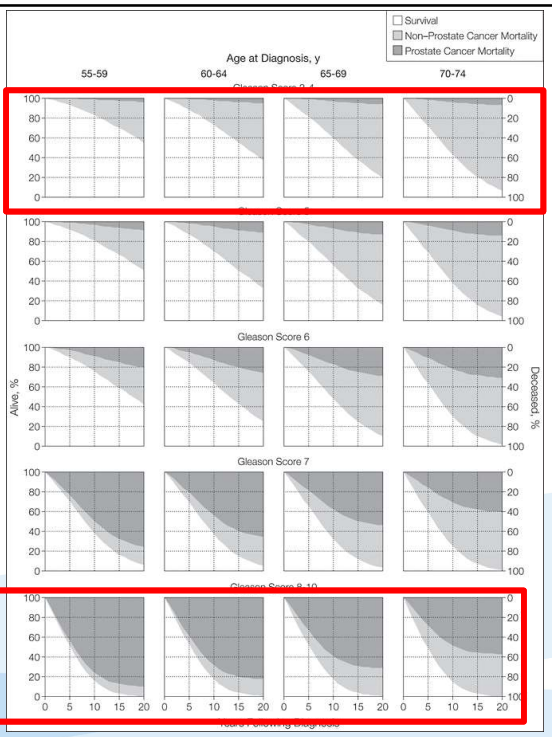
Albertsen PC. JAMA 2005;293:2095-2101



Annual mortality rate from prostate cancer appears stable 15 years from diagnosis.

Does not support aggressive treatment for localized low-grade prostate cancer

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Albertsen PC. JAMA 2005;293:2095-2101

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Active Surveillance

- Serial monitoring – PSA, DRE, Biopsy
- MRI augments risk stratification
- Limit overtreatment and over detection
- Variable inclusion criteria and follow up
- Treatment if PSA increasing rapidly or biopsy shows more aggressive cancer

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Goal: prevent or delay side effects of treatment without missing the window of opportunity for cure

Active Surveillance - Outcomes

- Between 50-68% of those eligible for AS may safely avoid treatment for >10 years
  - Reduced risk of unnecessary treatment of small, indolent ca
  - maintained QOL
- Between 32% - 50% of patients on AS will undergo treatment by 10 years
  - Delays do not seem to impact cure rate
  - Very low risk (<0.5%) of cancer progression to regional or metastatic

IR pts with higher rates of metastasis

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NCCN v. 1.2023

Klotz et al, JCO 33:272-277, 2015

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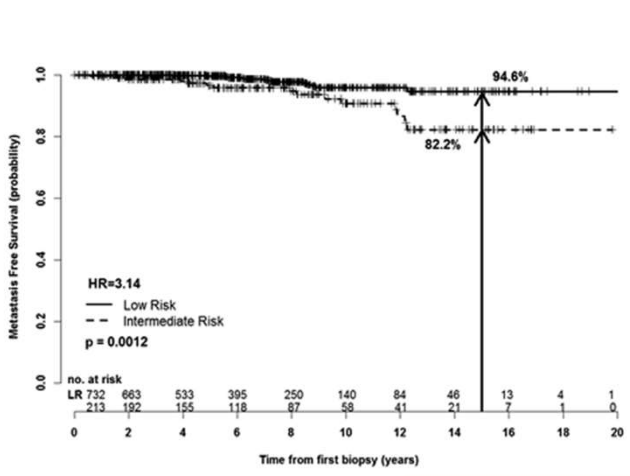

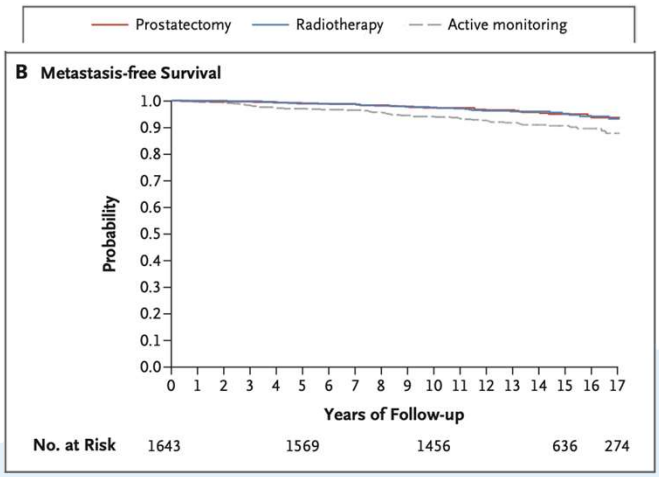

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J Urol 2016;196:1651

N Engl J Med 2023;388:17

Radiation Modalities

- External Beam (EBRT)
  - Conventional vs. Hypofractionated
    - Stereotactic Body (SBRT)
  - 3D-Conformal (3DCRT)
  - Intensity Modulated (IMRT)
- Proton Beam
- Brachytherapy
  - Low dose vs. High dose

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Radiation Side Effects

- Urinary symptoms
  - Urgency, obstruction, hematuria
- Bowel symptoms
  - Rectal toxicity
- Erectile dysfunction *(impact of concurrent ADT)*
- Secondary malignancy (<1%)

RP associated with greater decrease in urinary and sexual function than EBRT or AS

Barocas, JAMA 2017;317:1126-1140

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The PSA "Bounce" Effect

- Generally in scenarios without ADT
- Up to 5 years after radiation **(12 – 18 mos)**
- Inflammation vs. recurrent cancer

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Radiation – Low Risk PCa

- EBRT (IMRT, hypofractionated)
  - 79.2 Gy (75 – 79 Gy)
  - 10-yr bFRS - 93%
- Brachytherapy
  - LDR > HDR; Monotherapy

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. e25–e31, 2012

Radiation – Intermediate Risk

- EBRT (75 -81 Gy) +/- short course ADT (4-6 mos)
  - EBRT 10 yr PSA control: 70% for intermediate risk
- Brachytherapy monotherapy
- Brachytherapy + EBRT +/- ADT

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Zietman et al, JCO 2010

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Radiation – High Risk

- EBRT (75 -81 Gy) + long course ADT **(18-36 mos)**
- Brachytherapy + EBRT + ADT
  - Increased toxicity with EBRT + brachy
- Ascende-RT Trial
  - G3+ toxicity higher in EBRT+BT at every time point
  - Long Term Gr 3+ GU (Severe toxicity)
    - 2.2% in EBRT vs 8.6% EBRT+Brachy

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Morris et al, Int J Radiat Oncol Biol Phys 98:275-285, 2017
Bolla et al, Lancet Oncol 2010; 11: 1066–73

Radiation Therapy *(brief conclusions)*

- **Low or Favorable Intermediate Risk**
  - Monotherapy (EBRT or Brachy)
- **Unfavorable Intermediate Risk**
  - Multimodality therapy
  - EBRT plus 4-6 months ADT +/- brachy boost
- **High Risk**
  - Multimodality therapy
  - EBRT with 18-36 months ADT +/- brachy boost

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Adding ADT to Radiation

- Why?
  - Reduce tumor volume, eradicate microscopic dz away from prostate, downregulation of DNA repair/enhanced apoptosis
- Duration:
  - Unfavorable IR → 4-6 months
  - High risk →18 – 36 monts

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Consider adding abiraterone for very high risk and cN+ patients

Surgery

- Perform nerve sparing when oncologically appropriate
- Lymphadenectomy → staging information; no consistent data on MFS, CSS, OS
  - Use nomograms; extended > limited
  - If LN+ and PSA -, observation or adjuvant XRT ok
- Do not routinely offer adjuvant XRT post-RP
- Do not routinely offer neoadjuvant ADT
  - Decreased positive margins, improved PSA

(Gleave ME, J Urol 2001)

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Treatment vs. Conservative Management

Trial	Cohort	Intervention	Outcome
SPCG 4	695 Mostly Int-risk and High-risk Enrolled 1989-99 Followed for 23.2 yrs	Surgery (RP) vs. Watchful Waiting (WW)	- Improved overall and disease specific survival in RP group compared to observation
PIVOT	731 Mixed risk Older, infirm VA pts Enrolled 1994-2002 Followed for median 12.7 yrs. ***Underpowered**	Surgery (RP) vs. Watchful Waiting (WW)	- **No difference** in overall or disease specific survival in RP group compared to observation - BUT surgery reduced the risk of metastases (19.8% vs 8.1%; p=0.0001) among men with Gleason score ≥ 7 tumors.
PROTECT	1643 Mostly Low-risk Enrolled 1999-2009 Followed for 10 yrs ***Few events**	Surgery (RP) vs. Radiation (RT) vs. Active Surveillance (AS)	- **No differences** in overall or disease specific survival - RP and RT → better than AS for Clinical progression (p<0.001) and Metastatic disease (p=0.004)

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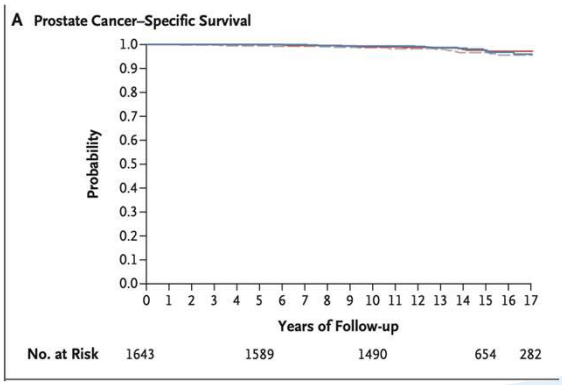
Adapted slide from Dan Barocas

Bill-Axelson et al. NEJM, 2014
Wilt et al. NEJM 2017
Hamdy et al. NEJM 2016

Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer



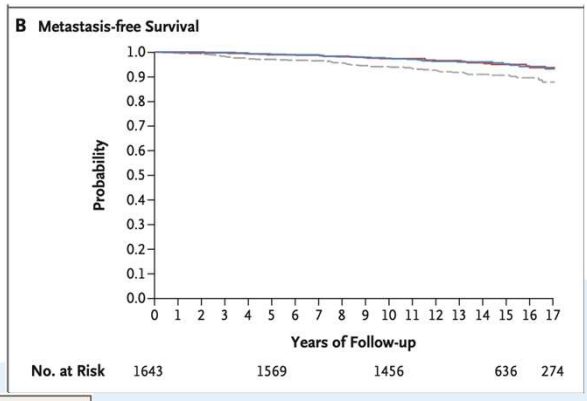


Table 2. Prostate Cancer Survival.*

Trial Group	Survival (95% CI)	
	At 10 Yr	At 15 Yr
	percentage of patients	
Active monitoring	98.7 (97.2–99.4)	96.6 (94.4–98.0)
Prostatectomy	99.0 (97.7–99.6)	97.2 (94.8–98.5)
Radiotherapy	99.4 (98.2–99.8)	97.7 (95.5–98.8)

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N Engl J Med. 2023;388:1547

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Surgery *(brief take home)*

- Better than watchful waiting for intermediate/high risk disease
- Predominately in
  - Younger Patients
  - Healthier patients
  - Longer life expectancy
- Decreases risk of metastatic disease and secondary treatments

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DEFINITIONS

- PSA persistence vs. PSA recurrence
- Prostatectomy
  - Undetectable PSA after surgery with a subsequent increases on 2 or more determinations above threshold of 0.2 ng/mL
- Radiation
  - RTOG-ASTRO Phoenix Consensus: PSA increase by $\geq$ 2 ng/mL above the nadir
  - Consider earlier evaluation in candidates for salvage local therapy (young, healthy)

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Imaging for Recurrence

- Bone Scan
- CT Scan
- MRI
- Plain film
- PET
  - F-18 Fluciclovine
  - F-18 NaF (bone)
  - Ga-68 PSMA
  - Piflufolastat F18 PSMA

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Adjuvant vs. Salvage XRT following RP

- Within 10 years of RP 15 – 40% with have PSA recurrence
- Adjuvant: RT with undetectable PSA in patients with high-risk features (pT3, PSM)
  - Genomic classifiers
- Salvage: detectable PSA

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Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data

Lancet. 2020 Sep 28:S0140-6736(20)31952-8

Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial

Lancet Oncol. 2020 Oct;21(10):1331-1340

Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial

Lancet Oncol. 2020 Oct;21(10):1341-1352

No difference in event-free survival
More GU toxicity and ED with adjuvant

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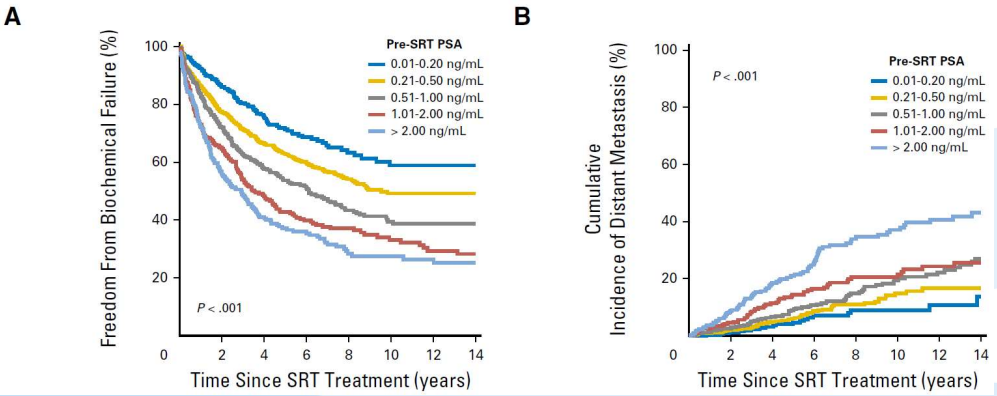
Salvage XRT

Multi-institutional Analysis of 2,460 pts with PSA recurrence after RRP
10 Academic Centers
Underwent salvage XRT at variety of PSA levels

Start salvage earlier !



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Tendulkar et al JCO, 2016

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Salvage RT + ADT

GETUG 16

- 743 Patients with PSA failure after RRP
  - PSA between 0.2 and 2 ng/mL
- 66 Gy RT vs 66 Gy RT plus 6 months ADT
- Improved ***progression free survival***

Carrie et al Lancet Oncol, 17: 747–56, 2016

RTOG 9601

- 760 Men with PSA failure after RRP
- RT vs RT plus 150 bicalutamide
- Improved ***overall survival***

Shipley et al , NEJM, 376:417-28, 2017

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Salvage Therapy Options

SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

What was primary therapy?

- Radical prostatectomy (22 statements)
- Radiation therapy (2 statements)
- Focal therapy (1 statement)

Regional recurrence (3 statements)

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A 62 y/o M with cT1c, PSA 8.2, GG 2 prostate cancer is treated with external beam radiotherapy. He tolerates this well, although does have transient increase in his lower urinary tract symptoms. His PSA nadirs at 0.5 but is noted to be 7.1 six months after he completes XRT, confirmed on repeat lab evaluation.

The likely cause of this elevation is:

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ADVANCED PROSTATE CANCER

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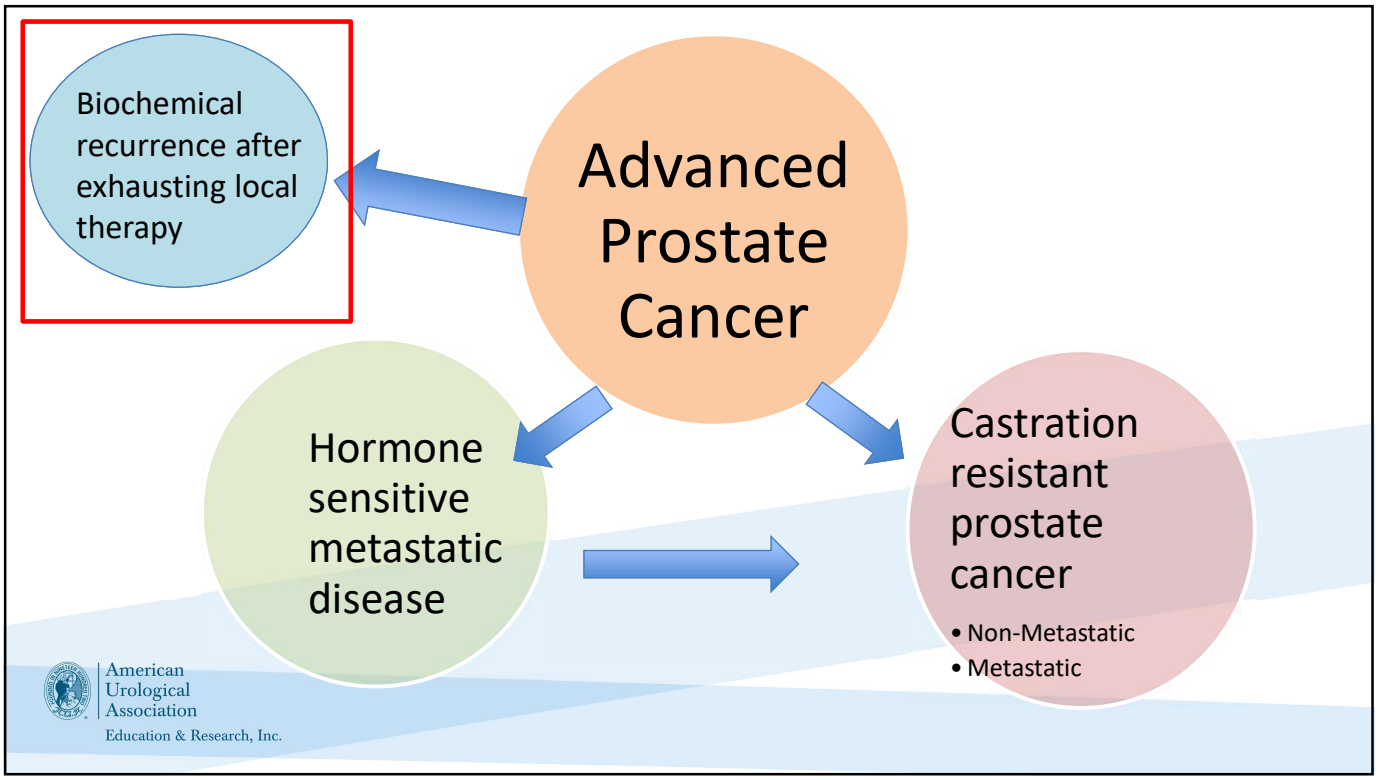

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BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE

Prognosis

Clinicians SHOULD

Inform patients regarding the risk of developing metastatic disease and follow patients with serial PSA measurements and clinical evaluation

Perform periodic staging evaluations consisting of cross sectional imaging (CT,MRI) and technetium bone scan in patients who are at higher risk for development of metastases

Clinicians MAY

Utilize novel PET-CT scans as an alternative to or in the setting of negative conventional imaging

Consider radiographic assessments based on overall PSA and PSA kinetics

Treatment

Clinicians SHOULD

Offer observation or clinical trial enrollment

Clinicians SHOULD NOT

Routinely initiate ADT

Clinicians MAY

Offer intermittent ADT in lieu of continuous ADT if ADT is initiated in the absence of metastatic disease

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TREATMENT AND MONITORING FOR PROGRESSIVE M0 CASTRATION-SENSITIVE PROSTATE CANCER (CSPC) AFTER MAXIMAL PELVIC THERAPY

Progressive M0 CSPC after maximal pelvic therapy →

Monitoring (preferred)

or

ADT[c,z,oo]

or

Useful in certain circumstances:
- Enzalutamide ± leuprolide[c,z,oo,pp]
- Apalutamide + ADT[c,z,oo,qq] (category 2B)

→ Monitoring:
- Physical examination + PSA every 3–6 mo
- Imaging for symptoms or increasing PSA[f]

→ Progression[f,ff]

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

N Eng J Med 2023;389:1453

PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

JCO 2024;42:114

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Hormonal Ablation

- **Goal:** Lower systemic testosterone
  - Induces apoptosis in prostate cancer cells
- Charles Huggins (1941)
- Medical castration
  - GnHR agonist/antagonist therapy
- Surgical castration bilateral orchiectomy

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Hormonal Therapy

Class	Site	MOA	Drug
GnRH Agonist	Pituitary	Stimulates release of LH	Goserelin Leuprolide
GnRH Antagonist	Pituitary	Blocks release of GnRH	Abarelix Degarelix Relugolix
Adrenal	Adrenal	Decreases androgen production	Abiraterone Ketoconazole
1st Gen Anti-androgen	Prostate/CaP	Blocks binding at the AR	Bicalutamide Flutamide Nilutamide
2nd Gen Anti-androgen	Prostate/Cap	Blocks AR, limits nuclear translocation + transcription	Enzalutamide Apalutamide Darolutamide

ADT - Side Effects

- Hot flashes
- Osteoporosis
- Fatigue
- Loss of libido, erectile dysfunction
- Cognitive dysfunction
- Loss of muscle, increased adiposity
- Metabolic syndrome
- Cardiovascular disease

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Intermittent ADT

- **Non-metastatic**, failed primary or salvage RT
  - No difference in OS but much better quality of life
    - Crook et al NEJM 2012
- **Metastatic**, hormone sensitive
  - Could not prove superiority or equivalence
    - Hussain et al NEJM 2013
  - Several meta-analyses reported **no difference in survival between iADT and cADT**

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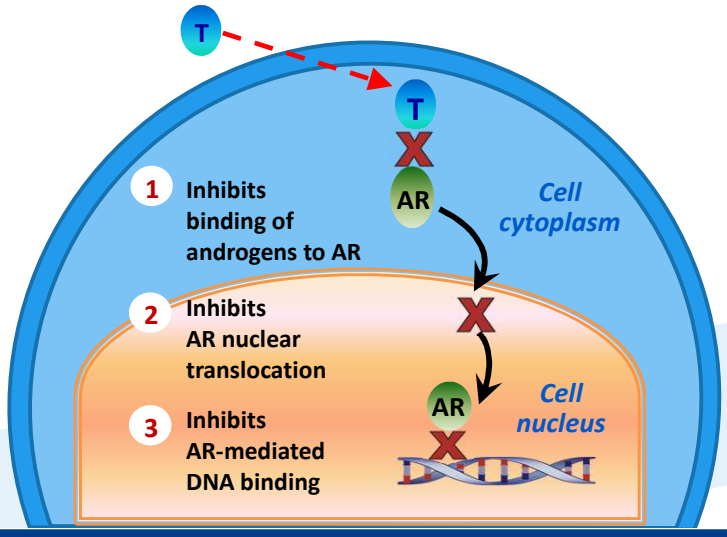
Androgen Receptor Blockade



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Enzalutamide, Apalutamide, Darolutamide, Bicalutamide, Flutamide

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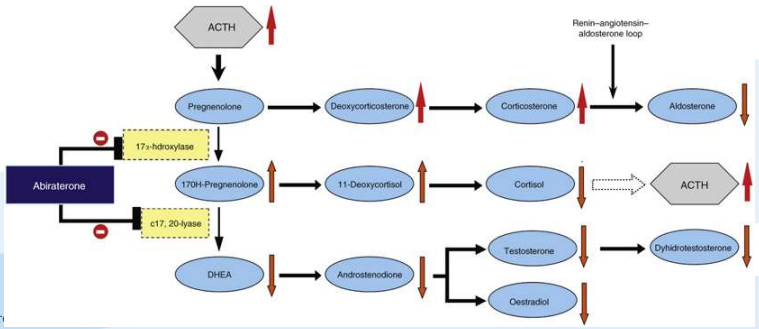
Abiraterone

- HTN, hypokalemia, fatigue, steroid induced hyperglycemia
- Avoid is those who cannot tolerate steroids (brittle DM, gastric ulcers, rapidly progressive)
- Avoid in liver disease, cardiac disease



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DeBono J, et al. Br J Canc.2009; 671-5.

Enzalutamide

- HTN, fatigue, constipation/diarrhea, hot flash, falls; **Rare: seizure**
  - Relative contraindication in seizure history
  - Avoid in older patients or those with significant fatigue

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Hoffman-Censits and Kelly, Clin Cancer Res 2013

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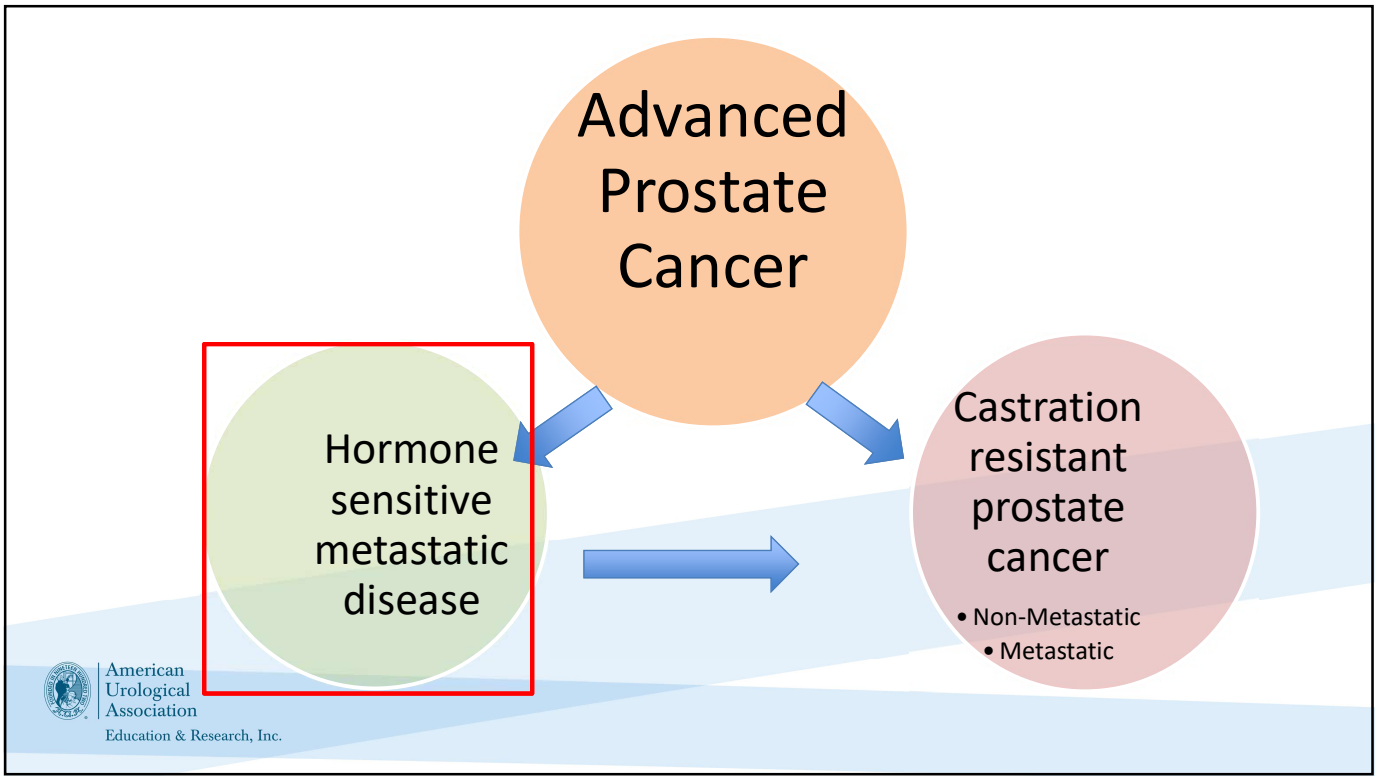

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Metastatic Disease (M1)

Volume of dz
Timing of mets

Hormone Sensitive M1

- ADT +
  - Abiraterone/Prednisone
  - Apalutamide
  - Enzalutamide
  - Darolutamide
  - Docetaxel + Abi/pred
  - Docetaxel + Darolutamide
  - EBRT in low volume M1

Castration Resistant M1

- ADT +
  - Abiraterone/Prednisone
  - Docetaxel
  - Enzalutamide
  - Radium 223
  - Mitoxantrone
  - Sipuleucel-T
  - PARP Inhibitors
  - Pembrolizumab

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ADT [illegible] therapy

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CHAARTED	ADT + Docetaxel	Improved OS	High volume disease → greater benefit
STAMPEDE	ADT + Docetaxel ADT + Abiraterone ADT + prostate EBRT	Improved OS	No difference with doce in high vs. low volume; EBRT for low volume *Presence of visceral metastases or >=4 bony lesions with at least 1 outside spine or pelvis
PEACE-1	ADT + Doce + Abi	Improved rPFS, OS	High volume, de novo; Modest increase in toxicity (HTN)
ARASENS	ADT + Doce+Daro	Improved OS, time to CRPC, time to pain progression	No significant difference in toxicity
LATITUDE	ADT + Abiraterone	Improved rPRS, OS	Needed 2/3 high risk features** Gleason score 8–10, ≥3 bone metastases, and visceral metastases
ENZAMET **ARCHES**	ADT + Enzalutamide	Improved OS Improved rPRS	More AEs in enza group (fatigue, seizures, HTN)
TITAN	ADT + Apalutamide	Improved rPFS, OS	More AEs in apa group (Rash)
ARANOTE	ADT + Darolutamide	Improved rPFS	Favorable safety profile

Metastatic Castration Sensitive

Take Home Message

M1 HSPC → ADT +

Abiraterone
Enzalutamide
Apalutamide
Darolutamide
Docetaxel + Abiraterone
Docetaxel + Darolutamide
EBRT to 1º tumor (low volume)

M1 HSPC ✗→ **ADT Alone**

Consider disease volume and performance status

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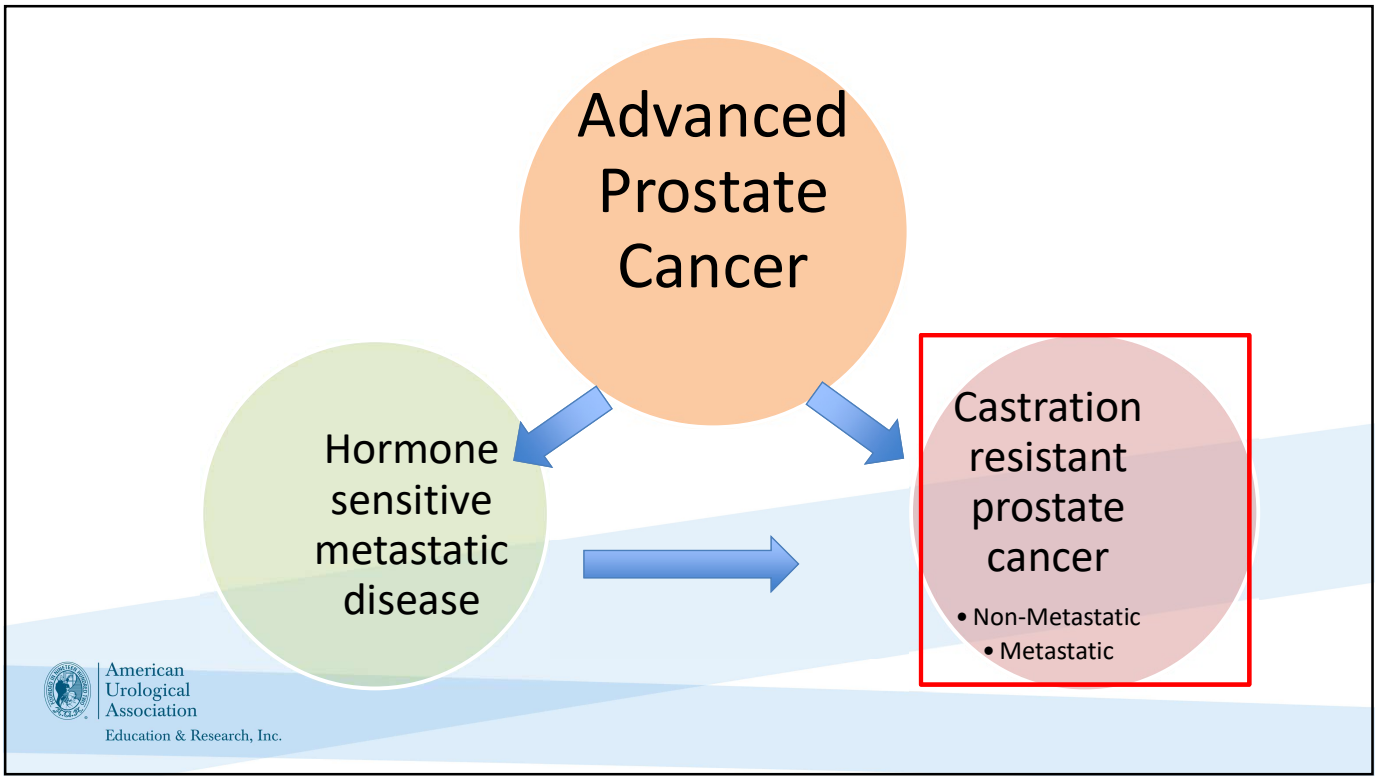

Castration Resistant Prostate Cancer (CRPC)

- Non-metastatic (M0) or metastatic (M1)
- Definitions (PSA working group)
  - Testosterone < 50ng/dL *and*
  - PSA greater than 2 ng/ml and rising
  - New radiographic or clinical metastasis on ADT *or*

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M0 CRPC

- Men with M0 CRPC and a rapidly rising PSA ***(<8-10 mos)*** are at high risk for metastases
  - Major cause of morbidity and mortality
- Three large phase III trials
  - Enzalutamide, Apalutamide, Darolutamide
- ***Preventing metastases = a major goal; MFS is a surrogate goal!***

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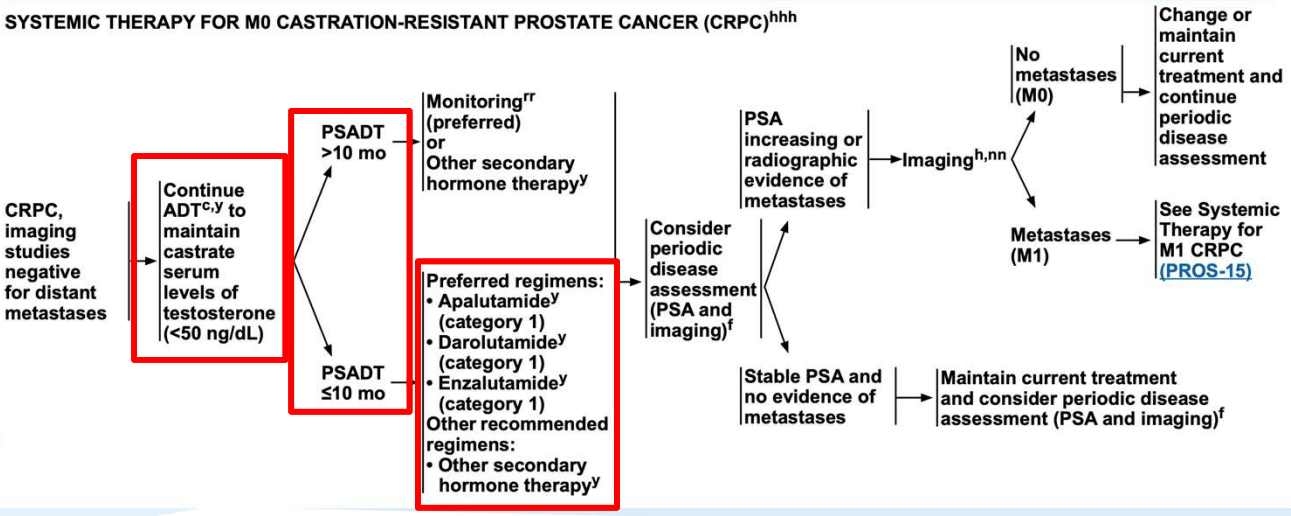
M0 CRPC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)[hhh]



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M0

- SPARTAN → Apalutamide
- PROSPER → Enzalutamide
- ARAMIS → Darolutamide

- Mature data show OS benefit too!

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Adverse Events

- **Apalutamide**: rash (24% vs. 5.5%), fracture (11% vs. 6.5%), hypothyroidism (8% vs. 2%).
- **Enzalutamide**: falls and nonpathologic fractures (17% vs. 8%), hypertension (12% vs. 5%), major adverse cardiovascular events (5% vs. 3%), mental impairment disorders (5% vs. 2%).
- **Darolutamide**: fatigue (12.1% vs. 8.7%), pain in an extremity (5.8% vs. 3.2%), rash (2.9% vs. 0.9%).

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N ENGL J MED 378;15 NEJM.ORG APRIL 12, 2018
N ENGL J MED 378;26 NEJM.ORG JUNE 28, 2018
N ENGL J MED 380;13 NEJM.ORG MARCH 28, 2019

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NON-METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

Obtain serial PSA measurements at three to six month intervals and calculate PSA doubling time starting at time of development of castration-resistance

Assess for development of metastatic disease using conventional imaging at intervals of six to twelve months

Treatment

Clinicians SHOULD

Offer apalutamide, darolutamide, or enzalutamide with continued ADT to patients at high risk for developing metastatic disease

Clinicians MAY

Recommend observation with continued ADT, particularly for those at lower risk for developing metastatic disease

Clinicians SHOULD NOT

Offer systemic chemotherapy or immunotherapy outside the context of a clinical trial

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M1 CRPC

No prior docetaxel/no prior novel hormone therapy[iii]	Progression on prior novel hormone therapy/no prior docetaxel[iii]
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1 if no visceral metastases) ▸ Docetaxel[ddd] (category 1) ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Docetaxel (category 1)[ddd] ▸ Olaparib for *BRCA* mutation[lll] (category 1) ▸ Rucaparib for *BRCA* mutation[lll] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[lll] ▸ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[z]
Progression on prior docetaxel/no prior novel hormone therapy[iii]	**Progression on prior docetaxel and a novel hormone therapy[iii]**
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1) ▸ Cabazitaxel[ddd] ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Niraparib/abiraterone[z, lll,mmm] for *BRCA* mutation ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Cabazitaxel[ddd] (category 1) ▸ Docetaxel rechallenge[ddd] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[ppp] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Olaparib for HRR mutation[lll] (category 1 for *BRCA* mutation) ▸ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb[ddd] ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]

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What to do??

- Data to inform the optimal sequence for delivery of these agents in patients with metastatic CRPC is limited
- Choice of therapy is based largely on clinical considerations, which include patient preferences, ***prior treatment***, presence or absence of ***visceral disease***, ***symptoms***, and potential side effects.

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M1 CRPC

ADT + Abiraterone; ADT + Enzalutamide

- **COU-AA-301** – ADT + Abiraterone
  - Prior docetaxel
- **COU-AA-302** – ADT + Abiraterone
  - No prior docetaxel
  - chemotherapy naïve
- **AFFIRM** – ADT + Enzalutamide
  - Prior docetaxel
- **PREVAIL** – ADT + Enzalutamide
  - No prior docetaxel
  - chemotherapy naive

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M1 CRPC

Chemotherapy

- **Docetaxel** (TAX 327, SWOG 9916)
- **Cabazitaxel** (TROPIC, FIRSTANA)
  - FDA approved after docetaxel
- **Mitoxantrone** (CALGB 9182)
  - Currently limited role in mCRPC

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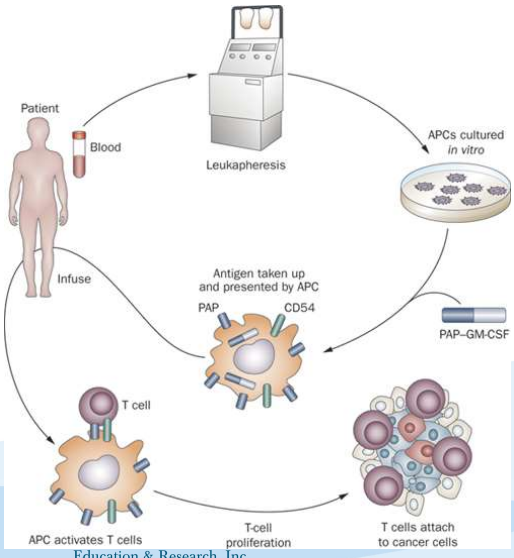
M1 CRPC
Immunotherapy

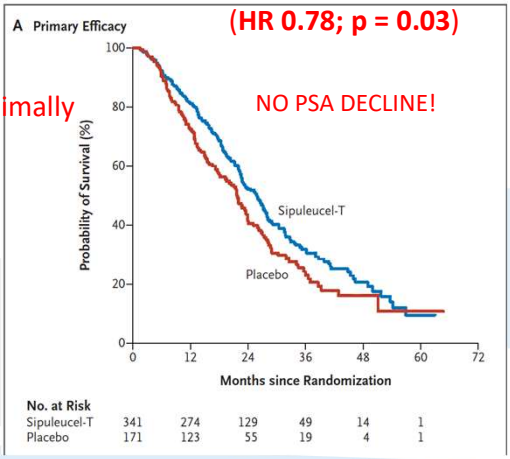
Sipuleucel-T
IMPACT



*Asymptomatic, minimally symptomatic
No liver mets
ECOG 0-1

Median OS 25.8 mos vs 21.7 mos
(**HR 0.78; p = 0.03**)

NO PSA DECLINE!



Kantoff et al, NEJM 2010

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Di Lorenzo, G. et al. Nat Rev Clin Onc. 2011

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Genetic Testing

Germline (inherited)

- Regional or metastatic
- High risk or very high risk
- FHx of high risk germline mutation
- A positive FHx of cancer
- Intraductal, cribriform

Somatic (acquired)

- Metastatic
- Regional (consider)

BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, HOXB13

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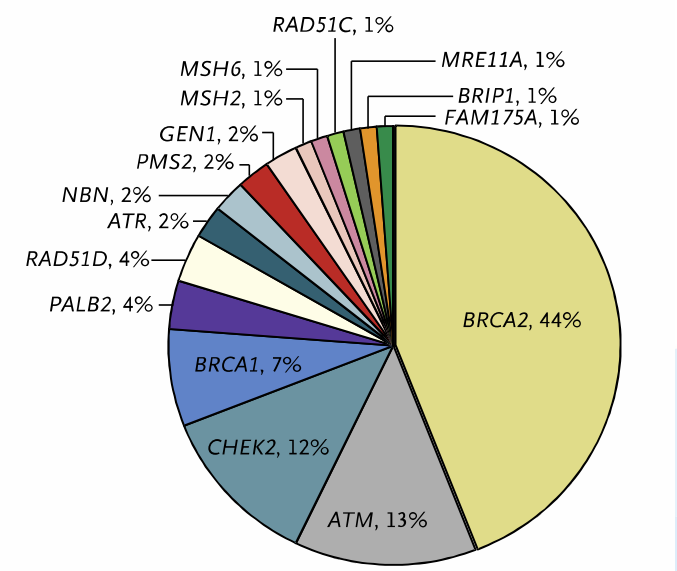
Prostate Cancer: Genetics



ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

- 692 men with metastatic PCA
- Sequenced their genome
- 84 germline DNA-repair gene mutations
- **82 men (11.8%)**
- Mutations were found in 16 genes

Pritchard et al N Engl J Med. 2016;375(5):443-453.

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PARP Inhibitors – Mechanism of Action

- poly-ADP ribose polymerase (PARP) repairs DNA damage
- PARPi are oral agents that block the repair mechanisms
- In the setting of certain mutations → "***Synthetic lethality***"
  - Block the dependent pathway
  - Cancer cell death

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PARP Inhibitors

Study	Drug	Patients	Endpoints
NCT01576172	Abi + PBO vs. Abi + veliparib	2nd Line mCRPC, unselected	PSA50, mPRS, mRR
NCT01972217	Abi + Olaparib vs. Abi + PBO	2nd Line mCRPC, unselected	rPFS, mOS, mPFS, mDOR
PROFOUND	Olaparib vs. ARPI	2nd Line mCRPC A: BRCA1/2, ATM; B:12 HRR alterations	rPFS, mOS, ORR
TRITON 3	Rucaparib vs. Physicians Choice	2nd Line mCRPC BRCA1/2, ATM	rPFS, OS, ORR, time to pain prog
TALAPRO 2	Talazoparib + Enza vs. PBO + Enza	1st Line mCRPC	rPFS, OS, ORR, PFS2, time to PSA prog, time to chemo
MAGNITUDE	Niraparib + Abi vs. PBO + Abi	1st Line mCRPC HRR+; HRR-	rPFS, OS, ORR, time to PSA prog, time to chemo
PROPEL	Olaparib + Abi vs. PBO + Abi	1st Line mCRPC	rPFS, mOS, ORR, PFS2, Time to sub therapy

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Level 1 Evidence in M1 CRPC

Clinical Trial(s)	Intervention	Control	Comments
COU-AA-301 **COU-AA-302**	Abiraterone + ADT (Prior docetaxel) Abiraterone + ADT (No docetaxel)	ADT + PBO	OS; 2º PFS
AFFIRM **PREVAIL**	Enzalutamide + ADT (Prior docetaxel) Enzalutamide + ADT (No docetaxel)	ADT + PBO	OS
TAX 327 **SWOG 9916**	Docetaxel + ADT Docetaxel + estramustine	Mitoxantrone + pred Mitoxantrone + pred	OS OS
TROPIC **FIRSTANA**	Cabazitaxel Cabazitaxel	Mitoxantrone + pred Docetaxel	OS (post chemo) OS (pre chemo)
	Mitoxantrone + pred	Pred	No OS benefit – improved QOL
IMPACT	Sipuleucel-T	PBO	OS
PROFOUND **TRITON2***	Olaparib + ADT Rucaparib + ADT	Physicians Choice *(phase 2)	PFS; 2º: OS (HRRm) ORR; (BRCA)
ALSYMPCA	Radium 223	PBO	OS; time to SRE
VISION	Lutetium Lu 177	SOC	OS; PSMA PET +

Anti-PD-1 Antibody
Pembrolizumab

- Unresectable or metastatic MSI-high or mismatch repair deficient solid tumors
- Progressed on prior treatment
- No satisfactory alternatives

34. In patients with mismatch repair deficient or microsatellite instability high mCRPC, clinicians should offer pembrolizumab. (Moderate Recommendation; Evidence Level: Grade C)

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FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors

- Adult, pediatric patients
- Unresectable or metastatic
- MDI-H or dMMR solid tumors
- Progressed following prior treatment without alternative treatments
- Shared tumor biology across different tumors based on ORR
- ***First time the FDA has approved a cancer treatment for an indication based on common biomarker rather than primary site of origin***

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Clin Cancer Res 2019;25:3753

METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prognosis

Clinicians SHOULD

Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status

Assess the extent of metastatic disease using conventional imaging at least annually or at intervals determined by lack of response to therapy

Offer germline and somatic tumor genetic testing

Treatment

Clinicians SHOULD

Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide

Consider prior treatment in sequencing agents and recommend therapy with an alternative mechanism of action

Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm

Treatment (cont.)

Clinicians SHOULD (cont.)

Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide

Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy

Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high CRPC

Clinicians MAY

Offer sipuleucel-T to asymptomatic/minimally symptomatic patients

Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide

Offer platinum-based chemotherapy to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy who cannot use/obtain a PARP inhibitor

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Bone Health

Clinicians SHOULD

- Discuss the risk of osteoporosis associated with ADT and assess the risk of fragility fracture
- Recommend preventative treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to patients on ADT
- Recommend preventative treatments with bisphosphonates or denosumab to patients at high fracture risk due to bone loss and recommend referral to physicians who have familiarity with the management of osteoporosis
- Prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events

Osteonecrosis of the jaw can occur with both zoledronic acid and denosumab

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Thank You
and
Good Luck!

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M1 HSPCa

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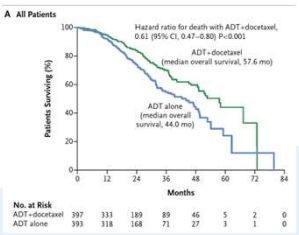
M1 Castration Sensitive (CSPC)

CHAARTED – ADT + *Docetaxel*

- 790 men with mHSPC randomized to ADT +/- docetaxel
  - Docetaxel 75mg/m^2 q3wks for 6 cycles
- Median f/u: 28.9mo
- **Median OS: 57.6 mo vs 44 mo (HR 0.61)**
- Also improved **PFS** and rate of PSA <0.2
- **Significant improvement in high-volume disease**
  - Presence of visceral metastases or >=4 bony lesions with at least 1 outside spine or pelvis



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Sweeney et al, NEJM 2015

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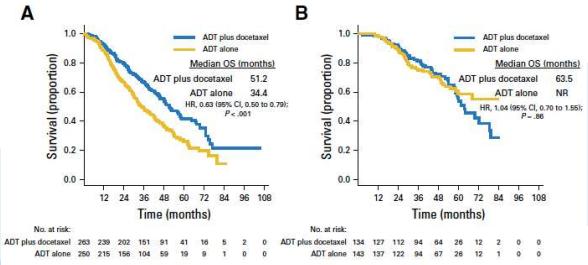
Metastatic Castration Sensitive

CHAARTED – ADT + *Docetaxel*

- **Long term follow up**
- Median f/u 53.7 mo
- **Median OS 51.2 mo vs. 34.4 mo (HR 0.63, p<0.001)**
- High volume disease → benefited more



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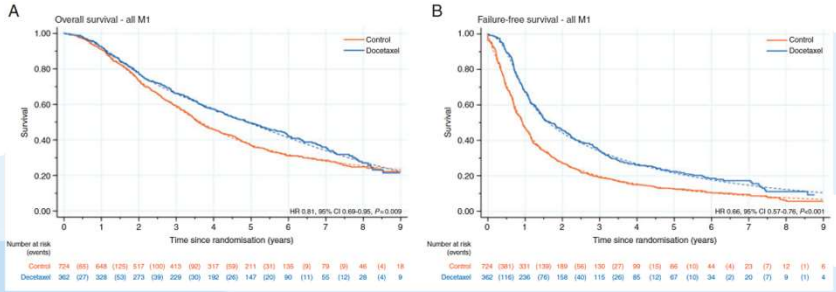
Kyriakopoulos et al, J Clin Oncol 2018

Metastatic Castration Sensitive

STAMPEDE – ADT + *Docetaxel*

- Long term follow up
- Median f/u 78.2 mos
- **Median OS 59.1 mo vs. 43.1 mo (HR 0.81, p = 0.003)**
- No difference in low vs. high volume disease



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Clarke et al. Annals of Onc 2019

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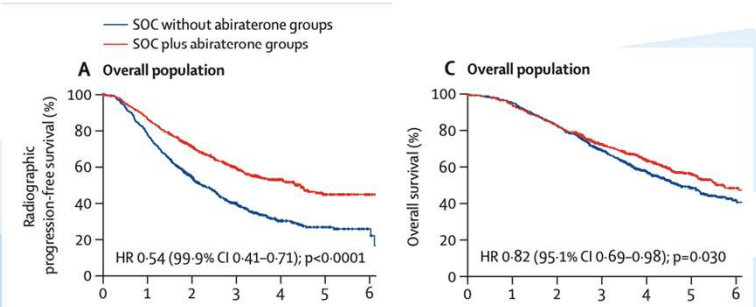
Metastatic Castration Sensitive

PEACE-1 – ADT + *Docetaxel + Abiraterone*

- De novo, mHSPCa
- SOC (ADT +/- doce) vs. SOC + XRT vs. SOC + Abi vs. SOC + XRT + Abi
- **Longer RPFS (HR 0.54, p = 0.0001), OS (HR 0.82, p = 0.030)**
- High volume, de novo disease; chemofit



modest increase in toxicity: HTN

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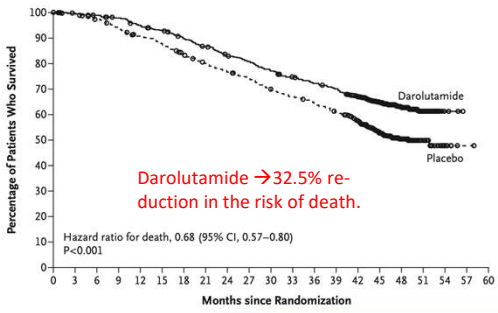
Lancet 2022; 399: 1695–07

Metastatic Castration Sensitive

ARASENS – ADT + *Docetaxel + Darolutamide*

- mHSPCa (86% de novo, 14% progressive)
- ADT + Docetaxel + darolutamide vs. ADT + Doce + matching PBO
- Improved OS (HR 0.68, p<0.001)



- ✓ Time to CRPC
- ✓ Time to pain progression
- ✓ No sig increase in tox

n engl j med 2022; 386;12

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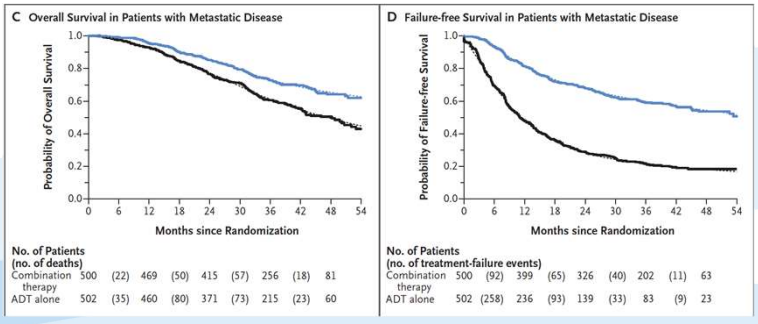
Metastatic Castration Sensitive

STAMPEDE – ADT + *Abiraterone*

- 1917 men with mHSPC randomized to ADT +/-Abiraterone (1000 mg daily + prednisolone)
- Median f/u: 40 mo
- 37% relative improvement in survival (HR 0.63, P <0.0001)

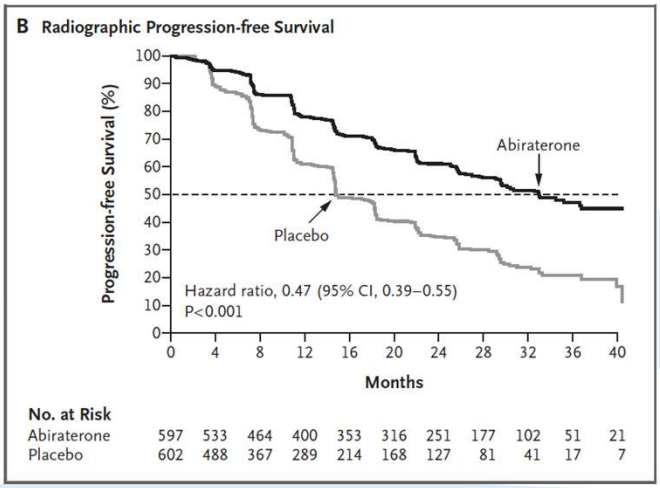


James, NEJM 2017

Metastatic Castration Sensitive

LATITUDE – ADT + *Abiraterone*

- 1199 patients receive ADT +/- abiraterone acetate + prednisone
  - 50% symptomatic at baseline
- Needed 2of 3 high risk features
  - Gleason >=8, >=3 bone lesions, visceral mets
- **OS** and **radiographic PFS** primary endpoints
- Median f/u 30.4 months



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Fizazi et al, NEJM 2017

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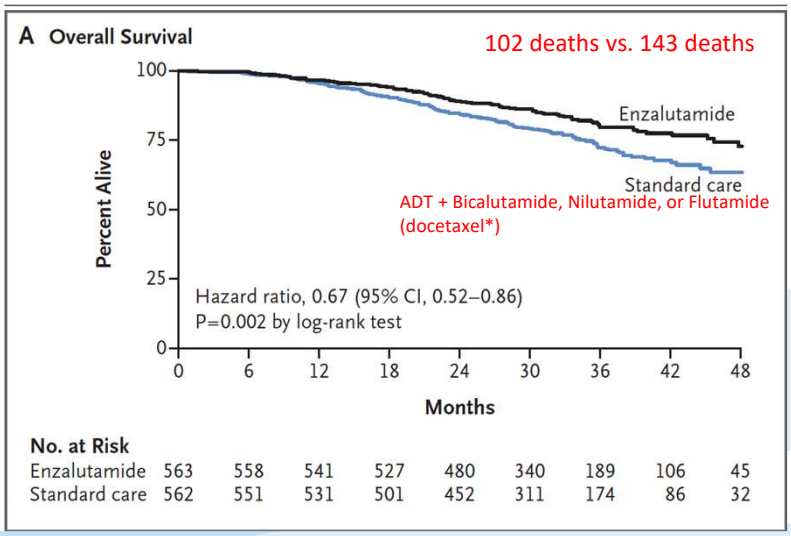
Metastatic Castration Sensitive

ENZAMET – ADT + *Enzalutamide*

More AEs in Enzalutamide group



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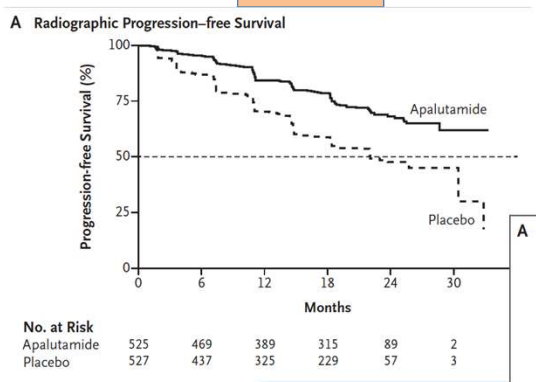
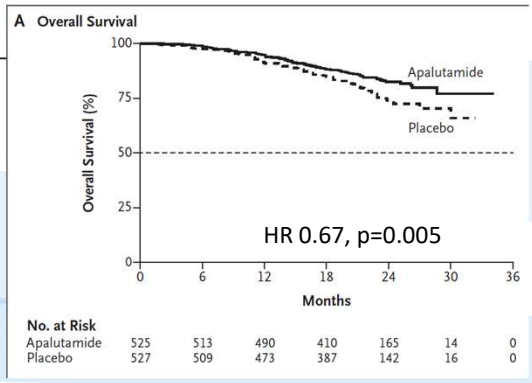
Davis et al. NEJM 2019

Metastatic Castration Sensitive

TITAN - ADT + *Apalutamide*





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Chi et al. NEJM 2019

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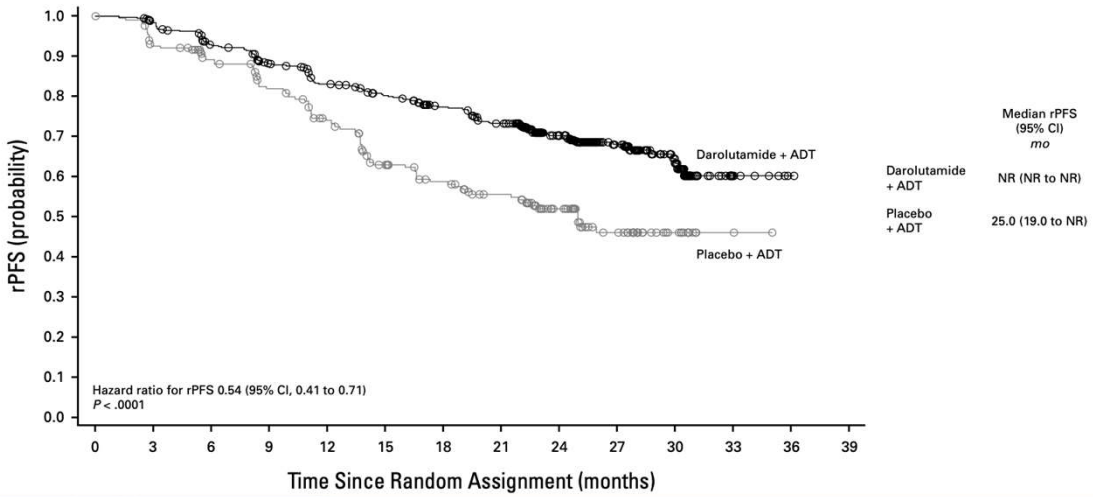
Metastatic Castration Sensitive

ARANOTE - ADT + *Darolutamide*



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JCO 2024;24:4273

Metastatic Castration Sensitive

STAMPEDE - ADT + *Prostate EBRT*

- **What about the value of local therapy in M1 disease?**

- STAMPEDE
  - 2061 men randomized to ADT (doc) v. ADT (doc) plus EBRT
  - Median **OS** - 48 mo (EBRT) v. 46 mo (Control)
  - All Patients - HR: 0.92, 95% CI: 0.80–1.06; p=0.266
  - ***Low met burden*** - HR 0.68, 95% CI 0.52–0.90; ***p=0·007***

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Parker et al Lancet 392: 2353–66, 2018

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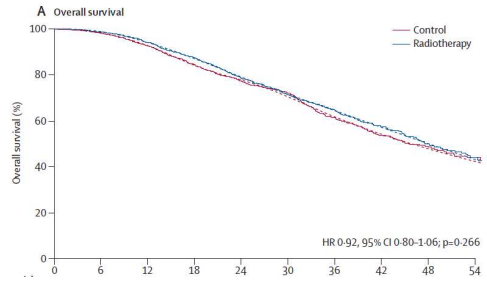
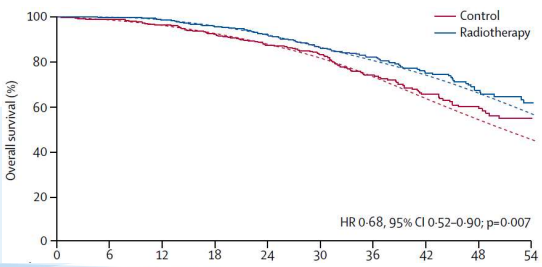
Overall Survival - STAMPEDE



All Patients - HR: 0.92, 95% CI: 0.80–1.06; p=0.266

Low volume- HR 0.68, 95% CI 0.52–0.90; ***p=0·007***



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Parker et al Lancet 392: 2353–66, 2018

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M0 CRPC

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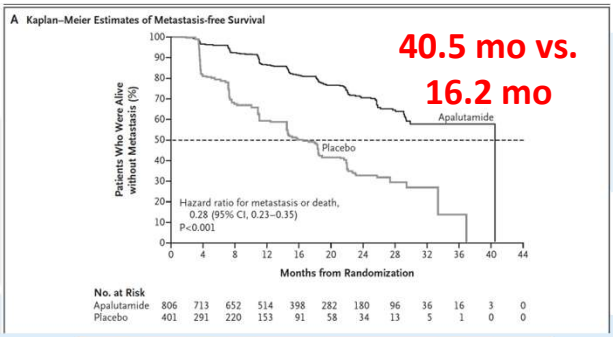
Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

- **Phase 3 SPARTAN Trial**
  - Apalutamide + ADT vs. placebo + ADT
- M0 CRPC, PSADT </= 10 mos
- 1207 patients
- Median f/u 20.3 mos
- 1º: MFS



40.5 mo vs. 16.2 mo

N ENGL J MED 378;15 NEJM.ORG APRIL 12, 2018

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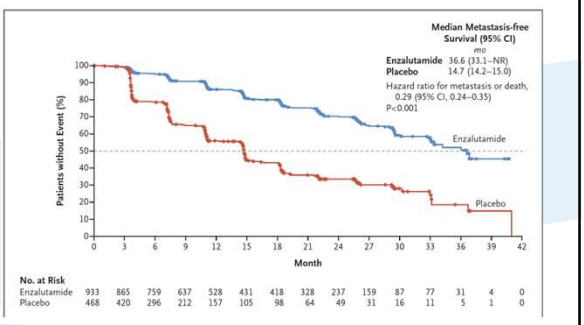
Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

- **Phase 3 PROSPER**
  - Enzalutamide + ADT vs. Placebo + ADT
  - Double blinded
- M0 CRPC, PSADT </= 10 mos
- 1401 patients
- 1º: MFS



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N ENGL J MED 378;26 NEJM.ORG JUNE 28, 2018

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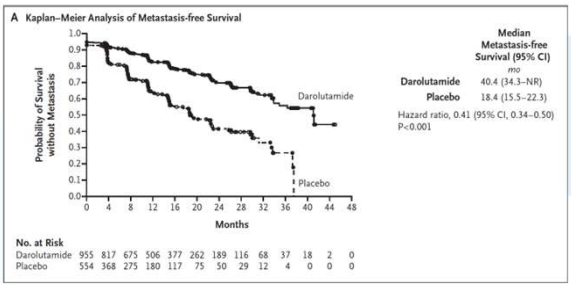
Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

- **Phase 3 ARAMIS**
  - Darolutamide + ADT vs. Placebo + ADT
- M0 CRPC, PSADT </= 10 mos
- 1509 patients
- Median follow up 17.9 mos
- 1º: MFS
- FDA approval 7/30/2019



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N ENGL J MED 380;13 NEJM.ORG MARCH 28, 2019

M1 CRPC

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M1 CRPC

ADT + Abiraterone

- **COU-AA-301** – ADT + Abiraterone
  - Prior docetaxel
- **COU-AA-302** – ADT + Abiraterone
  - No prior docetaxel/chemotherapy naive

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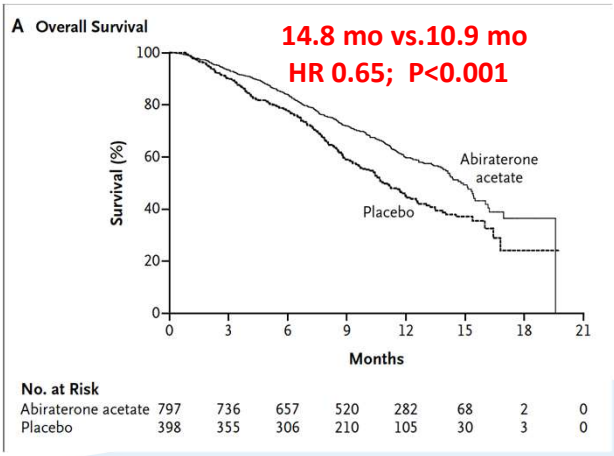
COU-AA-301



- All 2º end points
  - time to PSA progression (10.2 vs. 6.6 mos; P<0.001)
  - progression-free survival (5.6 vs. 3.6 mos; p<0.001)

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de Bono et al NEJM 2011

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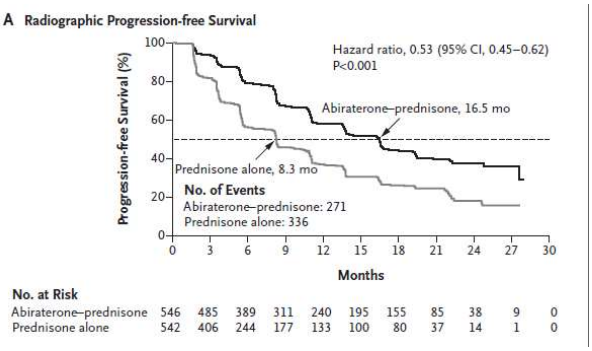
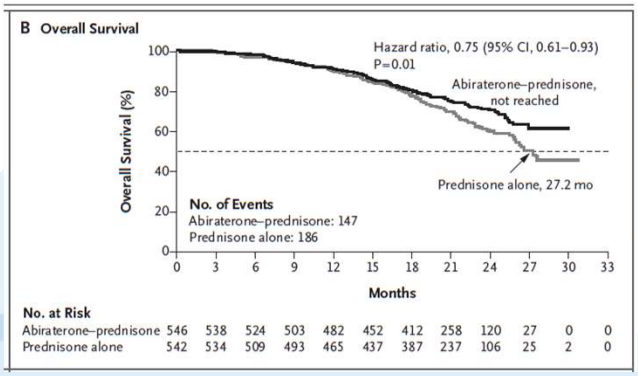
COU-AA-302





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Ryan et al, NEJM 2013

M1 CRPC

ADT + Enzalutamide

- **AFFIRM** – ADT + Enzalutamide
  - Prior docetaxel
- **PREVAIL** – ADT + Enzalutamide
  - No prior docetaxel/chemotherapy naive

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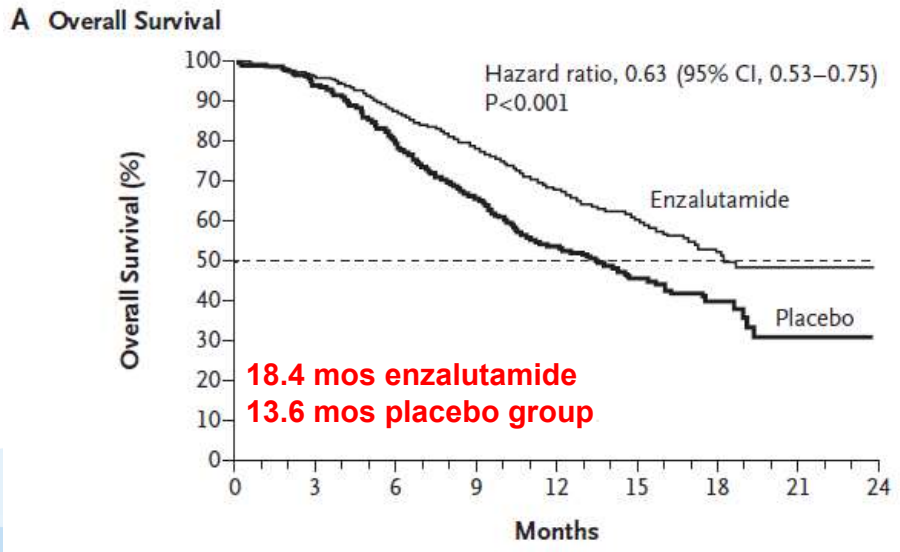
AFFIRM Trial – Prior Chemo



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Sher et al NEJM, 2012

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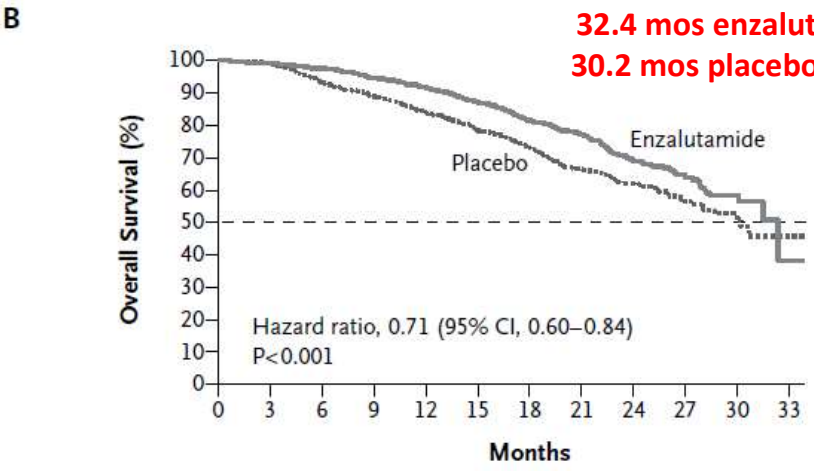
PREVAIL Trial – Chemo Naive



32.4 mos enzalutamide
30.2 mos placebo group

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Beer et al NEJM, 2014

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M1 CRPC

Chemotherapy

- **Docetaxel** (TAX 327, SWOG 9916)
- **Cabazitaxel** (TROPIC, FIRSTANA)
  - FDA approved after docetaxel
- **Mitoxantrone** (CALGB 9182)
  - Currently limited role in mCRPC

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M1 CRPC

Docetaxel (TAX 327)

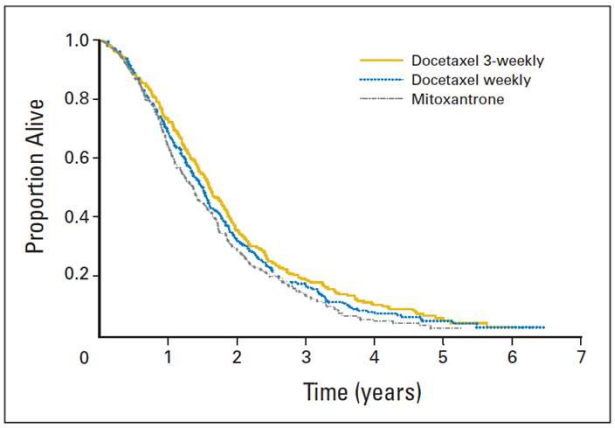

Fig 1. Overall survival data from March 2007, with 867 deaths among 1,006 randomly assigned patients.

Median OS
19.2 mos (p= 0.004)
17.8 mos
16.3 mos

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Tannock et al. NEJM 2004
Berthold et al. JCO 2008

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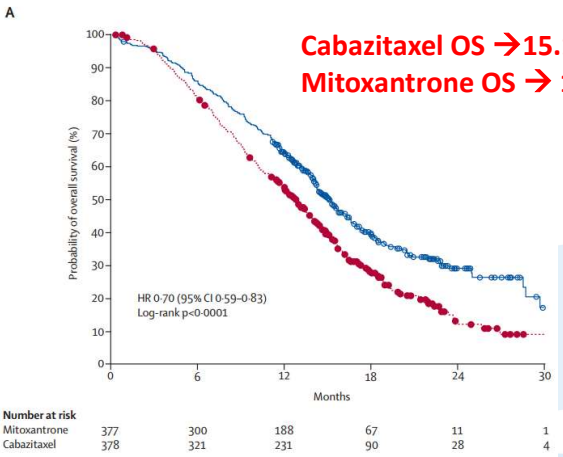
M1 CRPC

Cabazitaxel (TROPIC)



Cabazitaxel OS →15.1 mos
Mitoxantrone OS → 12.7 mos

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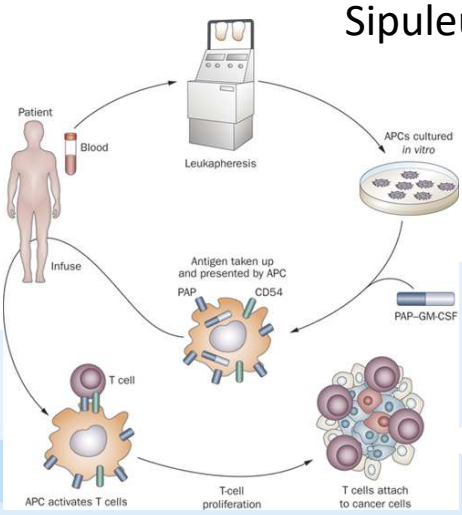
De Bono et al, Lancet 2010

M1 CRPC
Immunotherapy

Sipuleucel-T



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Di Lorenzo, G. et al. Nat Rev Clin Onc. 2011

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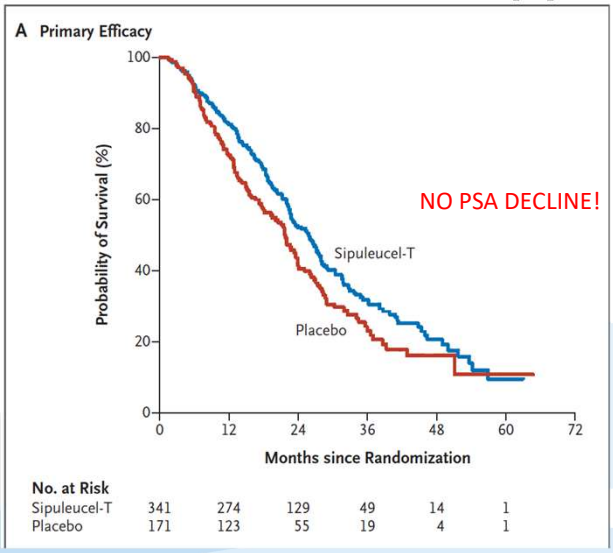
M1 CRPC
Immunotherapy



NO PSA DECLINE!

Median OS 25.8 mos vs 21.7 mos (**HR 0.78; p = 0.03**)

Median of 34 months f/u
No diff in PFS

Sipuleucel-T
IMPACT

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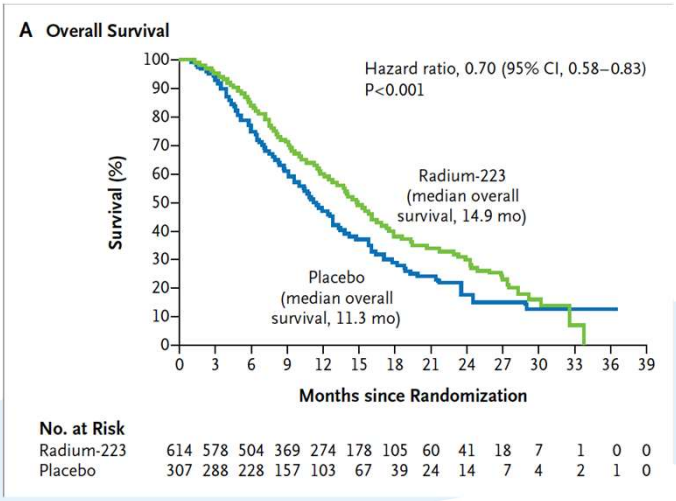
Kantoff et al, NEJM 2010

M1 CRPC (+bone mets)

Radium-223



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2º: SREs, biochem endpoints also showed benefit

Parker C et al, NEJM , 2013

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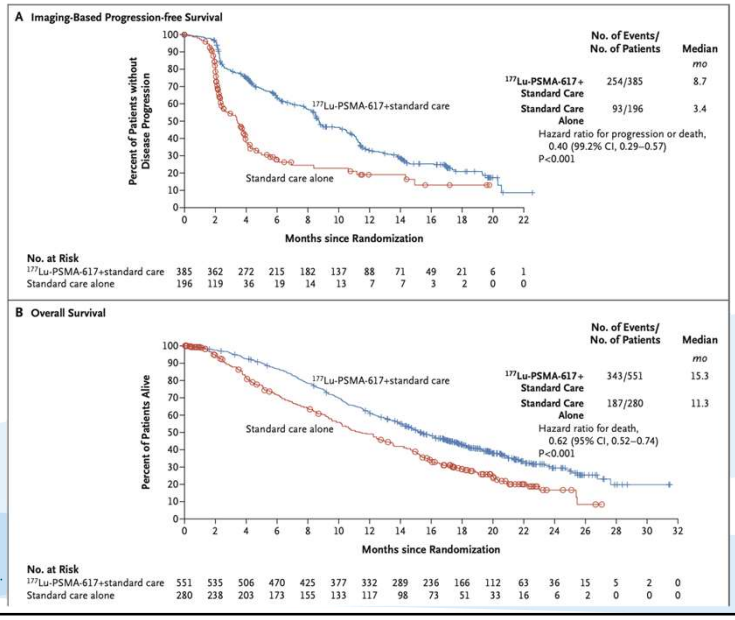
M1 CRPC

Lu-PSMA-617



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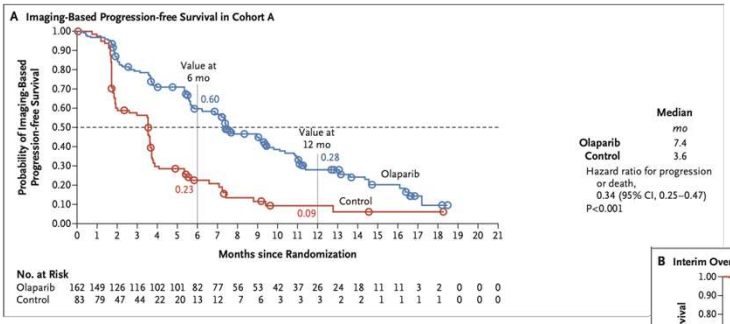
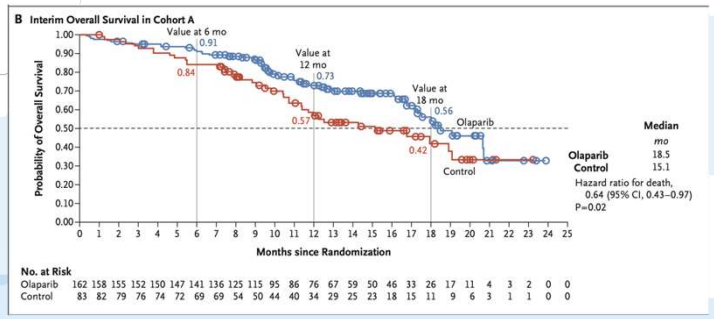
N Eng J Med 2021; 385;12

Olaparib for Metastatic Castration-Resistant Prostate Cancer



Phase 3 RCT in CRPC
Disease progression on NHT
All patients with prespecified gene alterations
A: BRCA1, BRCA2, ATM
B: 12 other gene alterations
Olaparib vs. physicians choice



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de Bono N engl j med 2020 382;22

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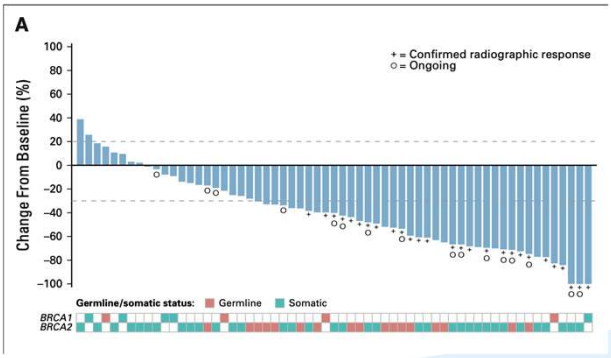
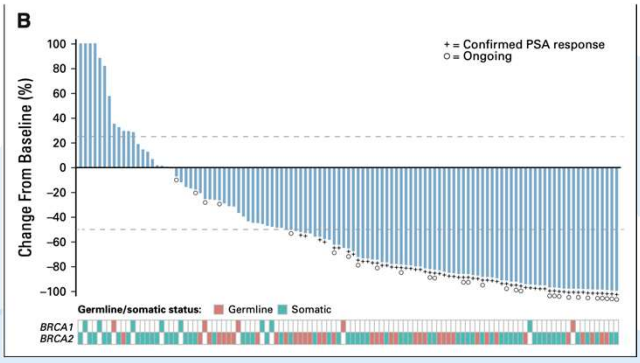
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration



Phase 2 RCT in CRPC
Disease progression on NHT *and* taxane
BRCA1, BRCA2 or another DDR deficiency
Efficacy and safety



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Abida J Clin Oncol 2020 38:3763-3772

4KScore is a serum-based test used to assess likelihood of cancer on prostate biopsy and includes, total PSA, human kallikrein 2, intact PSA and:

a) free PSA
b) ProPSA
c) PCA3
d) PHI

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A 71 year old male has GG2 prostate cancer and is considering his options. The additional texting that may be used to help assess prognosis and aid in decision making:

a) PCA3
b) OncotypeDx™
c) ConfirmMDx™
d) Germline testing

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A 65-year old male has an abnormal DRE (cT2b), a PSA of 11.0 ng/ml, and Gleason 3+3 (grade group 1). His risk category is:

a) Low risk.

b) Favorable intermediate risk.

c) Unfavorable Intermediate risk.

d) High risk.

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The PIVOT Trial compared outcomes in men with clinically localized prostate cancer managed with surgery vs. observation. The major finding was:

a) No difference in overall survival.

b) Improved survival with surgery.

c) Improved survival with watchful waiting.

d) Increased metastasis with surgery.

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A 72-year old male with favorable intermediate risk disease is interested in pursuing active surveillance. You inform him this is a possible management strategy but is associated with which of the following when compared to definitive local therapy:

a) Decreased disease specific survival.
b) Improved disease specific survival.
c) Lower risk of developing metastasis.
d) Higher risk of developing metastasis.

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The method of radiation that delivers highest dose of radiation per treatment over the shortest treatment duration is known as:

a) conventional fractionation
b) moderate hypofractionation
c) ultra-hypofractionation
d) High dose rate

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A 62 y/o M with cT1c, PSA 8.2, GG 2 prostate cancer is treated with external beam radiotherapy. He tolerates this well, although does have transient increase in his lower urinary tract symptoms. His PSA nadirs at 0.5 but is noted to be 7.1 six months after he completes XRT, confirmed on repeat lab evaluation. The likely cause of this elevation is:

a) prostatitis
b) PSA bounce
c) UTI
d) persistent prostate cancer

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A 73-year old man on androgen deprivation therapy and androgen targeted therapy has progressive metastatic disease. His PSA is 29 and his testosterone is < 50 ng/dL. His current disease state is:

a) Biochemical recurrence.
b) M1 Hormone-sensitive prostate cancer.
c) M1 Castration-resistant prostate cancer.
d) M0 Castration-resistant prostate cancer.

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Abiraterone is a CYP-17 inhibitor that blocks both androgen and glucocorticoid production resulting in an excess of mineralocorticoid production. This mechanism of action explains the side effects of abiraterone, including:

a) hypotension
b) hyperglycemia
c) hypokalemia
d) hyperkalemia

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A 68 y/o M has castration resistant metastatic prostate cancer and genetic testing reveals a germline mutation in DNA damage repair genes. This mutation is associated with:

a) prior prostate radiation
b) advanced age
c) resistance to PARP inhibition
d) family history of breast, ovarian, and pancreatic cancer

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Sipuleucel-T is an immunotherapeutic prostate cancer vaccine used for men with asymptomatic or minimally symptomatic castration resistant prostate cancer that results in improved:

a) overall survival
b) radiographic progression free survival
c) biochemical recurrence free survival
d) treatment free survival

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The agent that works by directly blocking the androgen receptor is:

a) Abiraterone.
b) Enzalutamide.
c) Relugolix.
d) Leuprolide.

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