

# GU Retreat 2019

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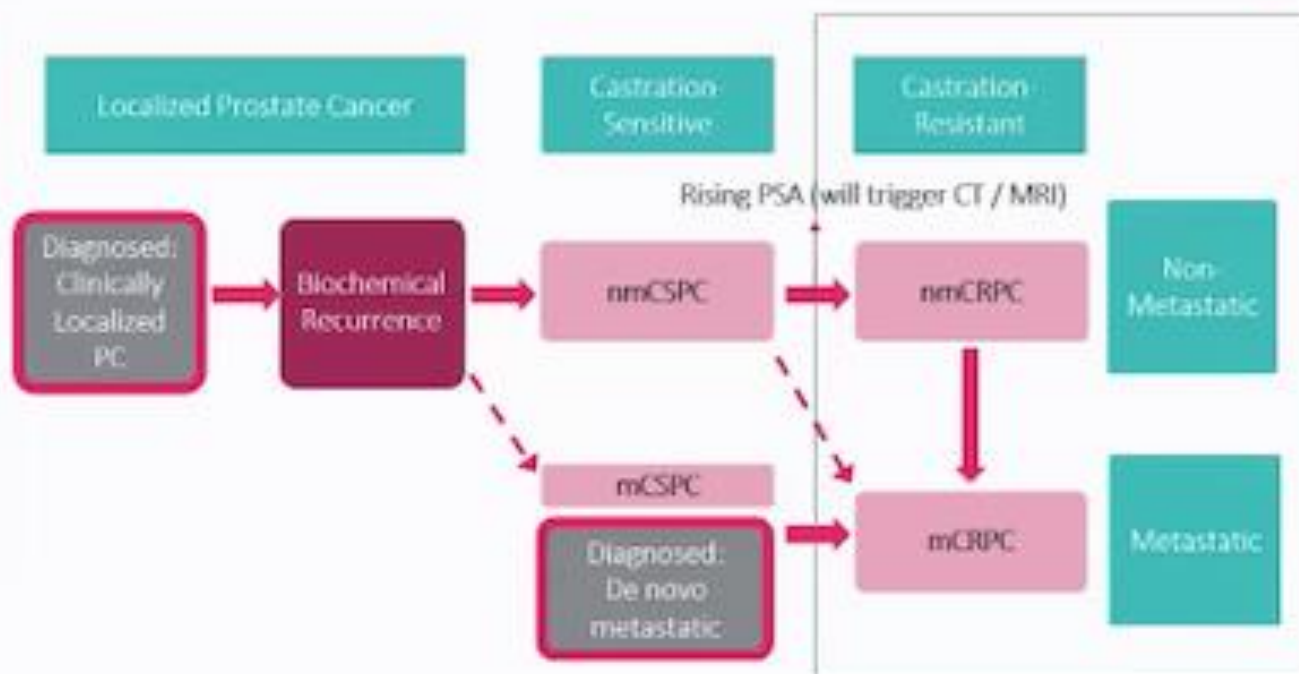


# Objectives

- Understand treatment options in CSPC
- Review the 2018 AUA guidelines for CRPC
- Anticipate new treatment possibilities

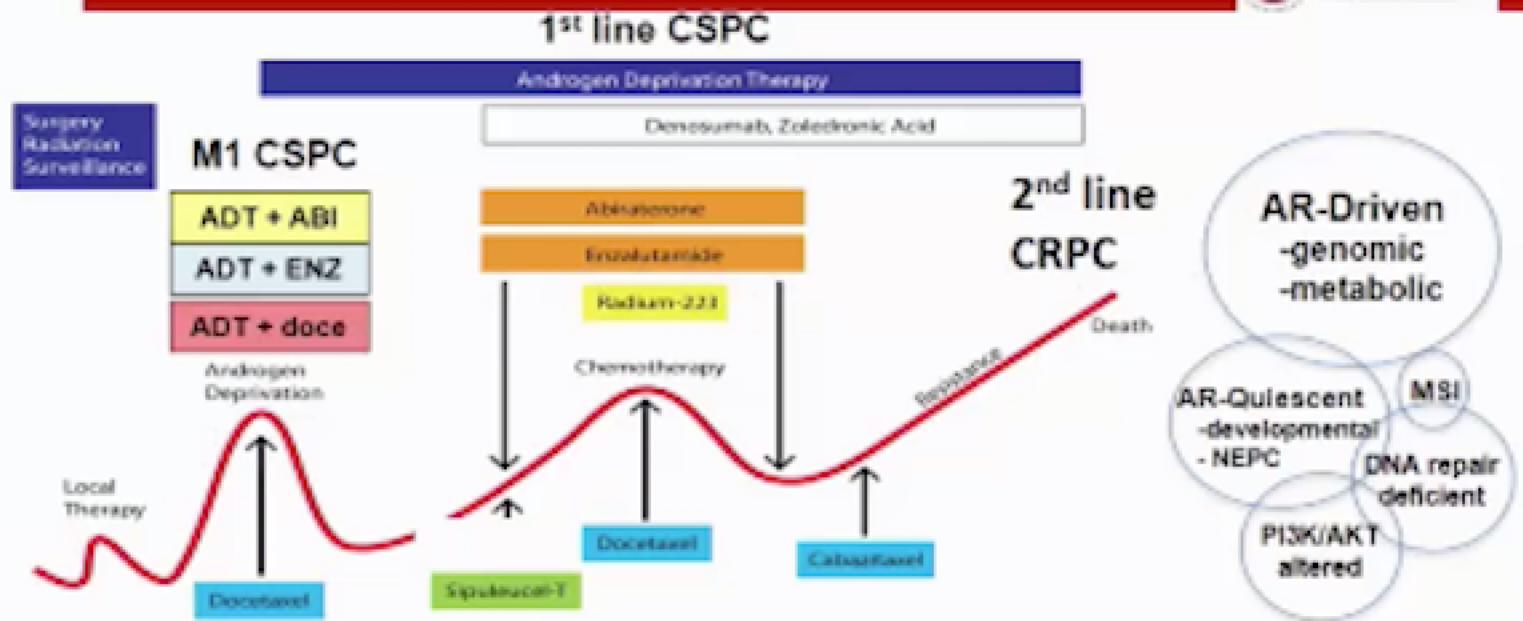
# Advanced Prostate Cancer

## Clinical States of Prostate Cancer



nmCSPC: non-metastatic castration-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PC: prostate cancer

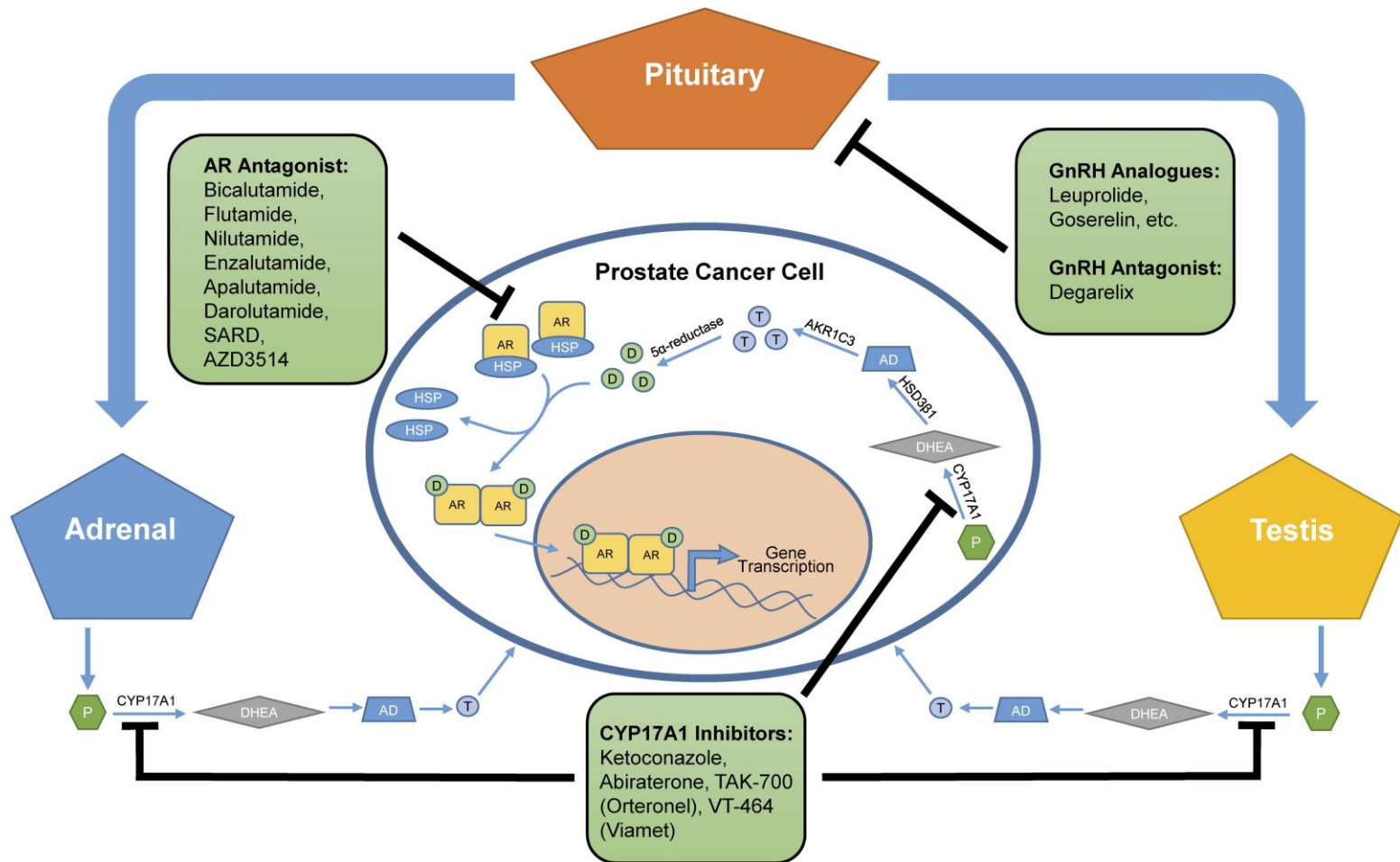
# AR Pathway Inhibitors have re-defined the Treatment Landscape in Advanced PCA: 2019



Moving docetaxel or ARPI earlier in combination with ADT improving outcomes  
 Combining, or sequencing, ABI and ENZA, not efficacious (due to cross-resistance)

Molecular sub-classification is key to begin stratified approaches to treatment – along with availability of drugs that specifically target biomarker-defined cancer vulnerabilities

# Androgen Receptor Pathway Inhibition



# Castrate Sensitive Metastatic Prostate Cancer

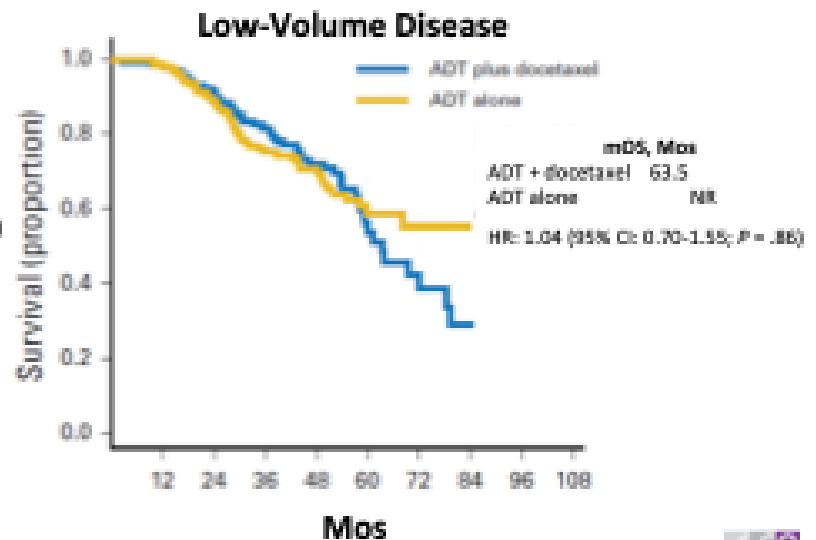
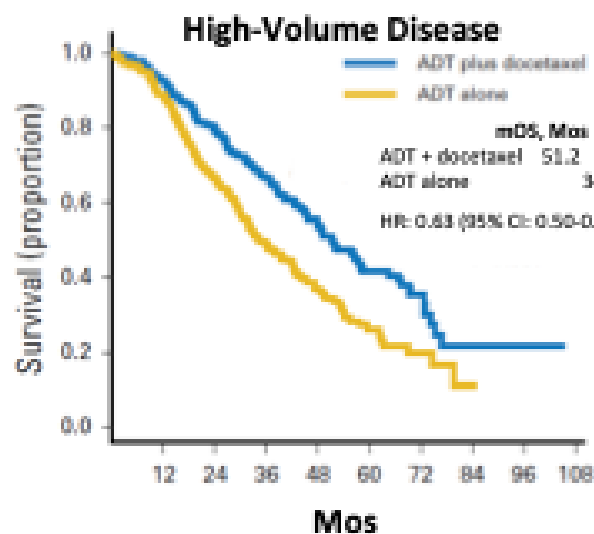
- 67-yr-old “healthy” retired accountant
- PSA 76 ng/mL
- Gleason score of 8
- prostate cancer with moderate back pain, and multiple bone metastases scattered in his ribs, spine, and pelvis
- he has had an active lifestyle and travel schedule that he wants to maintain as long as possible



# Castrate Sensitive Metastatic Prostate Cancer

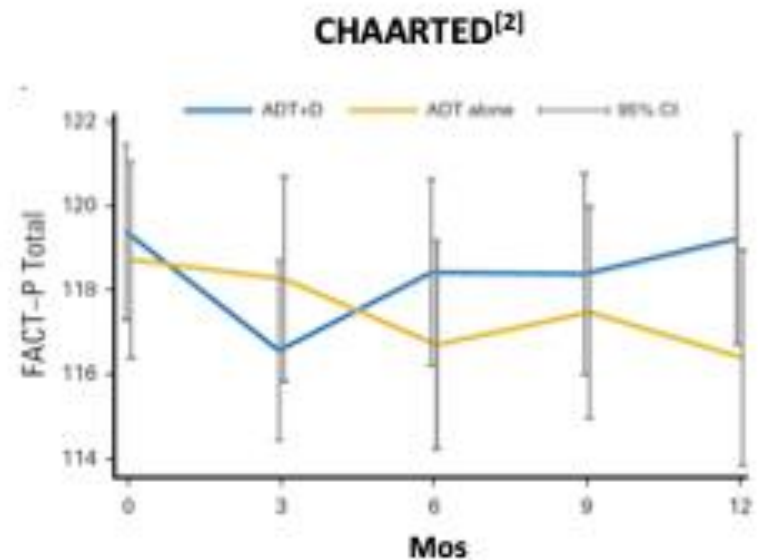
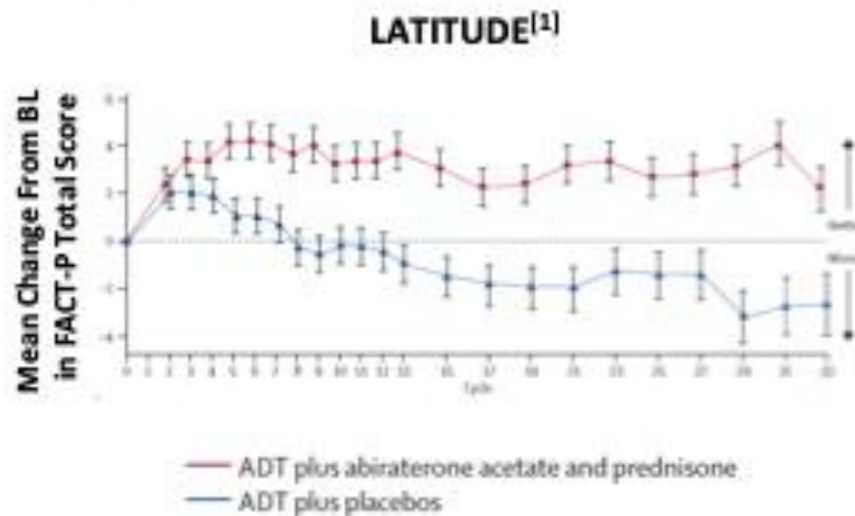
## Phase III CHAARTED Trial Long-term Follow-up: High-Volume vs Low-Volume Disease

- Median follow-up of 53.7 mos in patients with metastatic hormone-sensitive prostate cancer randomized to ADT + docetaxel vs ADT alone (N = 790)



# Castrate Sensitive Metastatic Prostate Cancer

## FACT-P Total Scores for ADT + Abiraterone or ADT Alone vs ADT + Docetaxel



1. Chi KN, et al. Lancet Oncol. 2018;19:194-206. 2. Morgans AK, et al. J Clin Oncol. 2018;36:1088-1095.



# Castrate Sensitive Metastatic Prostate Cancer

- **Consensus**: docetaxel + ADT appropriate for high-volume metastatic disease
- **Change**: STAMPEDE<sup>[2]</sup> and LATITUDE<sup>[3]</sup> in 2017 are the recent game changers (ADT ± abiraterone)
- **Controversy**: docetaxel + ADT debatable for low-volume metastases
  - New CHAARTED data negative for low volume subset<sup>[1]</sup>

1. Kyriakopoulos, et al. J Clin Oncol;36:1080-1087. 2. James ND, et al. N Engl J Med. 2017;377:338-351.

3. Fizazi K, et al. N Engl J Med. 2017;377:352-360. 4. Sydes MR, et al. Ann Oncol. 2018;[Epub ahead of print].

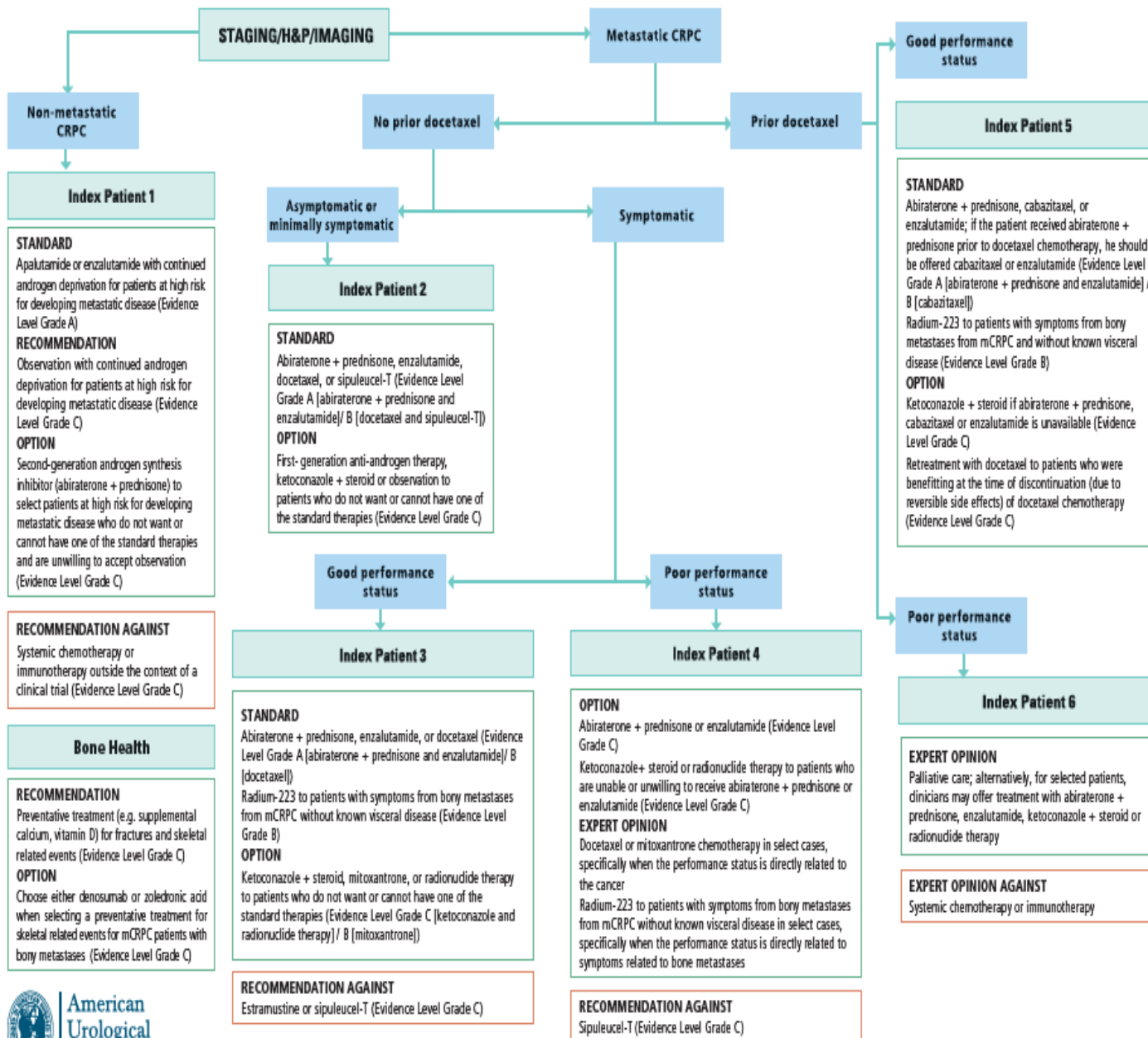


# Castrate Sensitive Metastatic Prostate Cancer

- 67-yr-old “healthy” retired accountant presents with PSA 76 ng/mL, Gleason score of 8, prostate cancer with moderate back pain, and 10 bone metastases scattered in his ribs, spine, and pelvis
- He presents telling you he has had an active lifestyle and travel schedule that he wants to maintain as long as possible
- Can offer:
  - ADT+ 6 cycles of docetaxel or
  - ADT+ abiraterone+prednisone until progression
  - Supportive care: Ca/Vit D/ weight-bearing exercise

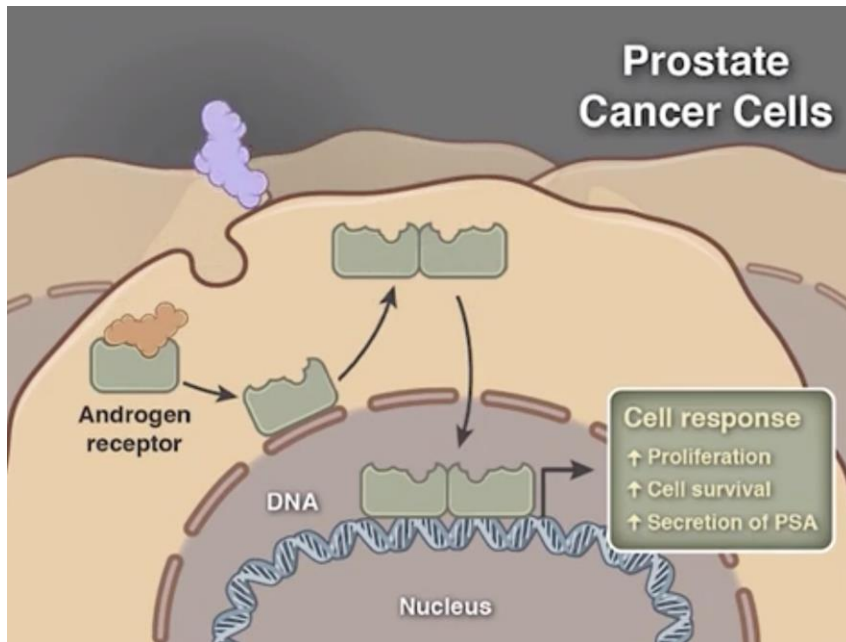


# Castration-Resistant Prostate Cancer: AUA Guideline 2018



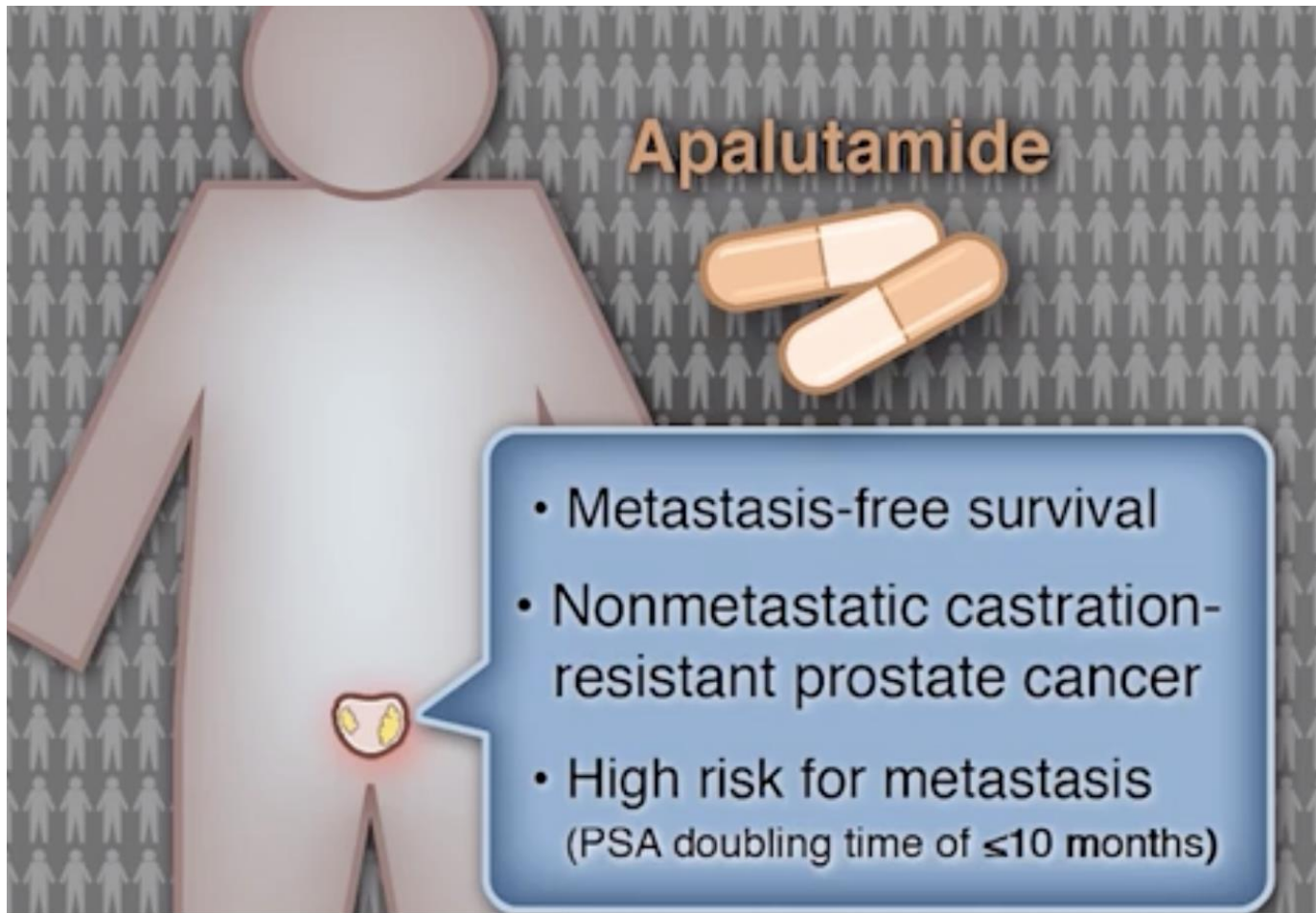
# SPARTAN RCT

## APALUTAMIDE VS PLACEBO



- PSA only failure
- Rising PSA >2ng/mL higher than nadir
- Rise has to be >25% over nadir
- Confirmed with 2<sup>nd</sup> PSA at least 3 weeks later
- Testosterone <0.5ng/dL
- No radiographic evidence of mets

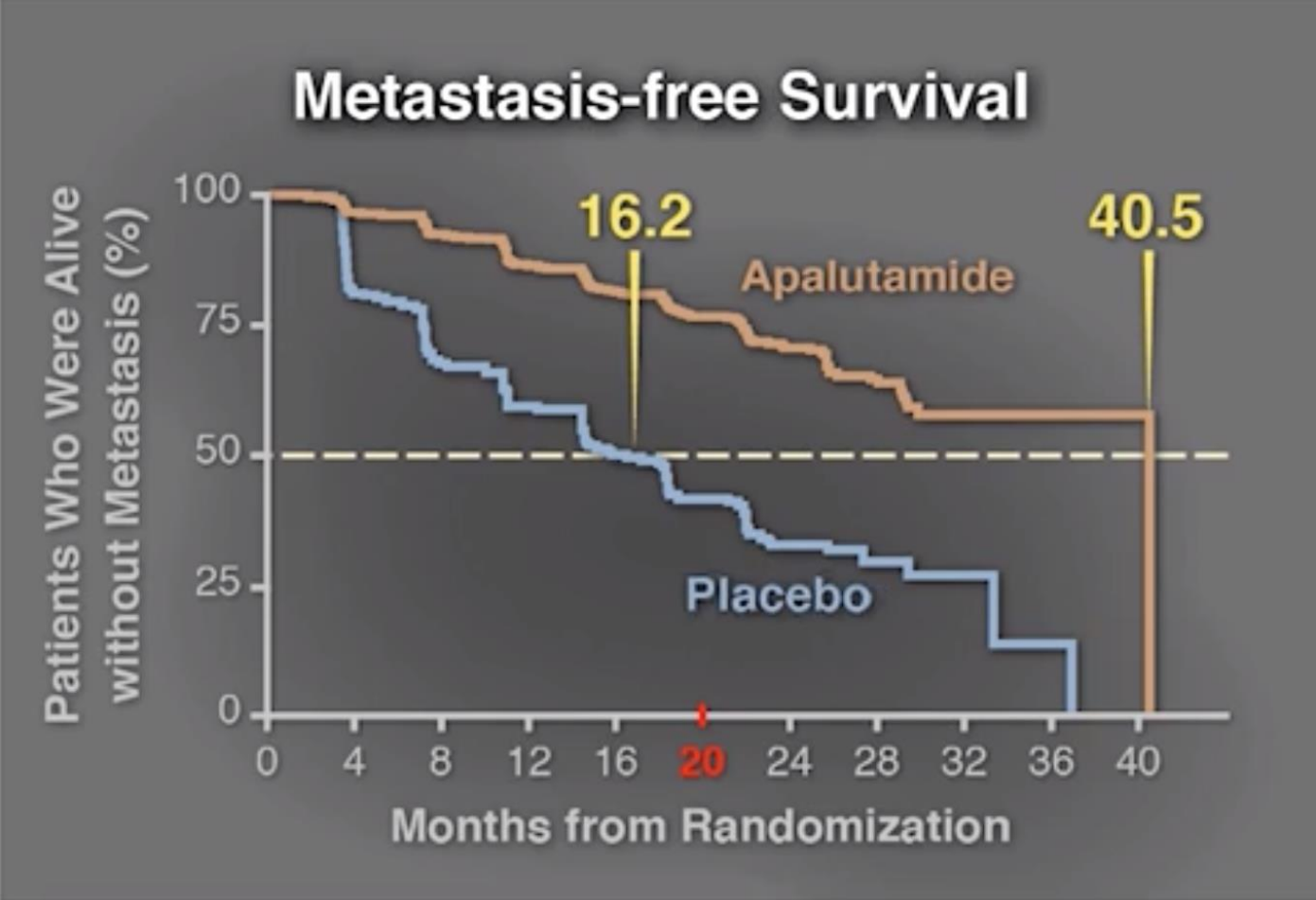
# CASTRATE RESISTANT NON-METASTATIC PROSTATE CANCER



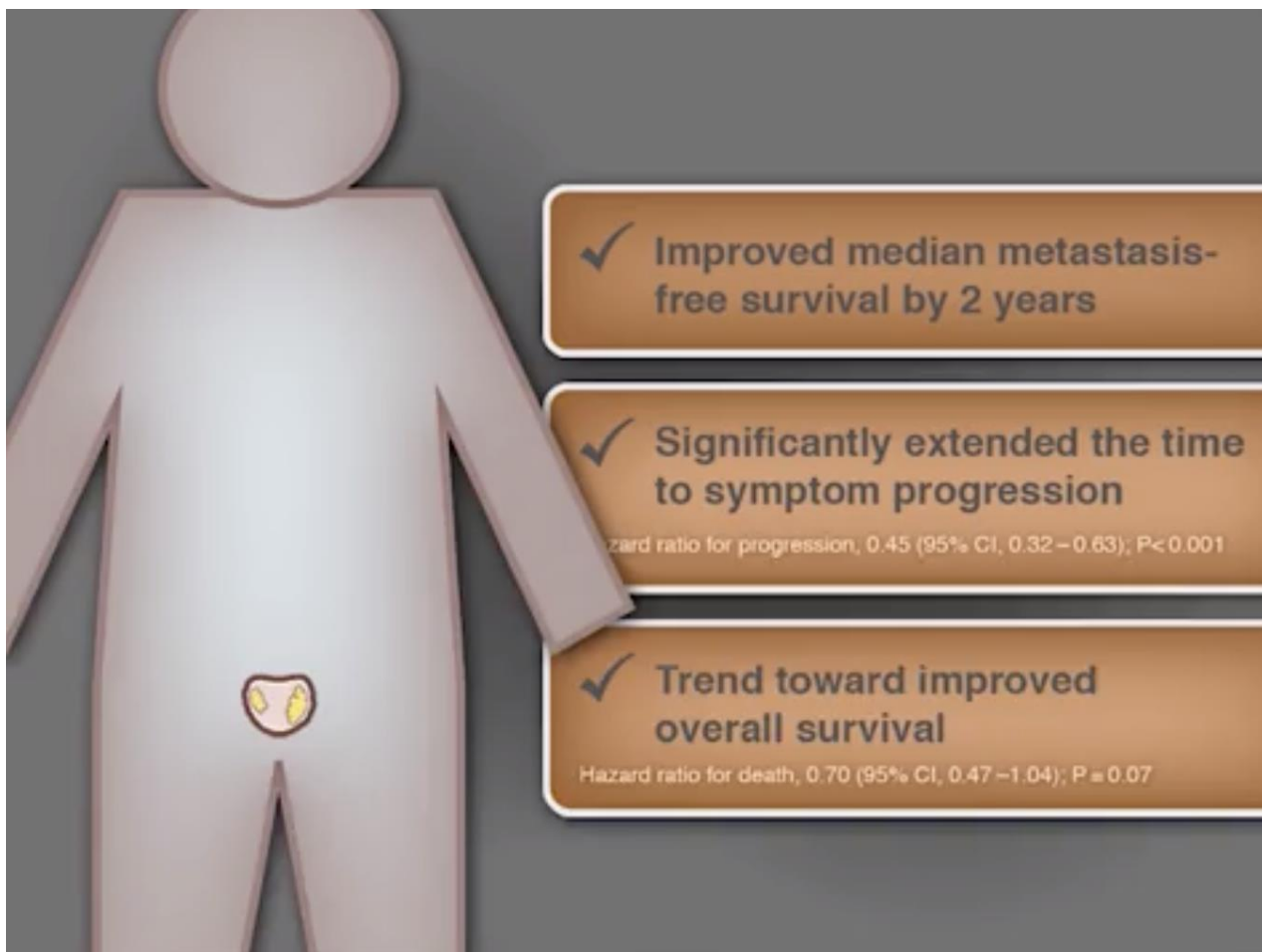
**Apalutamide**

- Metastasis-free survival
- Nonmetastatic castration-resistant prostate cancer
- High risk for metastasis (PSA doubling time of  $\leq 10$  months)

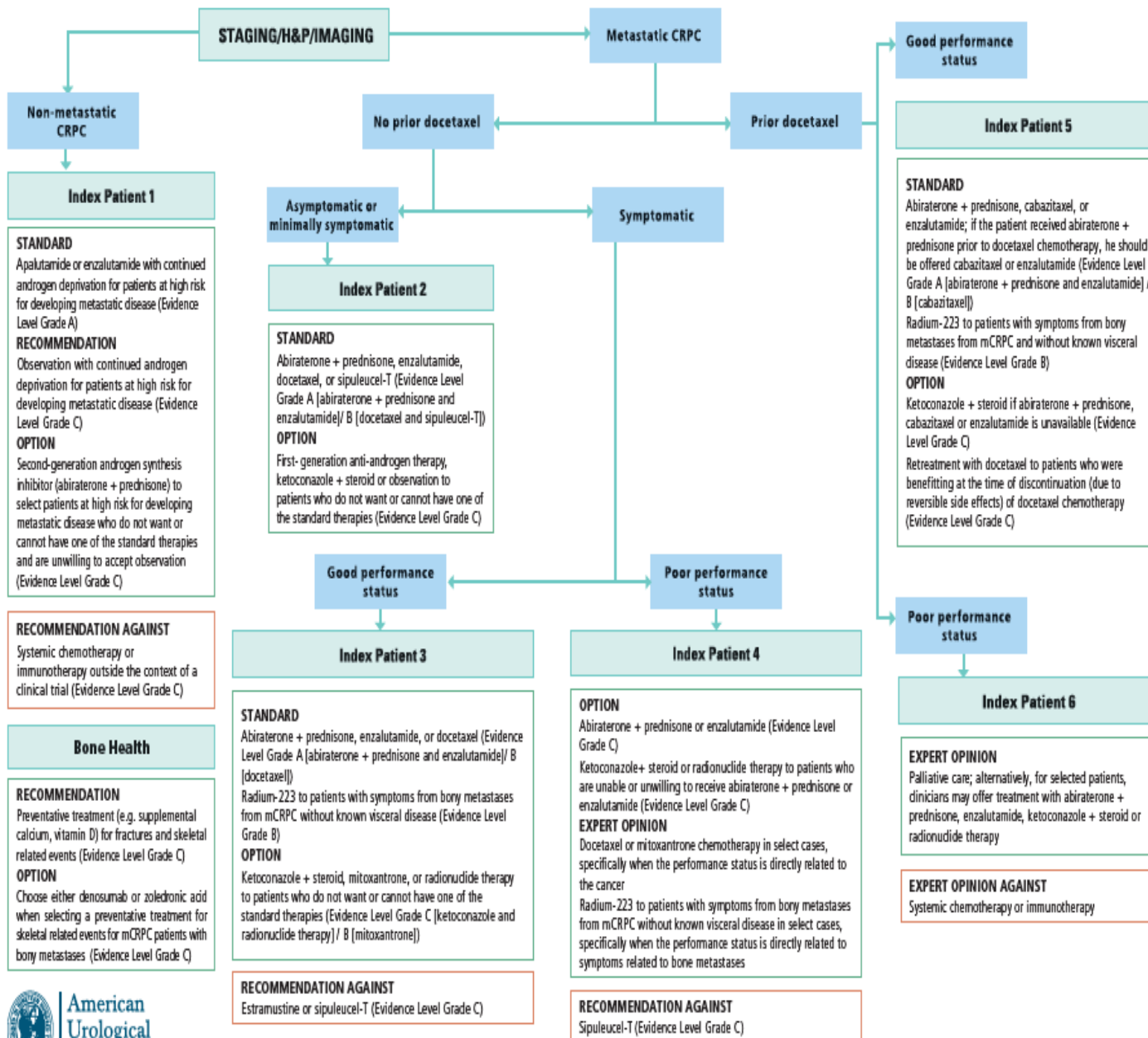
# Castrate Resistant non-metastatic Prostate Cancer-“M0”



# CASTRATE RESISTANT NON-METASTATIC PROSTATE CANCER



# Castration-Resistant Prostate Cancer: AUA Guideline 2018





# Castrate Resistant Metastatic PC Chemotherapy

## **Docetaxel**

- TAX-327 NEJM 2004
- 1<sup>st</sup> chemotherapy to show survival benefit
- 18m vs 16m

## **Cabazitaxel**

- TROPIC 2010
- Post docetaxel
- 15m vs 13m

# Castrate Resistant Metastatic PC

## AR Inhibitors

### Post Docetaxel

#### COU-301 2011

- Abi+prednisone vs pred
- OS benefit HR=0.65

#### AFFIRM 2012

- Enza vs placebo
- OS 18m vs 14m HR=0.63

### Pre Docetaxel

#### Minimally symptomatic

#### COU-302 2013

- Abi/pred vs pred
- OS benefit 35m vs 30m  
HR=0.81

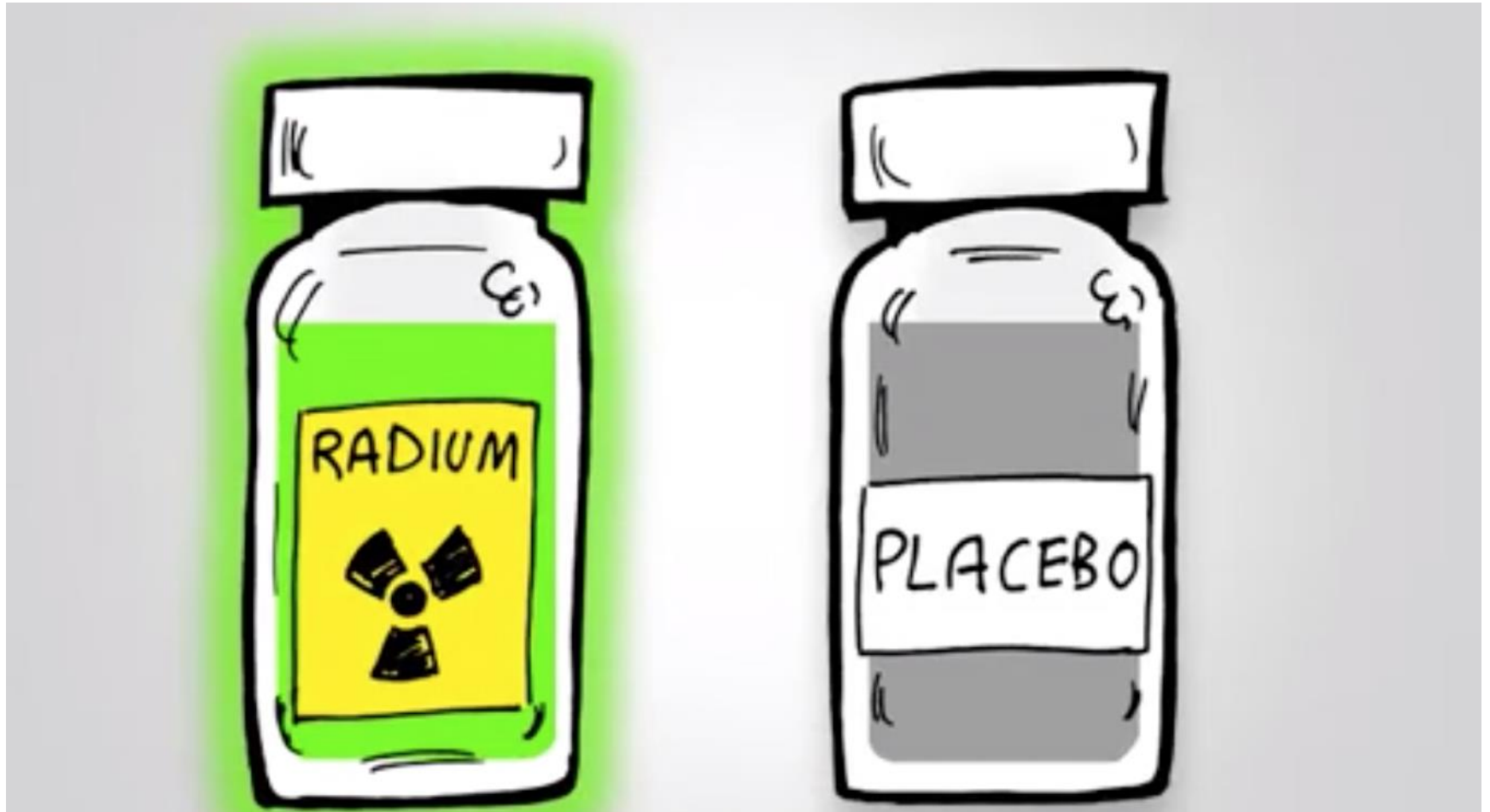
#### PREVAIL 2014

- Enza vs placebo
- 35m vs 31m
- HR=0.77

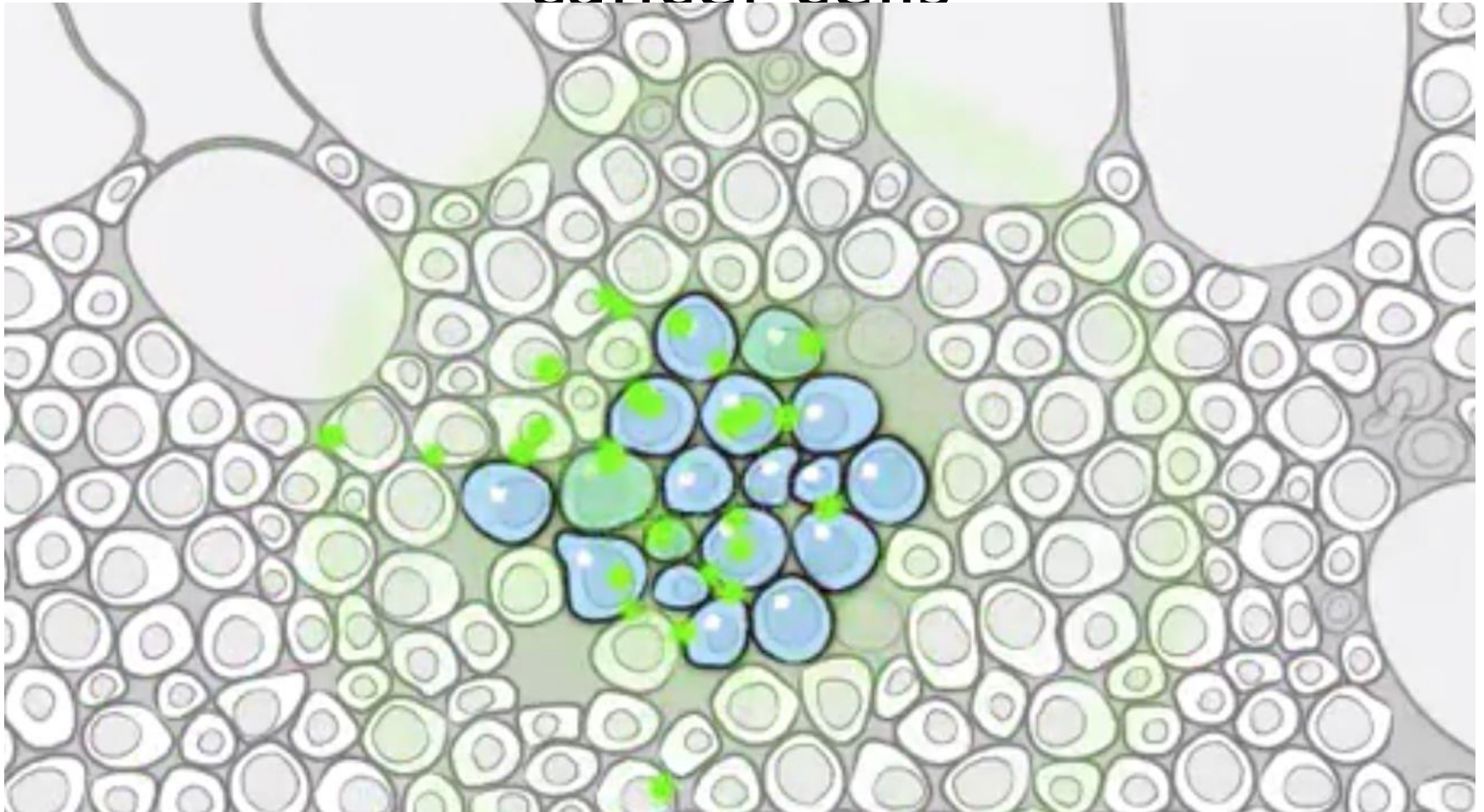
# Castrate Resistant Metastatic PC+ symptoms from bone mets



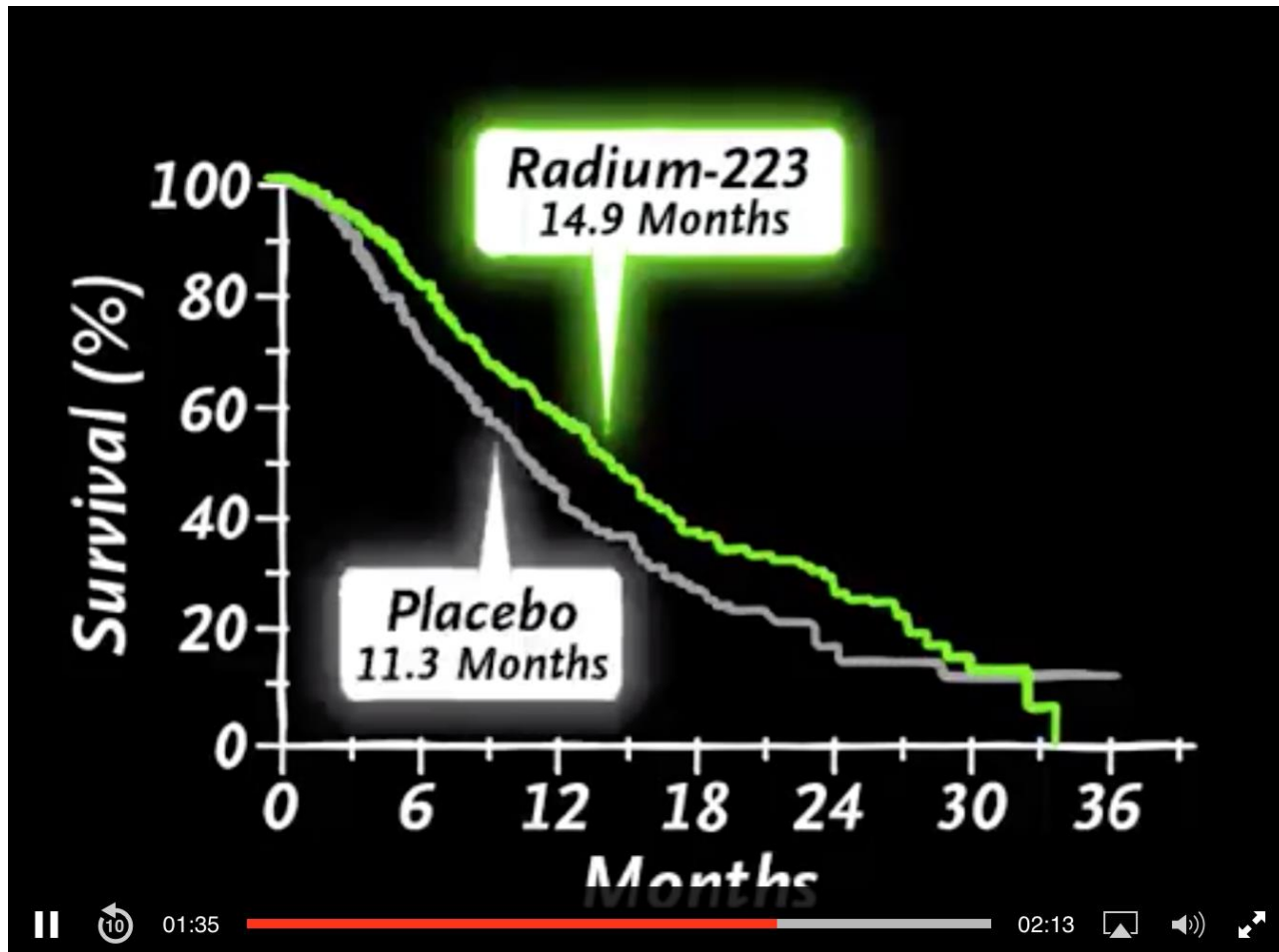
# ALSYMPCA 2013 NEJM



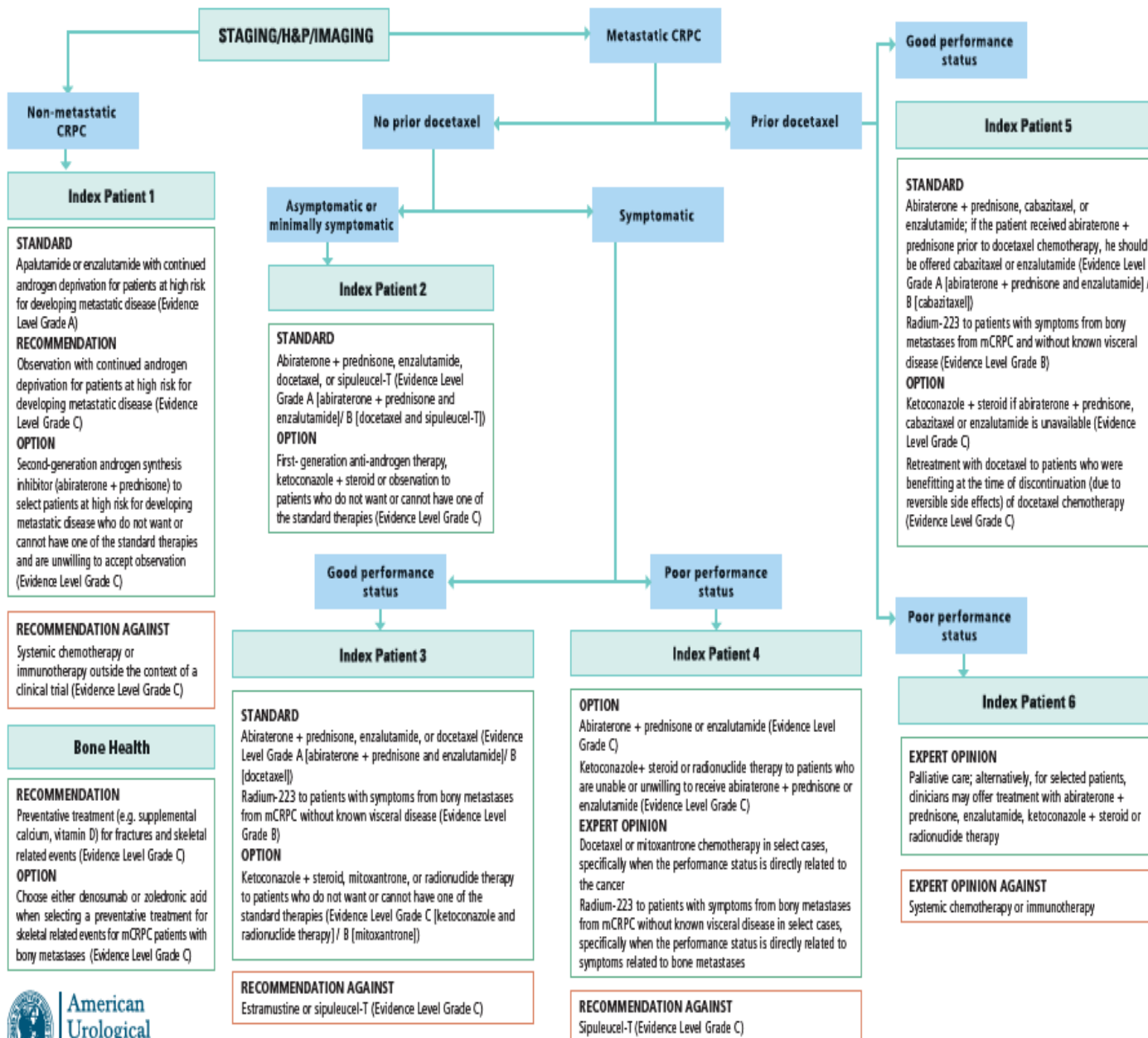
Rd223 isotope moves into bone and emits Alpha particles that destroy cancer cells



# Rd223 OS benefit in symptomatic metastatic CRPC



# Castration-Resistant Prostate Cancer: AUA Guideline 2018



# Castrate Resistant Metastatic PC

## Index pt 2

**Minimal symptoms**



**No prior chemo**

- Abi/prednisone
- Enzalutamide
- docetaxel



# Castrate Resistant Metastatic PC

## Index pt 3+4

### Symptoms



### No prior chemo

- Abi/pred
- Enza
- Docetaxel
- Rd223

# Castrate Resistant Metastatic PC

## Index pt 5+6

**Symptomatic**



**Prior docetaxel chemo**

- Cabazitaxel
- Abi/prednisone
- Enzalutamide
- mitoxantrone/ prednisone



# Genetic Features of CRPC

Defect in AR signaling

- AR-V7
- Resistance to AR inhibitors

Defect in DNA repair (12%)

- BRCA 1/2
- Parp inhibitors

Defect in Mismatch repair

- MSI-High
- immunotherapy

**oncotypeDX<sup>®</sup>**  
*AR-V7 Nucleus Detect*  
powered by Epic Sciences

**A more tailored  
treatment**

