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# Definition and Overview of Treatment Options in nmCRPC

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# Disclosures

**Consultant:** Janssen (U), Pfizer (U), Amgen (U), Bayer (U), Astra Zeneca (U), Menarini Silicon Biosystems (U)

**Grant/Research support to MSK:** Janssen, Janssen Research, EPIC Sciences, Thermofisher Scientific, Menarini Silicon Biosystems,

**Honoraria:** LUGPA, Elsevier

**Advisory Board:** WCG Oncology, Ambry Genetics

**I will discuss the investigational use in my presentation of:**

None

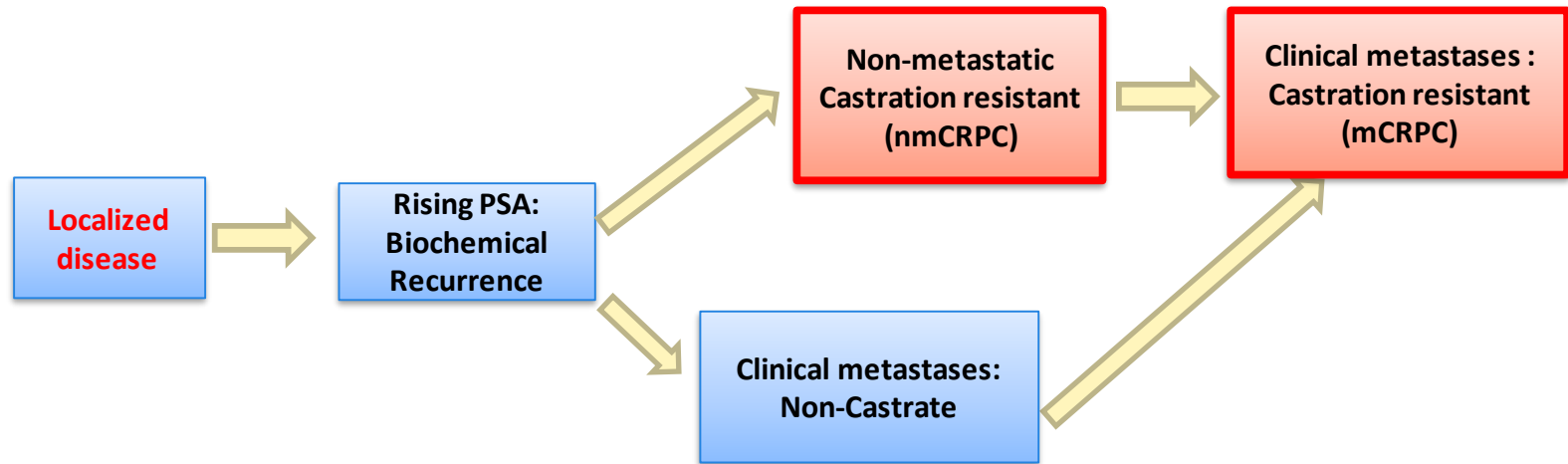


# nmCRPC: Overview of a Moving Target

1. **Definition: What is it?**
2. Who needs treatment: prognosis and competing risks.
3. Therapeutic options: drug approvals in the indication.
4. The times they are a changing!



# Non-Metastatic Castration Resistant Disease: Those Who **NEVER** Had Detectable Metastases On “Conventional/Standard” Imaging



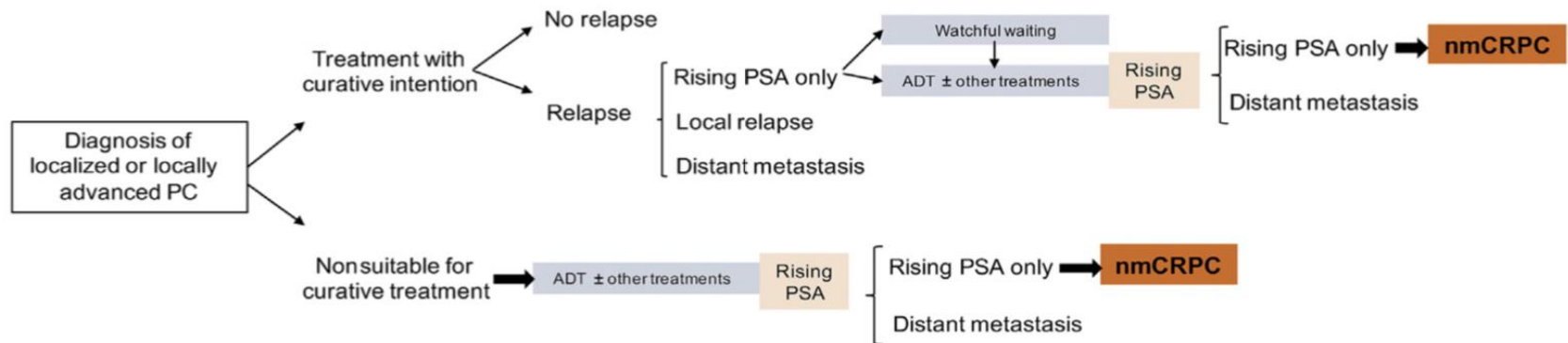
- Rising PSA with castrate levels of testosterone (<50 ng/dl)
- No detectable disease on conventional imaging:
  - Radionuclide bone scan
  - CT abdomen and pelvis, +/- MRI

Generally asymptomatic from the cancer itself with some symptoms from prior therapy(ies).



# The Population Can Be Very Heterogeneous Based on Intrinsic Biology and Differences in the Prior Local and Systemic Therapies Administered

	No ADT	Progressed on ADT
No distant metastasis CT/BS	Localized or locally advanced PC	<b>nmCRPC</b>
Distant metastasis	mHNPC	mCRPC



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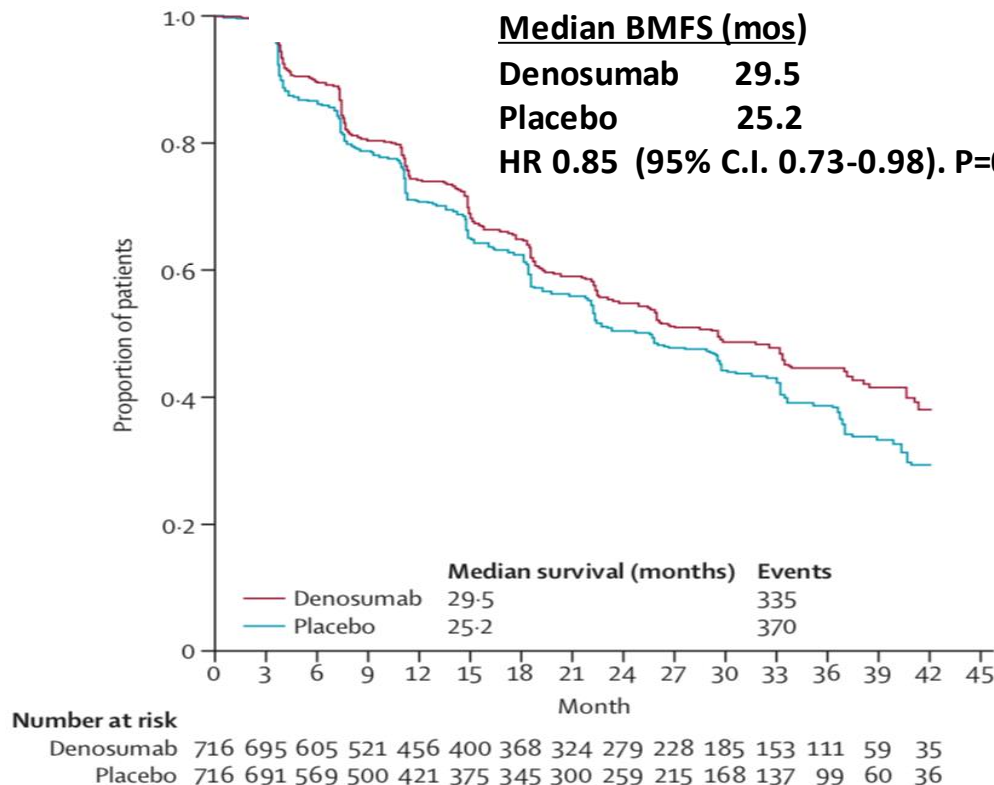
# Standards for **Trial Conduct** Were Established From the Phase 3 Trial of Denosumab vs. Placebo

1. 1432 men with nmCRPC randomized to denosumab or placebo.
2. Eligible patients had a **high risk** of metastatic disease: \*  
**PSA > 8 ng/dl and/or PSA doubling time  $\leq$  10 months**
3. Primary endpoint: **bone metastasis free survival (BMFS)**.
4. Statistics powered to a hazard ratio (HR) for denosumab versus placebo of 0.8.

**Which represents ~ one third of patients with a biochemical recurrence after radical surgery: Antonarakis et al., BJU International 109:32, 2011**



# A Significant Improvement in BMFS Was Seen but Median **4.2 Month** Difference Too Low for Approval by ODAC Based on Adverse Event Profile



OS was not prolonged:  
HR 1.1, 95% CI 0.85-1.20, p=0.91).

(<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugs/AdvisoryCommittee/default.htm>).

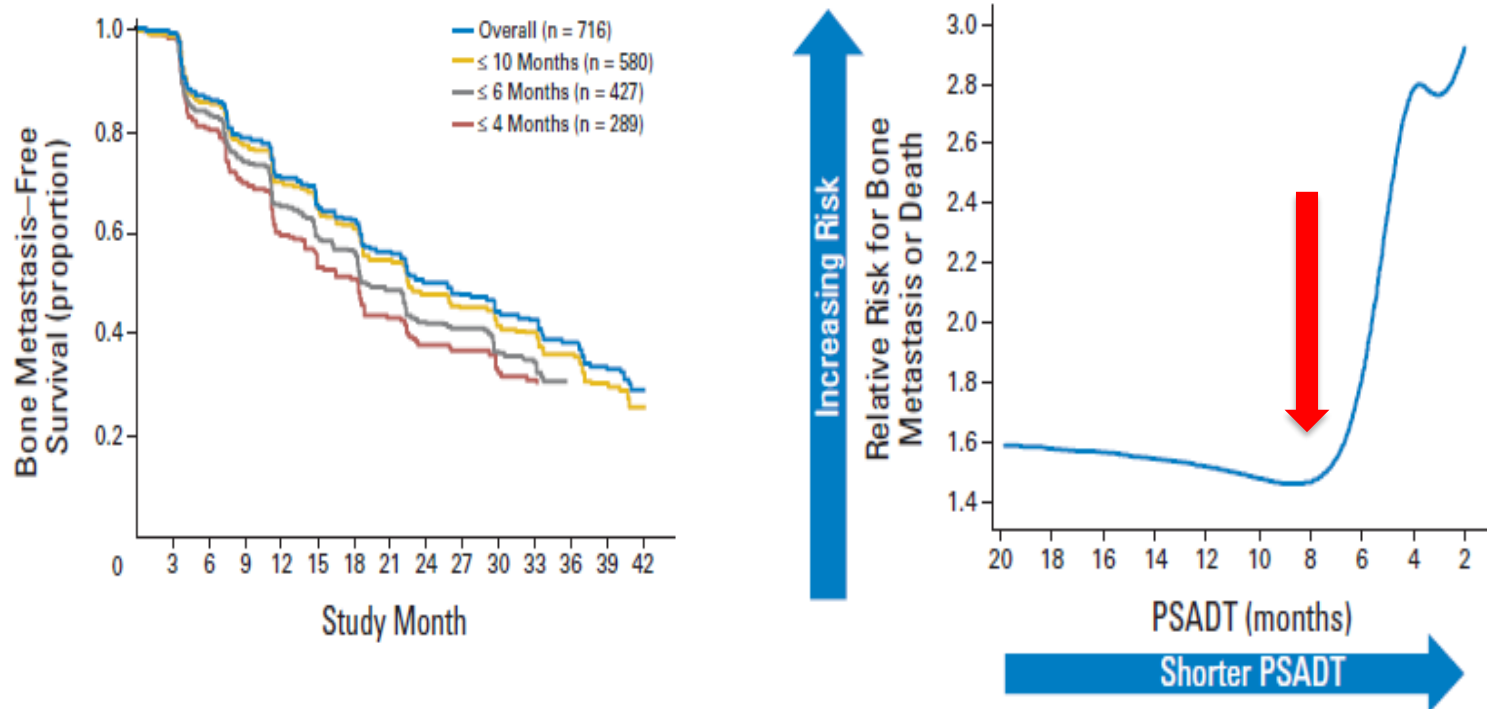


# Trial Designs Aim to Balance a Need for Treatment for Largely Asymptomatic Patients, Ensuring a Number of Events to Show Efficacy Relative to Safety

1. **PSA-doubling time (PSA-DT)** is the most widely used prognostic factor to determine risk, refined from the outcomes of patients treated on the placebo arm of the Phase 3 placebo controlled denosumab registration trial.
2. **Metastasis free survival (MFS)** is the primary endpoint – the time from randomization to the first detection of disease in bone or death from any cause.



# Relative Risk for Bone Metastases-Free Survival (BMFS) in the Placebo Arm of the Denosumab Phase III Trial: Note **Inflection Point of Risk**

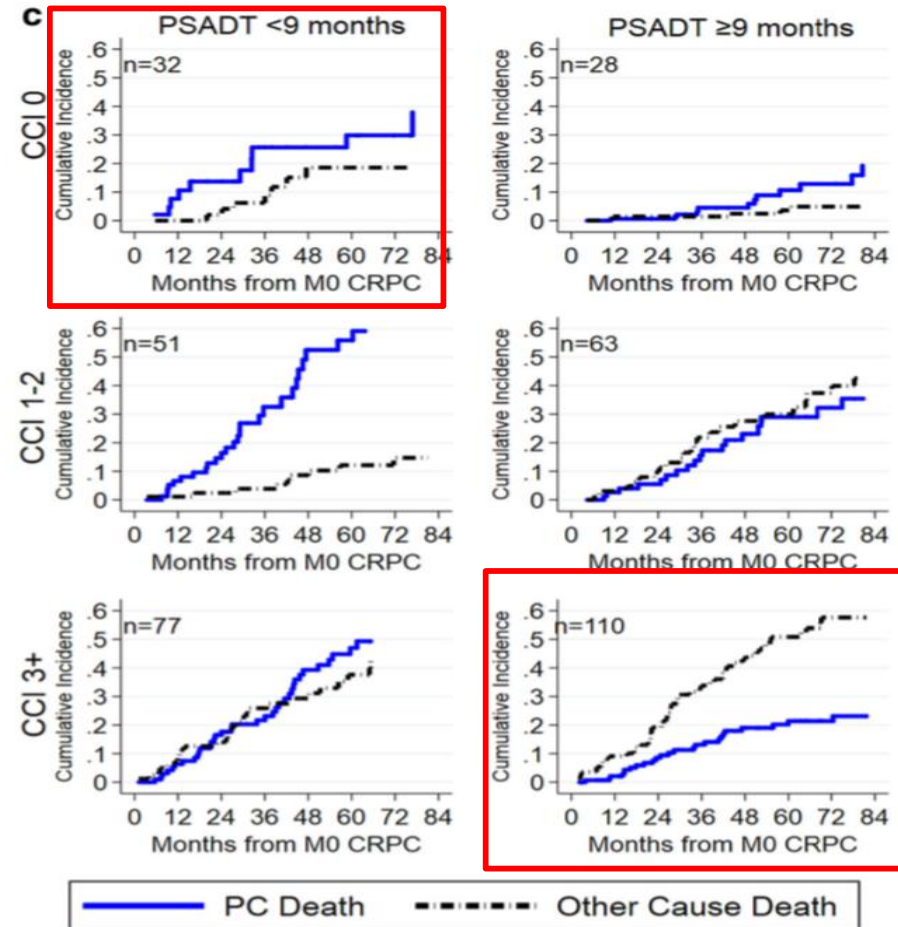
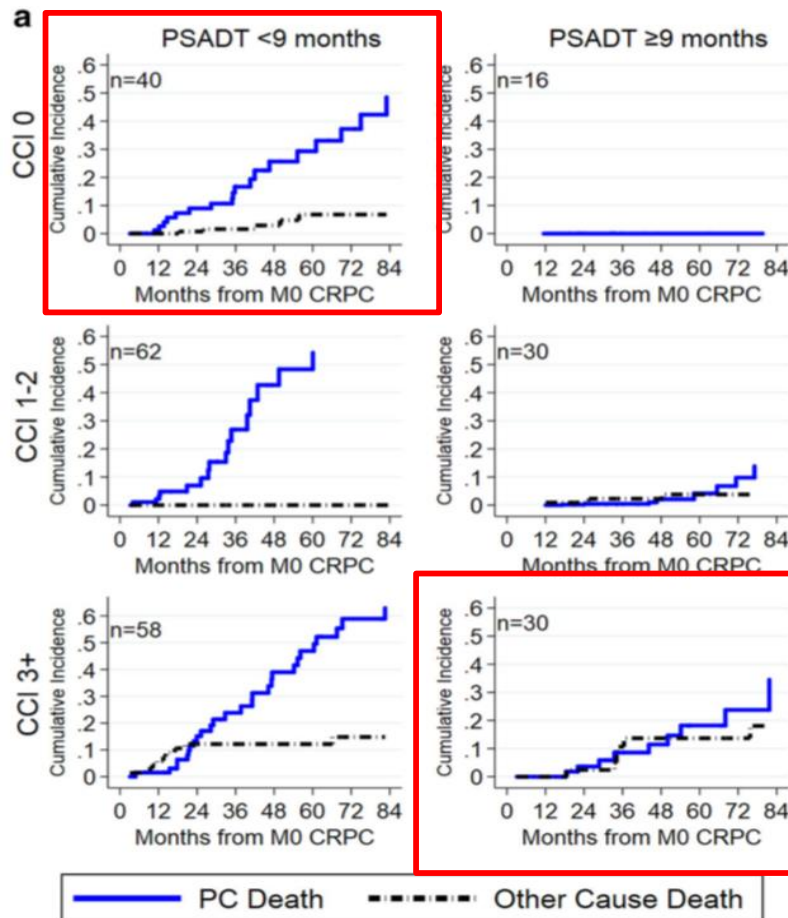


**Most contemporary trials use doubling times of < 8 or 10 months for enrollment.**

# Competing Risks: Death From Disease vs. Other Causes Based on Age, Comorbidities and PSA-Doubling Time

Age <70 Years

Age >80 Years



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# A Range of Therapies Have Been Evaluated: None Focused on the Microenvironment Alone Worked

1. Bone targeting agents:  
bisphosphonates - clodronate, zoledronic acid, denosumab
2. Endothelin receptor A antagonists: atrasentan, zibotentan
3. Miscellaneous = Bevacizumab, cilengitide, somatostatin, Octreotide
4. Next generation hormonal agents did show efficacy:

Enzalutamide	PROSPER
Apalutamide	SPARTAN
Darolutamide	ARAMIS

Abiraterone has not been evaluated in a phase 3 trial.



# The Landscape has Changed by the PROSPER (Ezalutamide), SPARTAN (Apalutamide) and ARAMIS (Darolutamide) Trials

PROSPER: 1492 933 and 468

BMFS: 35.6 vs. 14.7 (HR 0.29, 95% CI 0.24-0.35, p=0.001)

Smith et al., New Eng J Med 378:1408, 2018.

SPARTAN: 1207 806 and 401 men

BMFS: 40.5 vs 16.2 (HR 0.28, 95% CI 0.23-0.35, p=0.001)

Hussain et al., New Eng J Med 378:2465, 2018.

ARAMIS: 1509 955 and 544 men

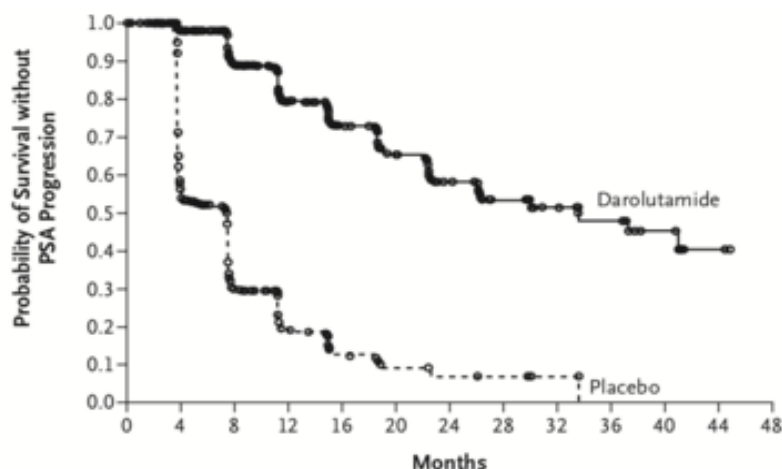
MFS: 40.4 vs. 18.4. (HR 0.41, 95% CI 0.34-0.50, p<0.001)

Fizazi et al., N Engl J Med 380:1235, 2019.

**Not surprisingly, no improvement in overall survival has been seen.**



# These Are Difficult Trials To Conduct: Keeping Patients with Rising PSA's on Study Until the Primary Metastatic Endpoint is Met



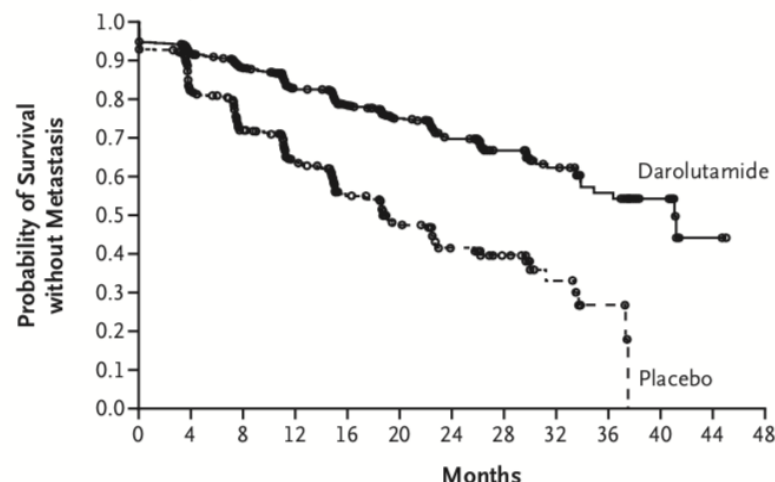
No. at Risk	0	4	8	12	16	20	24	28	32	36	40	44	48
Darolutamide	955	802	586	406	281	186	127	72	44	23	12	2	0
Placebo	554	249	98	44	18	10	6	4	2	0	0	0	0

Median  
Survival without  
PSA Progression  
(95% CI)

mo

<b>Darolutamide</b>	33.2 (25.9–NR)
<b>Placebo</b>	7.3 (3.9–7.4)

Hazard ratio, 0.13 (95% CI, 0.11–0.16)  
P<0.001



No. at Risk	0	4	8	12	16	20	24	28	32	36	40	44	48
Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

Median  
Metastasis-free  
Survival (95% CI)

mo

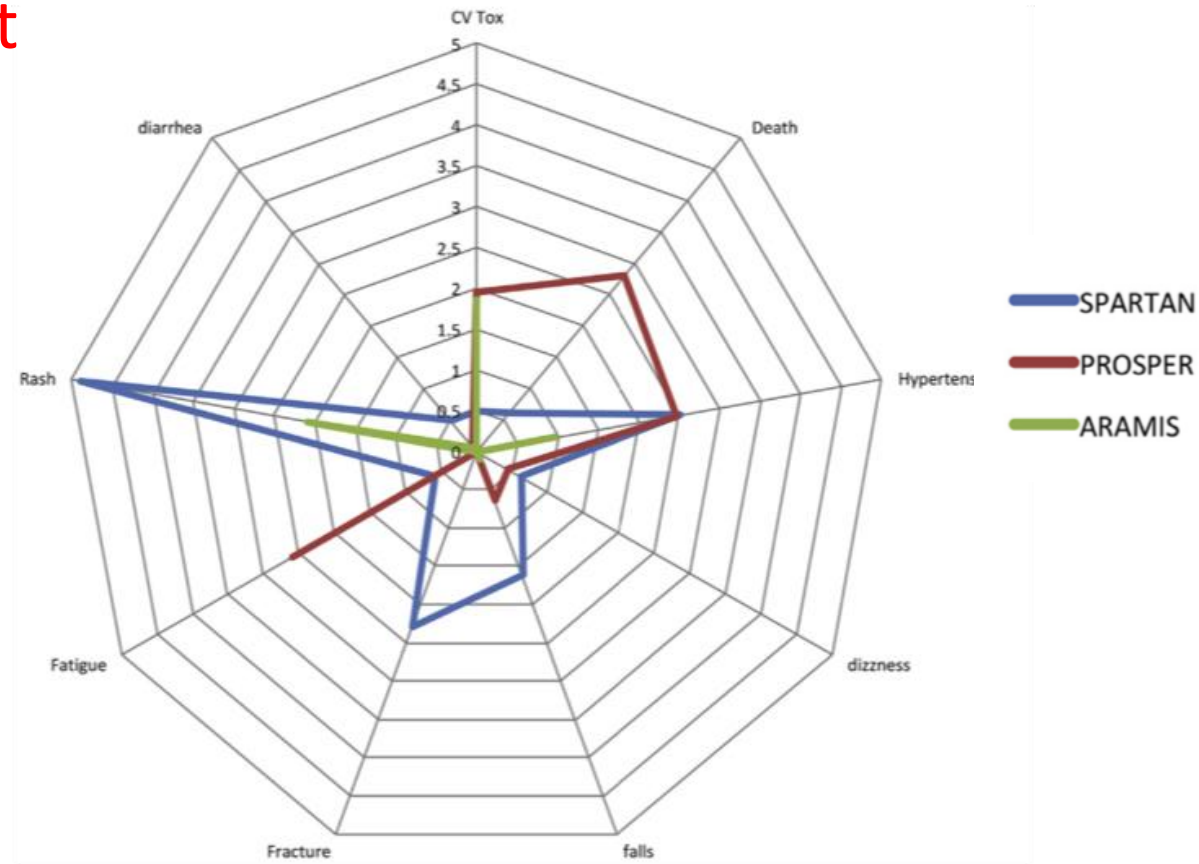
<b>Darolutamide</b>	40.4 (34.3–NR)
<b>Placebo</b>	18.4 (15.5–22.3)

Hazard ratio, 0.41 (95% CI, 0.34–0.50)  
P<0.001



# New Outcome Biomarkers to Balance Efficacy With Adverse Events: Cardiovascular, Hypertension, Fatigue, Fractures, Falls and Non-Cancer Deaths

## Radar Plot

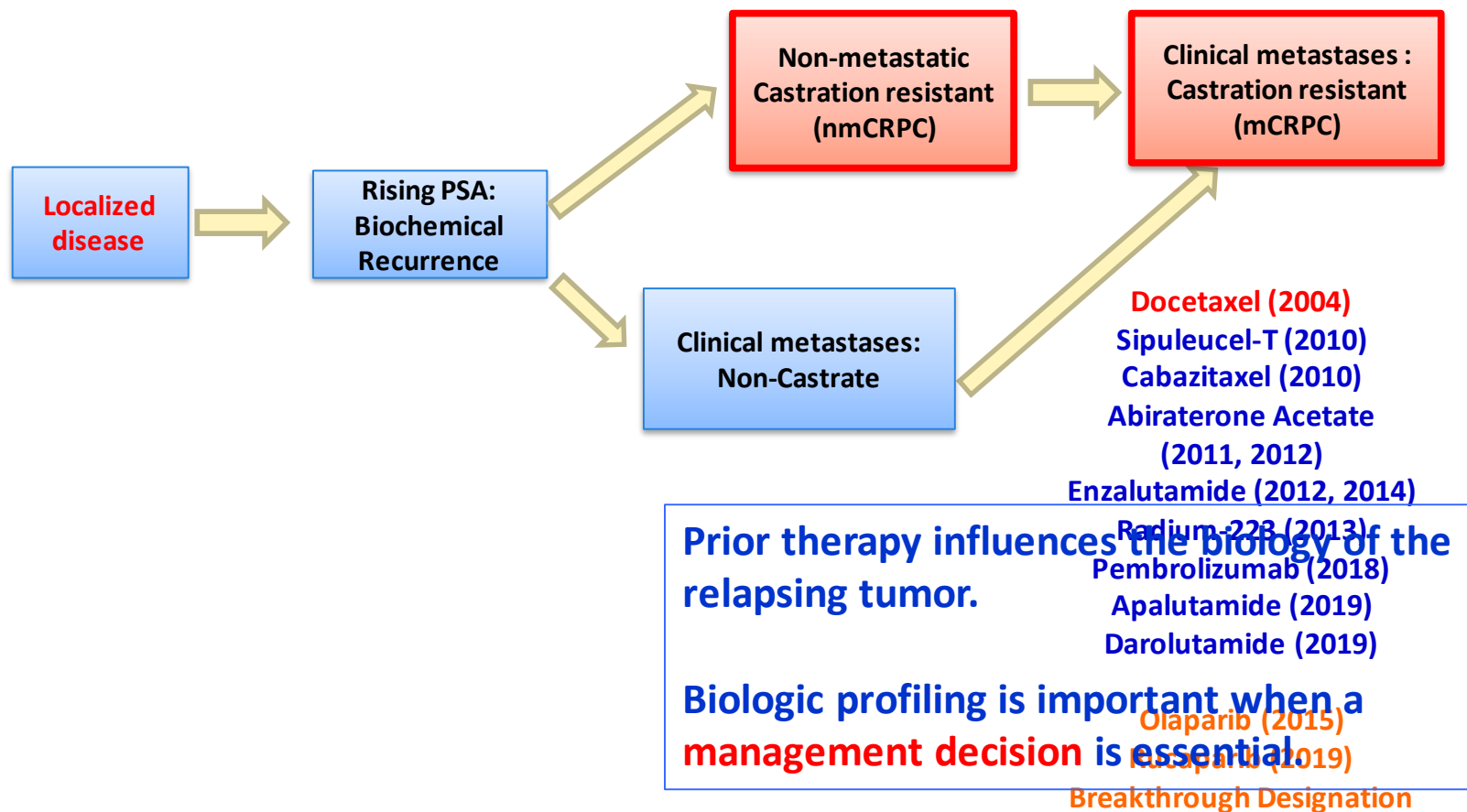


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# Now, As The Drugs Approved For **nm** and **mCRPC** Are Studied In Non-Castrate States, Progressing and Relapsing CRPCs Will be More Diverse Biologically



# Why Am I Showing a Picture of a Cowboy in at a Consensus Conference?

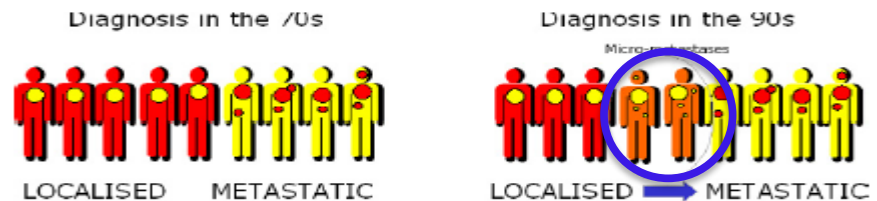


## THE WILL ROGERS PHENOMENON

### Stage Migration and New Diagnostic Techniques as a Source of Misleading Statistics for Survival in Cancer



When the Okies left Oklahoma and moved to California, they raised the average intelligence in both states.



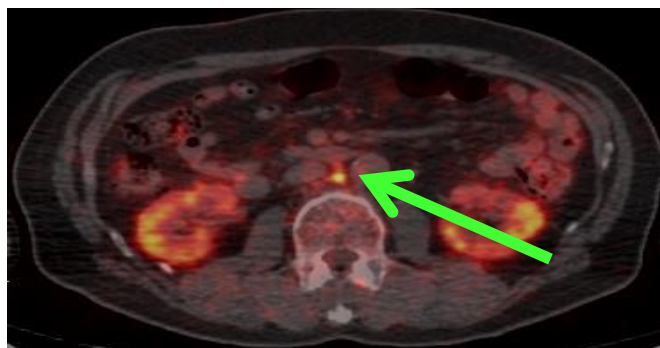
Feinstein AR et al., NEJM 312:1604, 1985



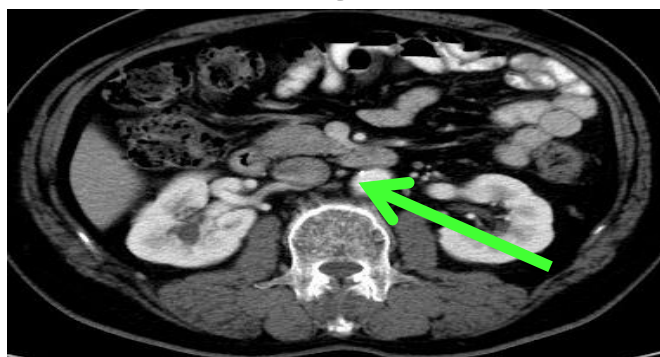
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# Stage Migration: CT and FDG (-), PSMA (+) - More Specific and Sensitive Imaging Renders Available Models Obsolete

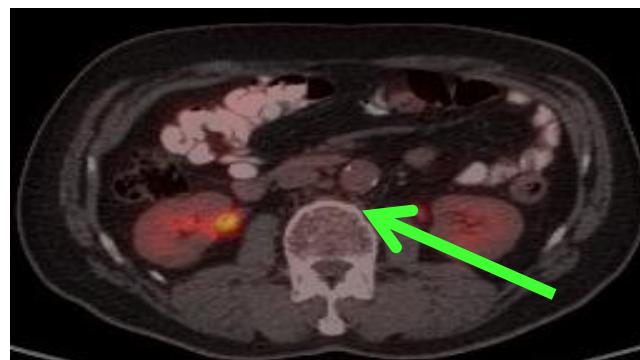
**PSMA-PET**



**CT**



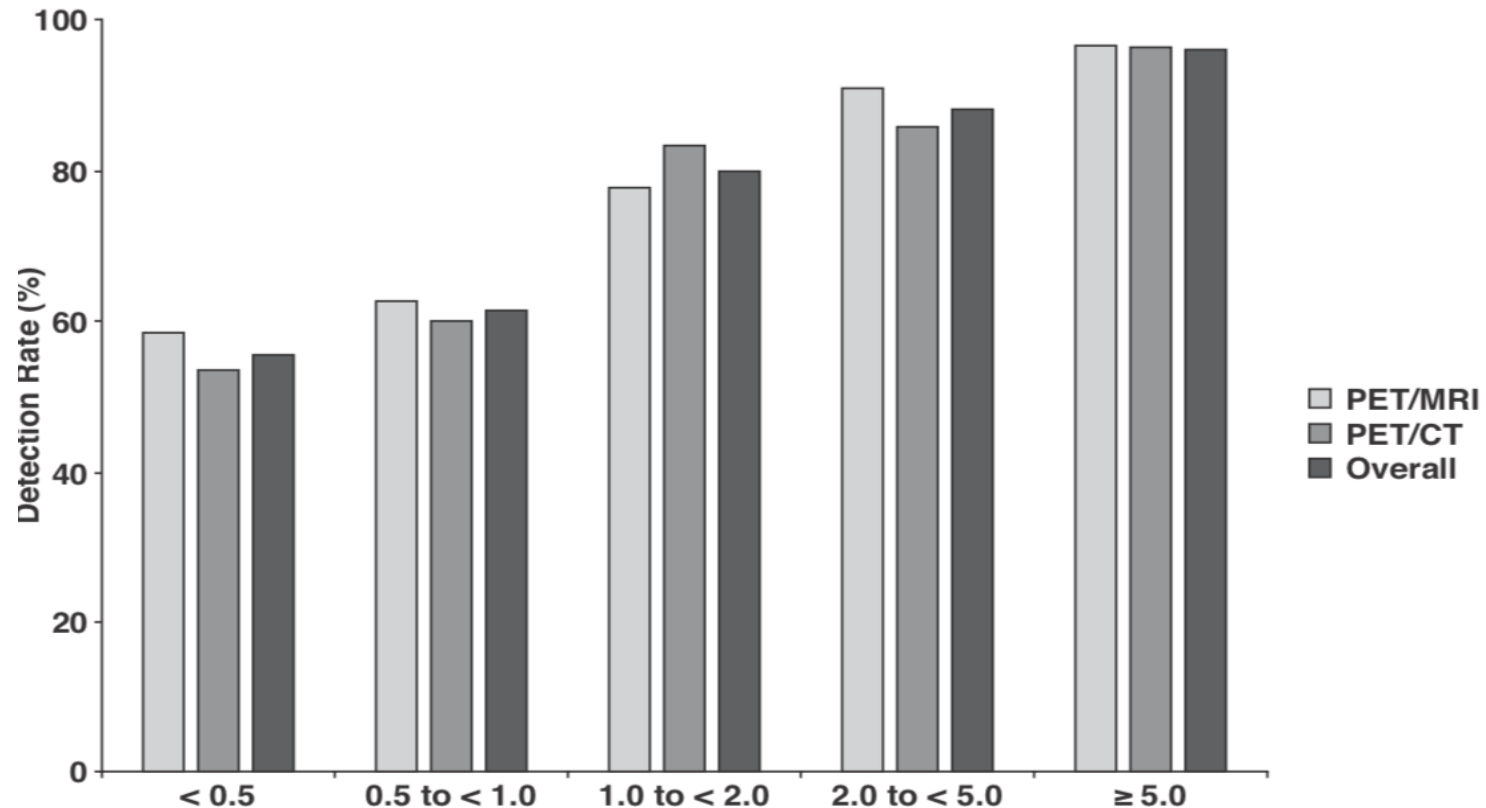
**FDG-PET**



## **Pathologically Confirmed:**

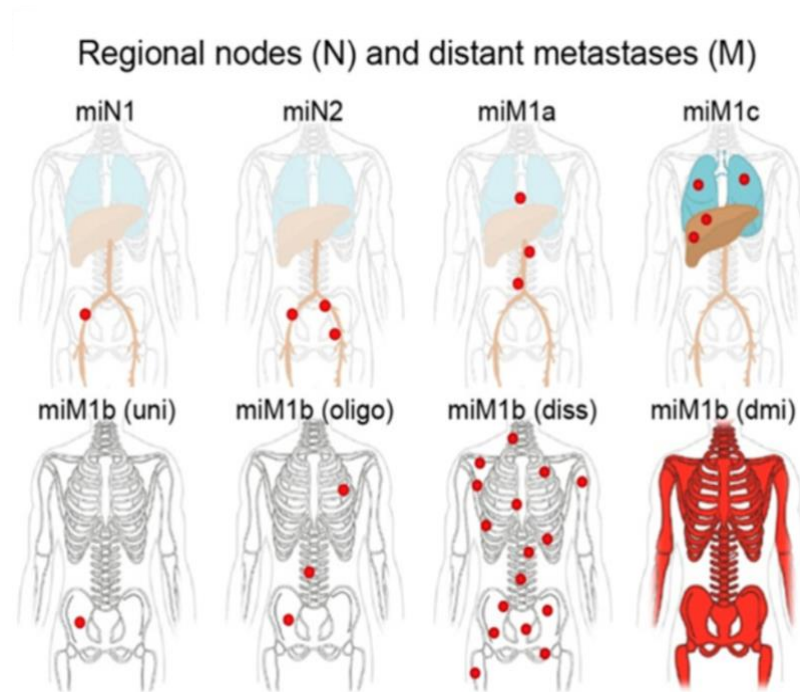
Aortocaval LN; biopsy: Prostatic adenocarcinoma involving lymphoid and fibroadipose tissue, PSA positive.

# Prospective Evaluation in Biochemical Recurrence – The Higher the PSA the Higher the Positivity Rate



**Fig. 1**—Chart shows  $^{68}\text{Ga}$ -labeled prostate-specific membrane antigen 11 (PSMA-11) PET positivity rate by prostate-specific antigen (PSA) level as 95% CIs. Number of patients per quintile are as follows (number positive/total number of patients): < 0.5 ng/mL,  $n = 15/27$ ; 0.5 to < 1.0 ng/mL,  $n = 8/13$ ; 1.0 to < 2.0 ng/mL,  $n = 24/30$ ; 2.0 to < 5.0 ng/mL,  $n = 22/25$ ; ≥ 5.0 ng/mL,  $n = 47/49$ .

# PROMISE – Prostate Cancer Molecular Imaging Standardized Evaluation New Reporting Metrics: Proposed **miTNM** to Interpret PSMA-Ligand PET/CT



**mi – molecular imaging**

# A Recently Completed Retrospective Pooled Analysis Study of 8000+ Patients Imaged at Different Centers Included **200** with nmCRPC

1. PSMA-PET positive in **196**: 44% in the pelvis (24% in the prostate bed); 55% with M1 disease.
2. High **interobserver agreement** on reads: ( $\kappa$  0.81- 0.91).
3. **Validation** by histopathology [26%], follow-up imaging [70%], or PSA after focal salvage therapy (5 [4%]): PPV 96% based on the composite reference standard.
4. **Clinical management** was recorded for 148 (76%) of the cases of which 122 (83%) had treatment altered.



# Imaging Biomarker Development: New Measurements and Evidence Generation Focused on a **Context of Use**

1. **Context of use:** The management / treatment decisions that the biomarker result will be used to inform.
2. **Method (Analytical) validation:** The process of ***assessing the device and its measurement performance characteristics***, and determining the range of conditions under which the assay will give reproducible and accurate data.

Includes image acquisition, interpretation and ***reporting***.

3. **Clinical validation:** The ***evidentiary process*** of linking a biomarker with biological processes and clinical endpoints.

The sequence of trials focused on the context of use.

4. **Clinical utility:** Showing that use of test to inform management improves patient outcomes relative to non-use of the test.

Changing management alone is not sufficient.



# nmCRPC: Overview of a Moving Target

1. “The FDA now recognizes that the development of metastatic disease is an objective and clinically relevant measure.”\*
2. The range of options has increased significantly but future cohorts presenting for treatment will be more biologically diverse.
3. PSMA PET is changing practice but nmCRPC still exists: further development needs more focus on pre-specified management decisions with regulatory / coverage considerations.
4. Optimal management should include shared decision making balancing patient needs and drug safety.

\*Beaver et al. NEJM 378:2459, 2018



# Thank You's For Sharing Prepublication Data

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