

# Introduction to advanced prostate cancer and the current treatment pathway

BAUN Study Day

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# Introduction

- What is advanced prostate cancer
- How and why do prostate cancers metastasise
- History of treatment types
- Why and how does CRPC develop
- What do the current guidelines tell us
- Brief overview of systemic therapies

# Advanced prostate cancer

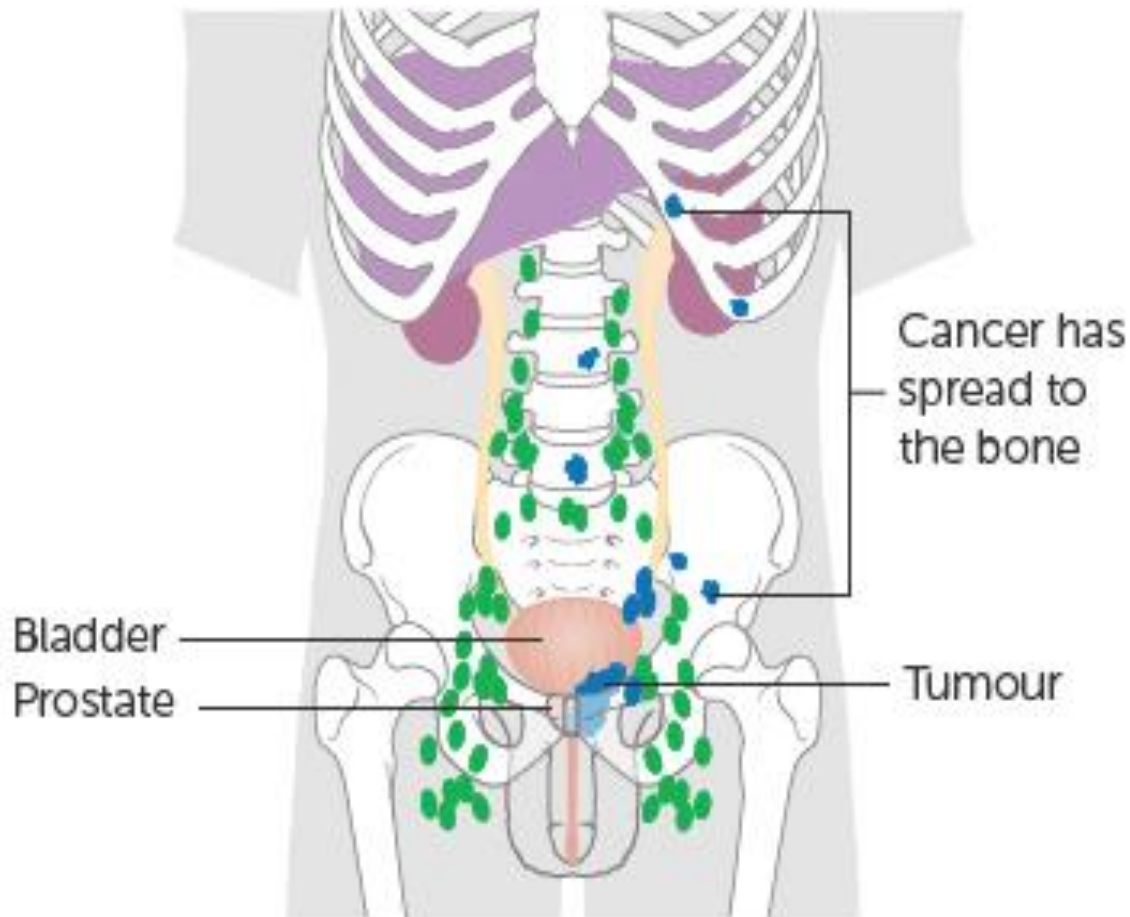
## Locally advanced

- T3 - Extension outside of prostate
- T4 - Fixed or invades adjacent structures
- N1 - Mets in regional lymph node(s)
- Confined to pelvis
- Potential for radical treatment

## Advanced

- M1 Distant mets
  - M1a - Nonregional lymph nodes
  - M1b - Bone(s)
  - M1c - Other

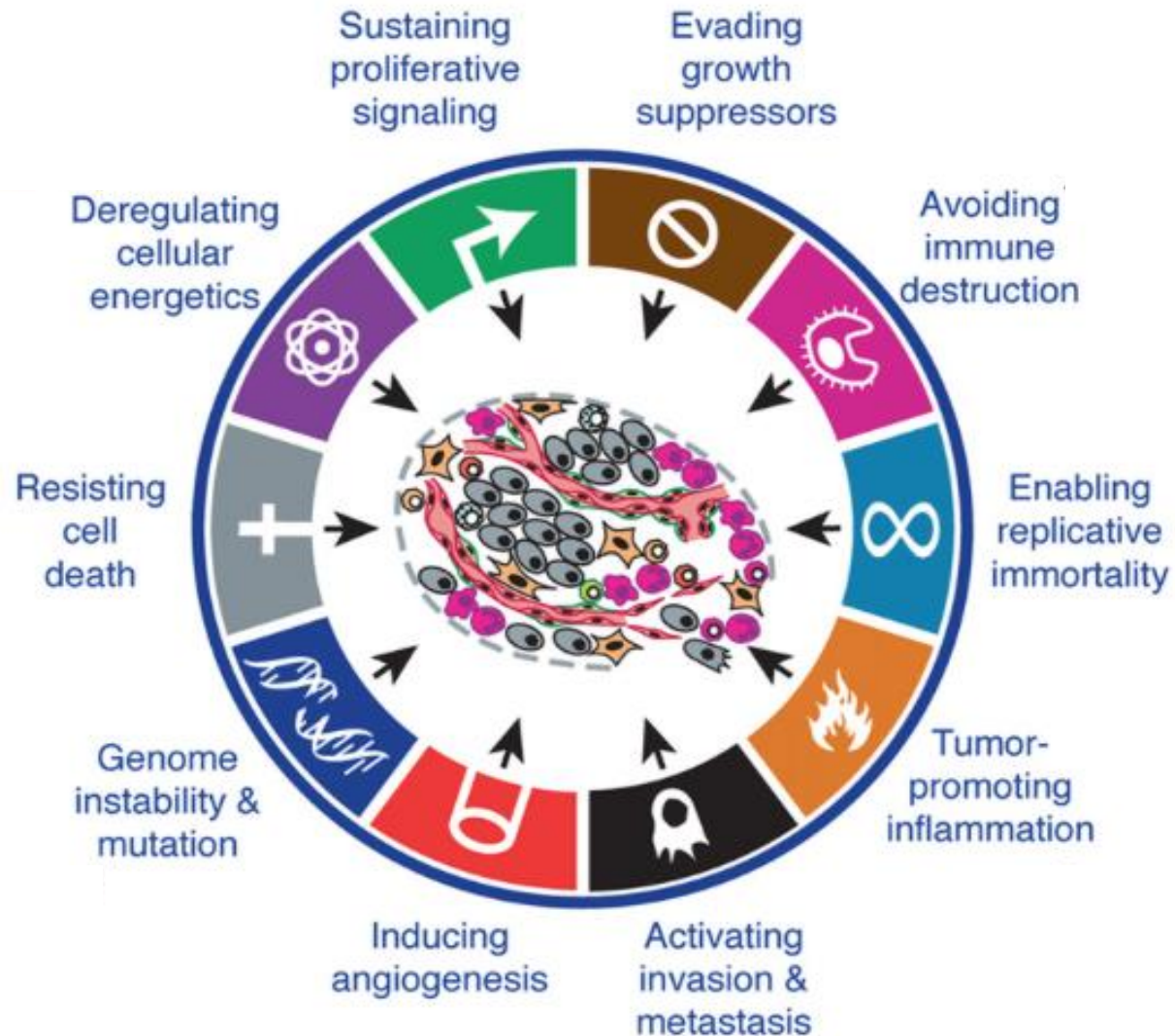
# How do prostate cancers metastasise



Steps in cancer cell metastasis:

- Local invasion
- Intravasation
- Circulation
- Arrest and extravasation
- Proliferation
- Angiogenesis

# Why do prostate cancers metastasise



# History of treatment types

- Surgical castration

**Charles HUGGINS, the father of hormone therapy**



**Charles HUGGINS**  
1901 – 1955  
Winner of 1966 Nobel Prize

## Studies in prostate cancer :

I. The effect of estrogens and androgen injection on serum phosphatases in metastatic carcinoma of the prostate

*Cancer Res., 1941*

II. The effect of castration on advanced carcinoma of the prostate gland

*Arch. Surg., 1941*

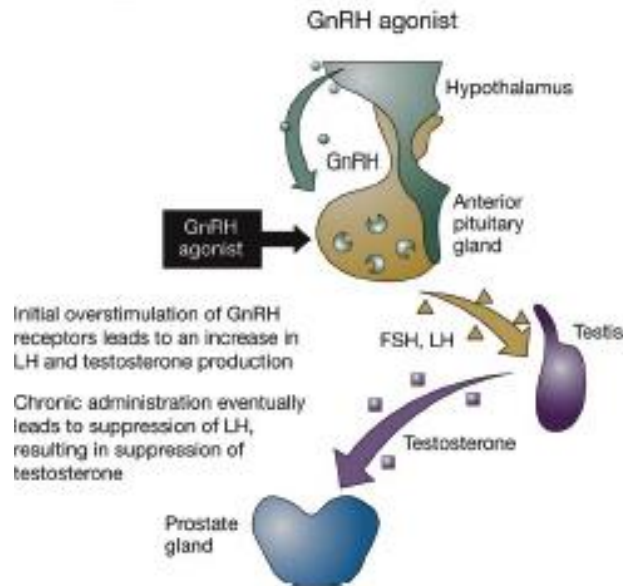
# History of treatment types

- Medical castration

## Andrew SCHALLY, the father of medical castration



Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists.  
*A Schally, Proc Natl Acad Sci., 1982*



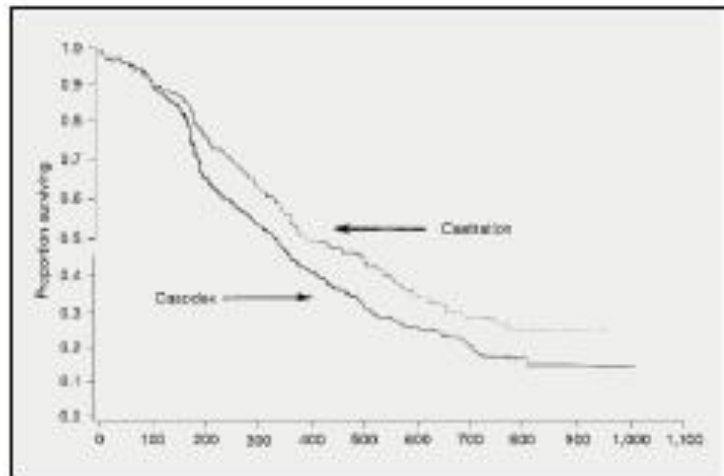
LHRHa	1 mth.	3 mths	6 mths
Eligard*	✓	✓	✓
Decapeptyl*	✓	✓	(✓)
Enantone*	✓	✓	✓
Lucrin Depot*		✓	
Lupron Depot*	✓	✓	
Suprefact Depot*		✓	
Zoladex*	✓	✓	

# Anti-androgen v LHRH agonist

## Bicalutamide 150 mg vs. GnRH

**M+**

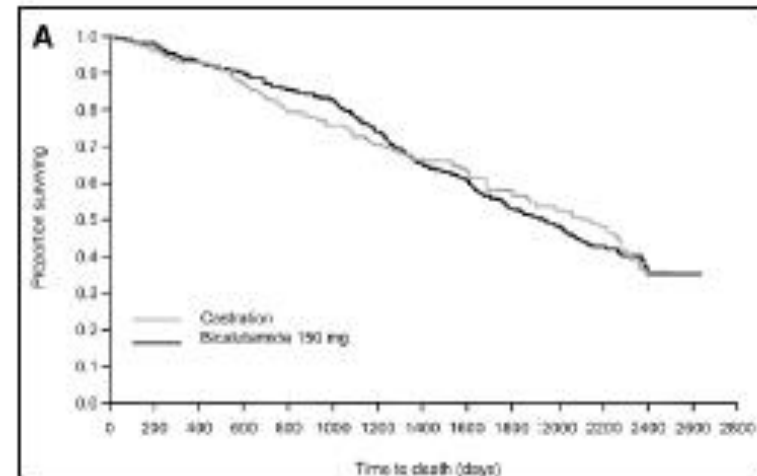
HR = 1.430;  $p = 0.0001$



**Tyrell et al Eur Urol (1998)**

**M0**

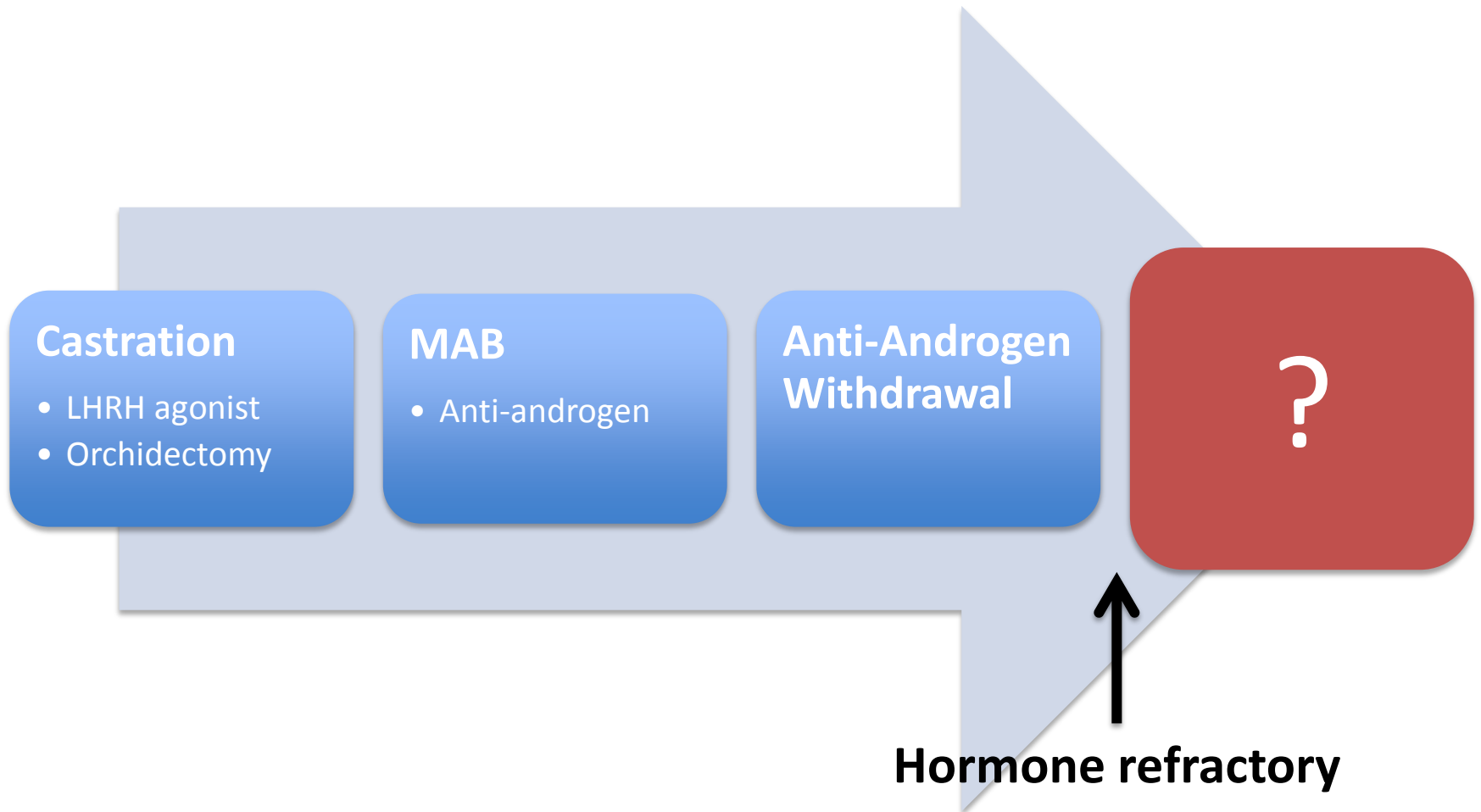
HR = 1.05;  $p = 0.70$



**Iversen et al Urology (2000)**



# Treatment Algorithm

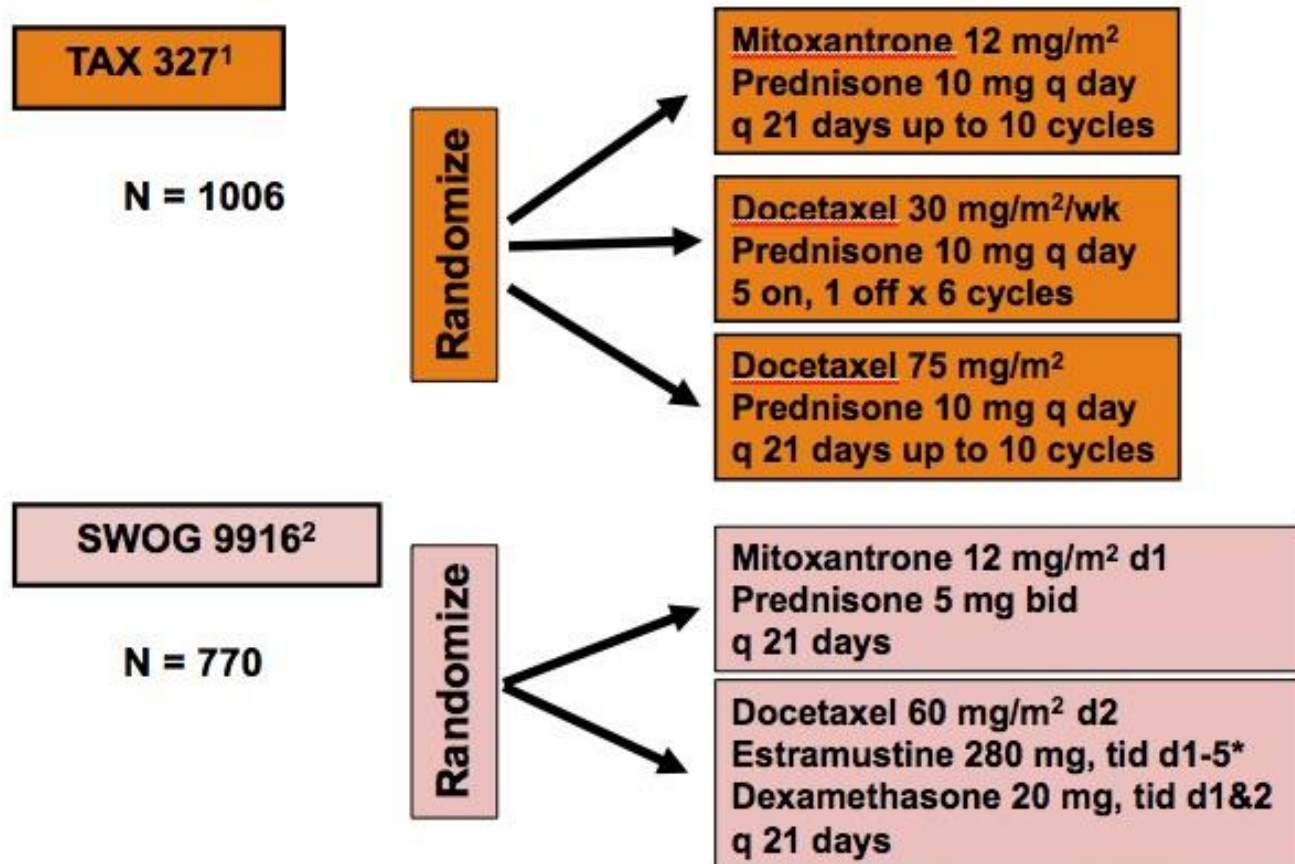


# What Next?

Intervention	Response Rate %	Duration of Response (months)	Survival Benefit
Alternative anti-androgen	4-50	4-11	No
Ketoconazole	27-63	3-9	No
Steroids	15-60	2-4	No
Oestrogens	12-80	2.5-4	No
Mitoxantrone	30	10	No

- Many have a short duration of response
- No proven survival advantage

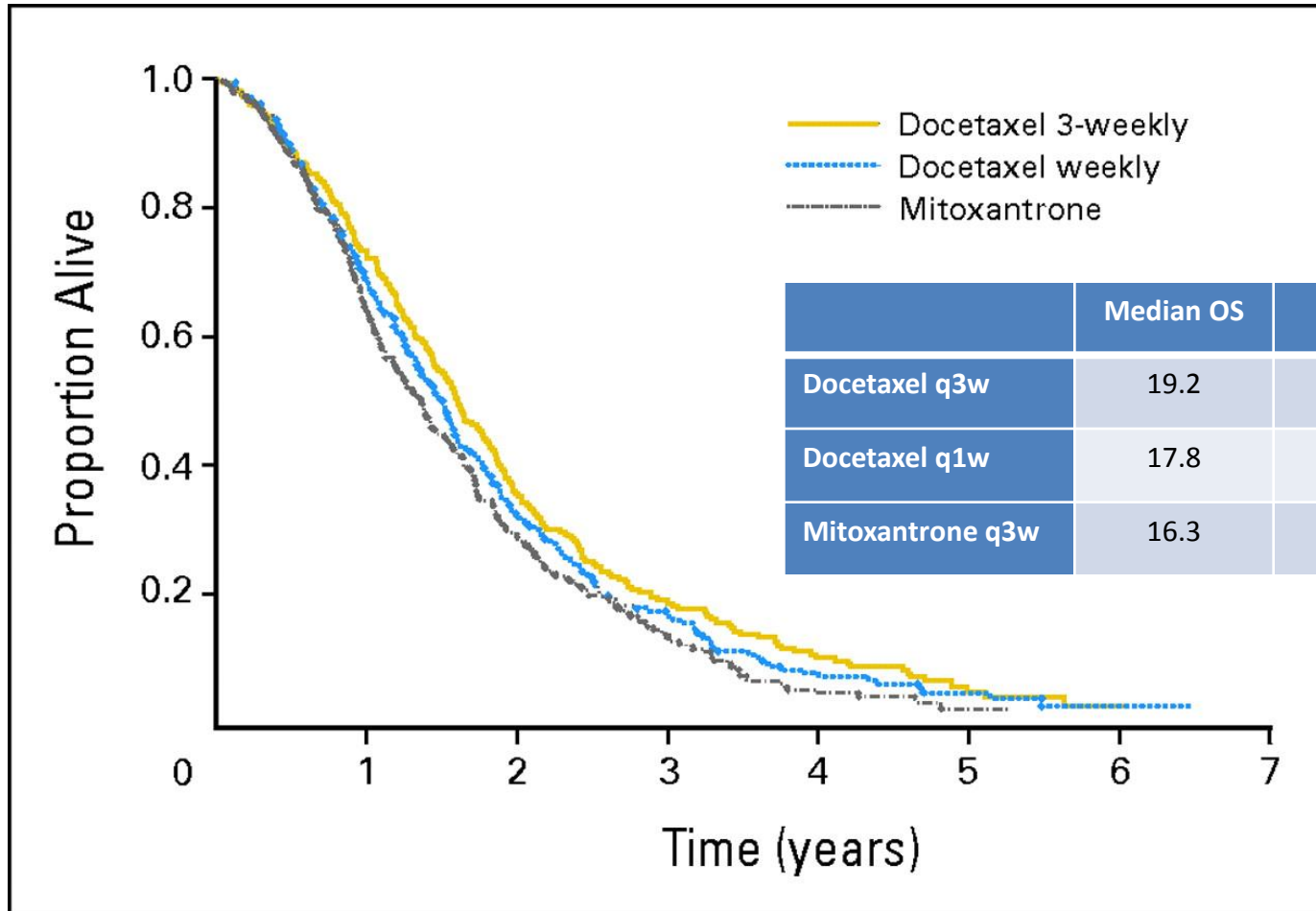
# Docetaxel: Phase III Studies



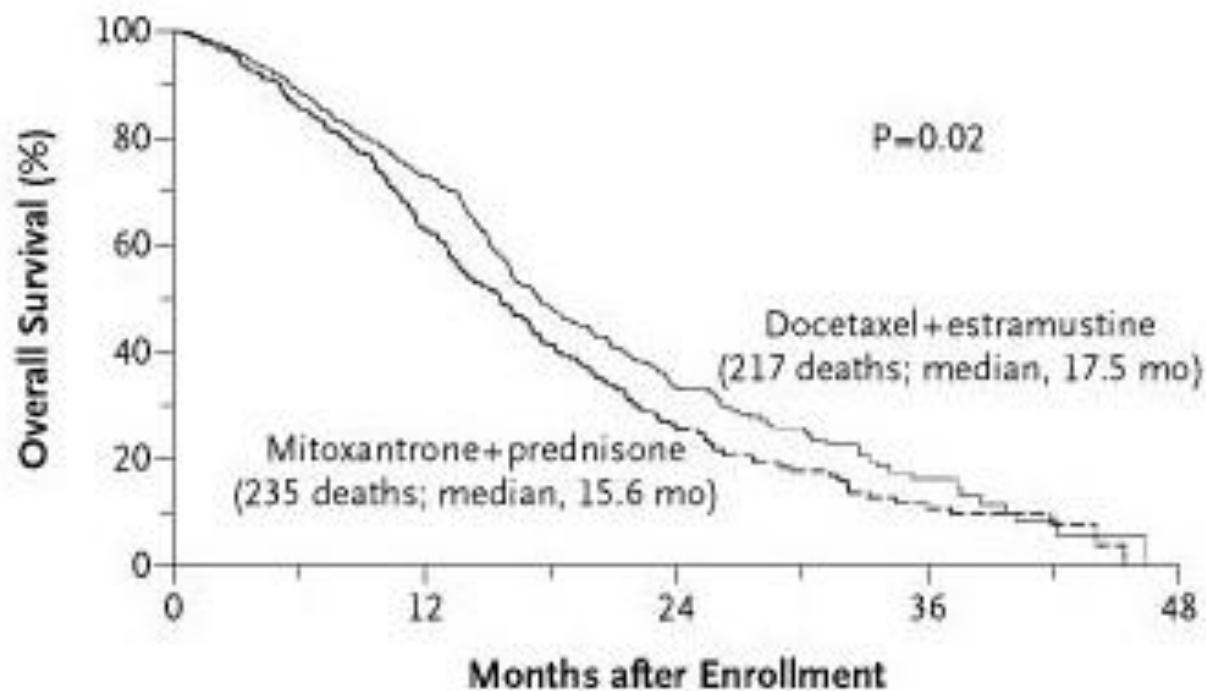
1. Tannock IF, et al. *N Engl J Med.* 2004;351(15):1502-1512.
2. Petryak DP, et al. *N Engl J Med.* 2004;351(15):1513-1520.

\*Warfarin and aspirin q day

# TAX 327: Overall Survival

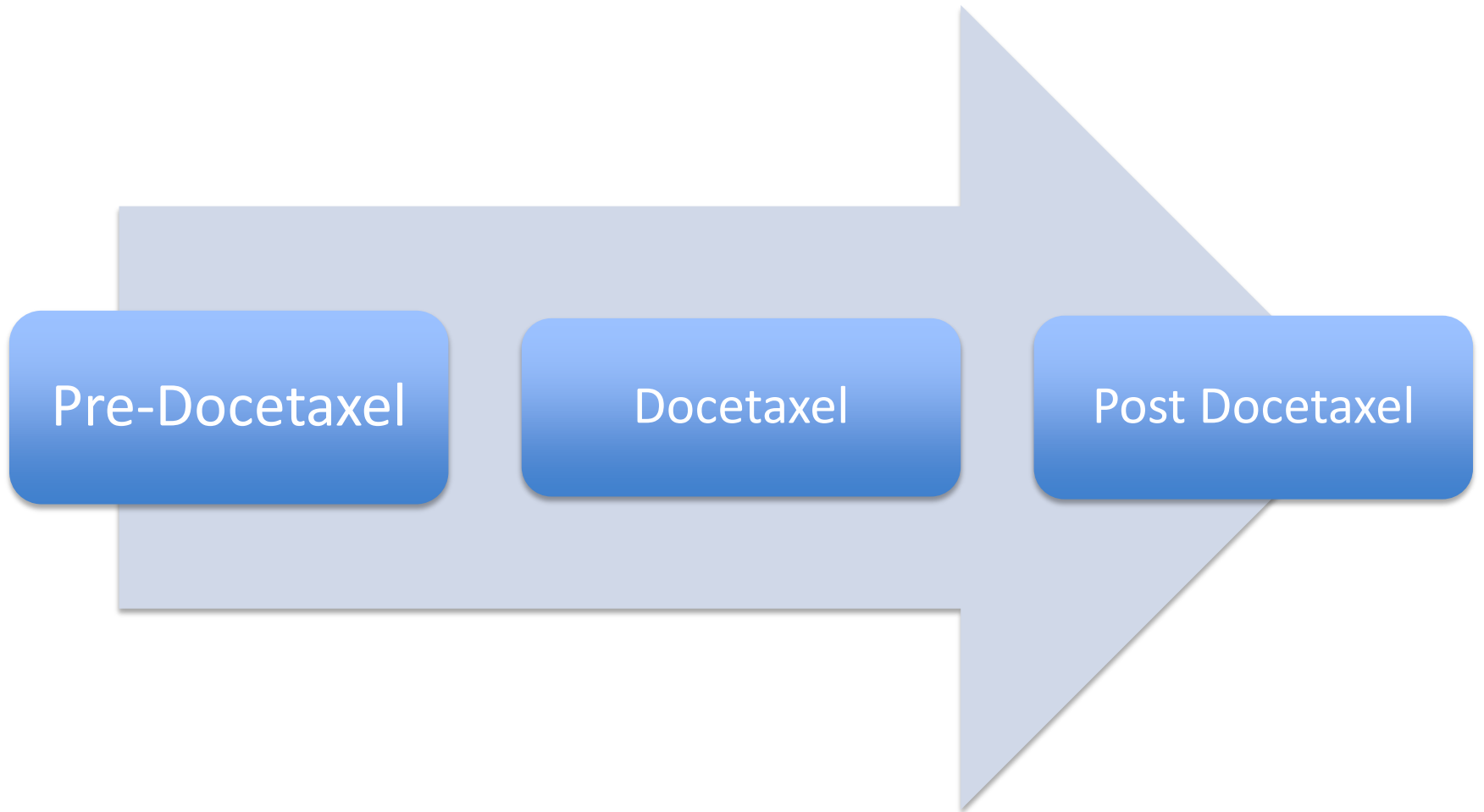


# SWOG 9916: Overall Survival



	Median OS	HR	P-value
Docetaxel Estramustine q3w	17.5	0.8	0.02
Mitoxantrone q3w	15.6	-	-

# Treatment algorithm



Pre-Docetaxel

Docetaxel

Post Docetaxel

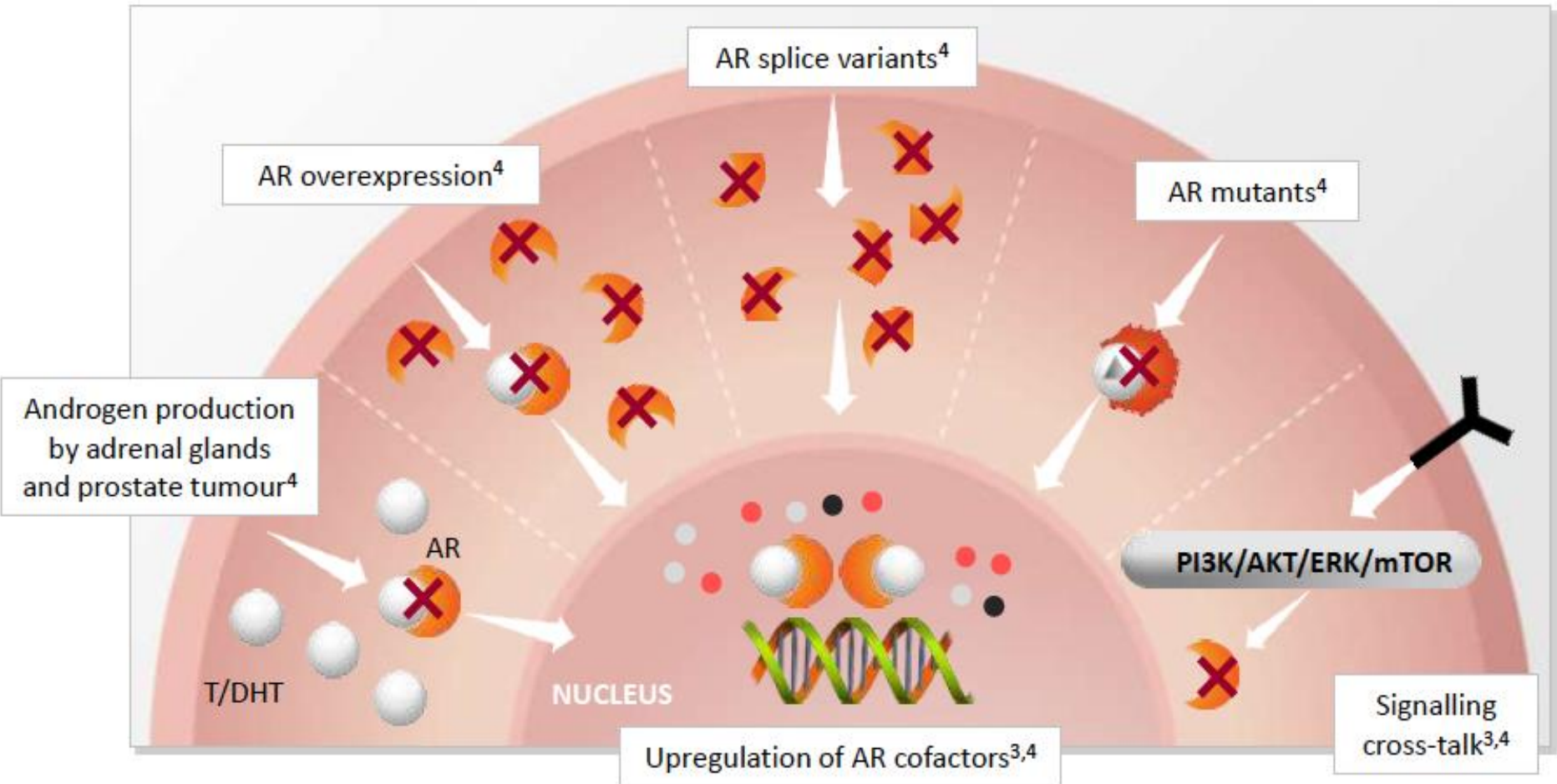
~~Hormone refractory prostate cancer~~

# Castrate resistant prostate cancer

- EAU definition
  - Castrate serum levels of testosterone (<50 ng/dl or < 1.7 nmol/l)
  - 3 consecutive PSA rises
    - 1 week apart
    - resulting in two 50% increases over the nadir WITH PSA > 2
  - Anti-androgen withdrawal for at least 6 weeks with bicalutamide
  - PSA progression despite consecutive hormonal manipulations
  - Progression of bone or soft tissue lesions/new lesions



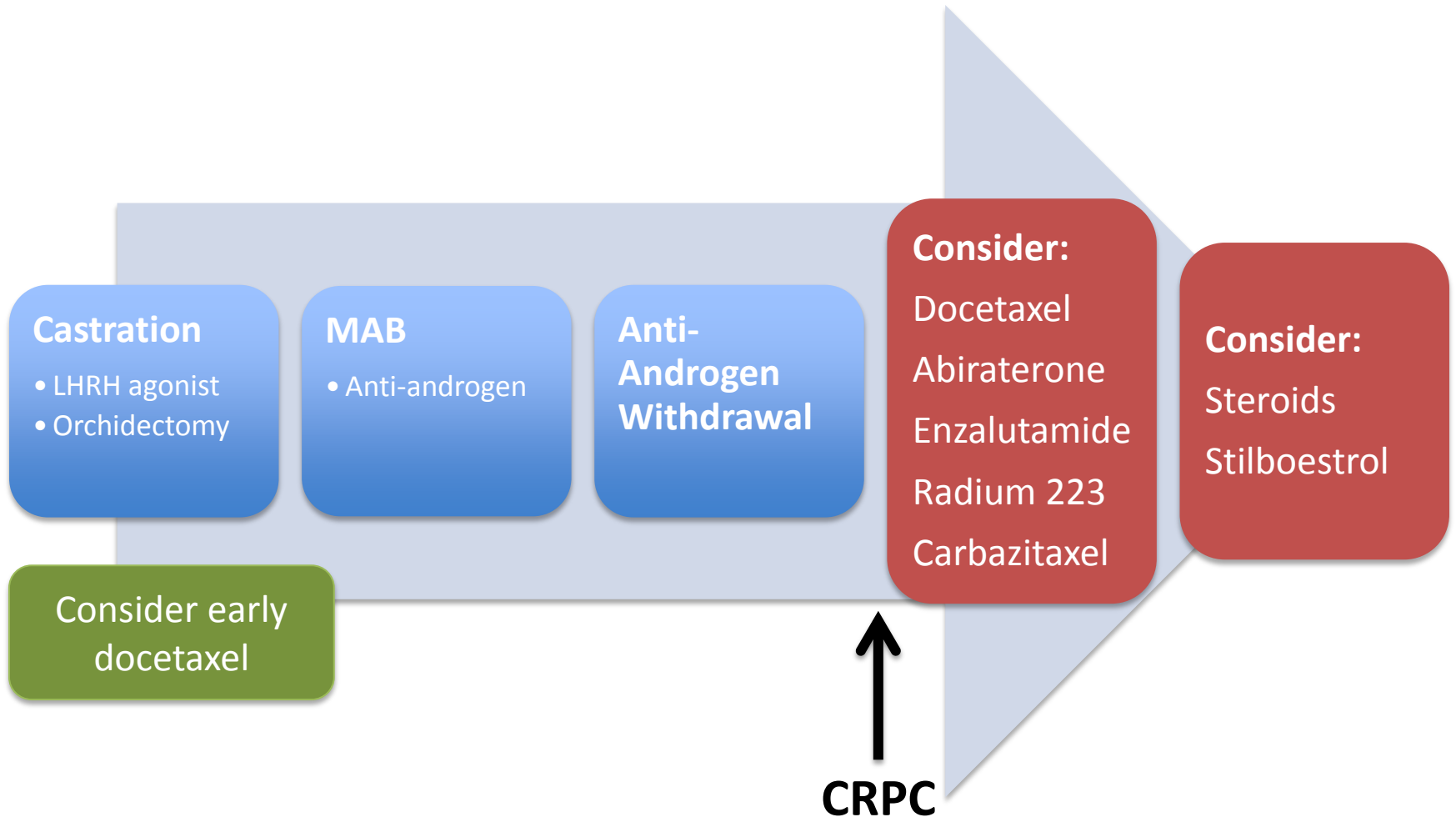
# How does CRPC develop



# Current guidelines - NICE

- New metastatic disease
  - ADT (offer bilateral orchidectomy as alternative)
  - Anti-androgen bicalutamide
    - Accept adverse impact on OS, retain sexual function

# Treatment Algorithm



Any questions?