



# Hormone Therapy in Prostate Cancer

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# Introduction and Epidemiology

- Second most common cause of cancer among men worldwide.
- Sixth leading cause of cancer death among men worldwide.
- In the United States 11% of male cancer deaths (expected in 2014)
- The worldwide burden is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030 simply due to the growth and aging of the global population.
- Prostate is the second leading site of cancer among males in large Indian cities like Delhi, Kolkatta.
- Third leading site of cancer in cities like Bangalore and Mumbai and it is among the top ten leading sites of cancers in the rest of the PBRCs of India.

# Risk Factors

- There are three well-established risk factors for Prostate Cancer:
  - Increasing age
  - Ethnic origin (African- Americans)
  - Heredity
    - 1<sup>st</sup> degree relatives diagnosed below the age of 60
    - BRCA 2 mutation
    - Lynch Syndrome

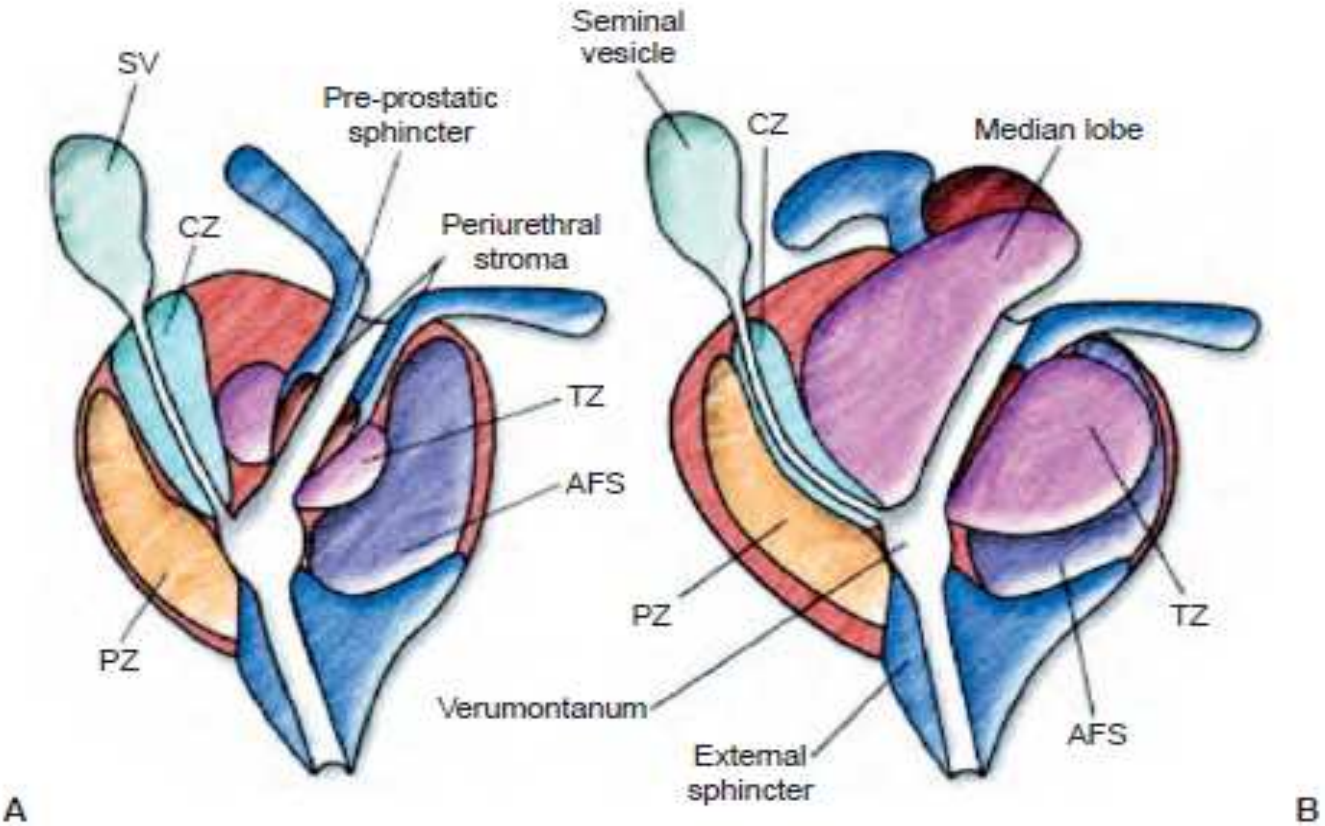
# PROSTATE CANCER IS DIFFERENT FROM OTHER MALIGNANCIES

- It is a chronic disease
- Clinically Insignificant Cancer
  - No benefit from early diagnosis
  - Are overdiagnosed and overtreated
  - Quality of Life impaired on account of treatment
- Clinically Significant Cancer
  - Tumor will/ or have metastasis
  - At a risk for impaired Quality of Life (Symptomatic)
  - Shortened life expectancy
  - Benefit from early diagnosis

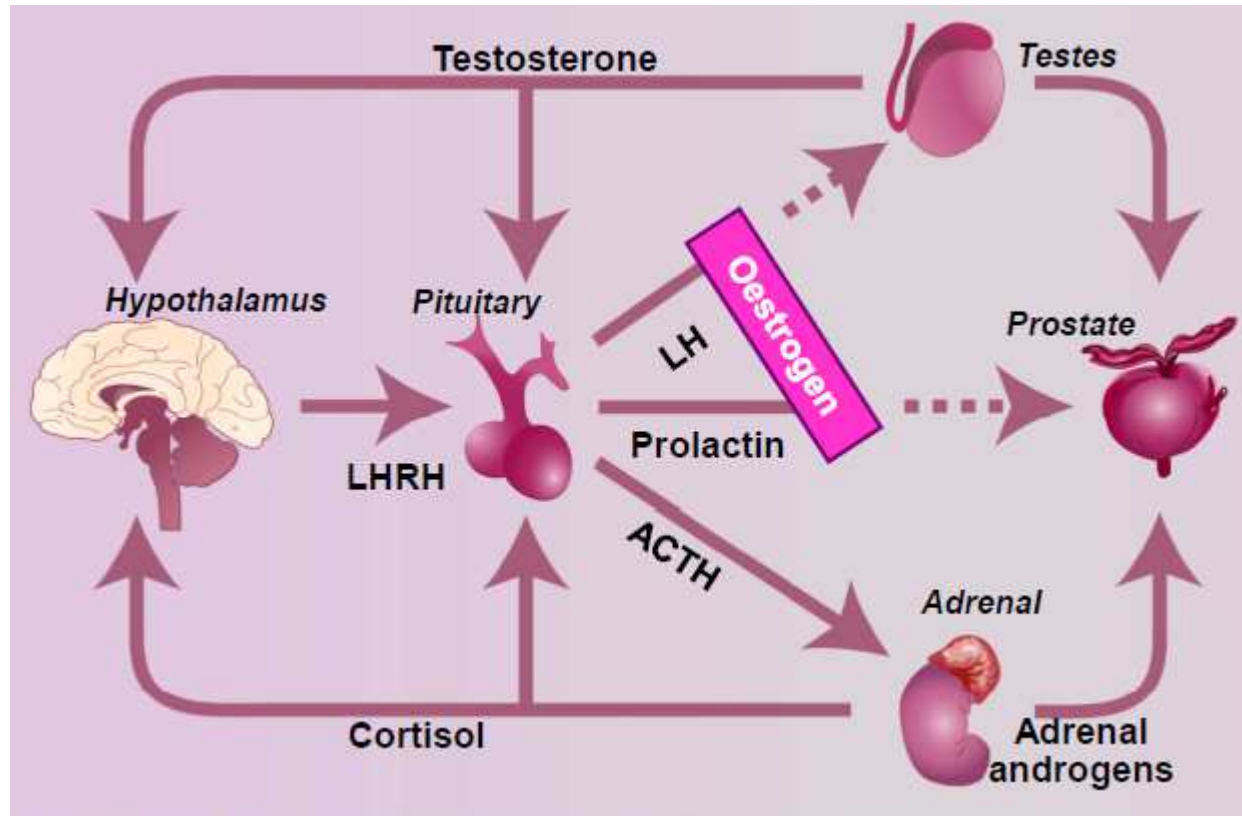
# CHALLENGES IN PROSTATE CANCER

- Symptoms of BPH and Cancer Prostate Overlap
- Anatomical Location
- Proximity to vital structures
  - Venous plexus
  - External Sphincter
  - Rectum
- Castration Resistant

# How Anatomy Changes?



# Pathophysiology



# Hormones and Prostate

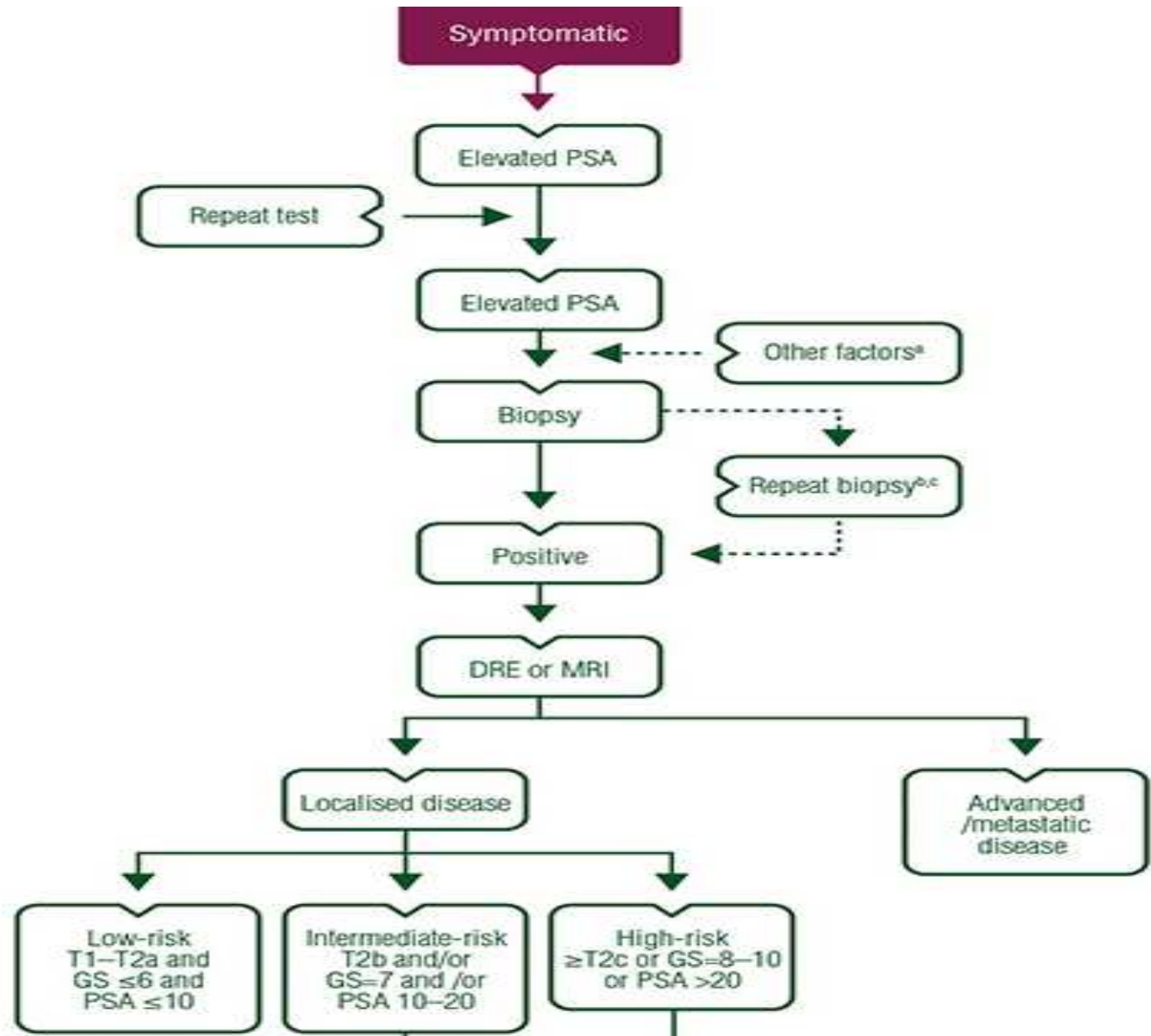
- Finasteride (a competitive inhibitor of type II 5 $\alpha$ -reductase)
- Blocks the conversion of testosterone to dihydrotestosterone (DHT) within prostatic cells.
- Reduces the size of the prostate and relieves voiding symptoms
- Effective drug for benign prostatic hyperplasia (BPH).
  
- Before the age of 40 – hypopituitarism or orchidectomy – reduces the real risk of prostatic cancer



# Time line

- 1940's : **Surgical removal of testes / exogenous estrogen**
- 1945's : Surgical Adrenelectomy following disease progression
- 1980's : **Non steroidal Anti androgens**
- 1980's : **LHRH agonists**
- 1990's : **Combined Androgen Blockade era**
- 2004 : Docetaxel
- 2010 : Cabazitaxel, Sipuleucel-T, Radium-223, Denosumab  
**Abiraterone Acetate, Enzalutamide**

# WORK UP and RISK STRATIFICATION



# RISK STRATIFICATION

## Very low:

- T1c
- Gleason score  $\leq 6$ /Gleason grade group 1
- PSA  $< 10$  ng/mL
- Fewer than 3 prostate biopsy cores positive,  $\leq 50\%$  cancer in each core
- PSA density  $< 0.15$  ng/mL/g

## Low:

- T1-T2a
- Gleason score  $\leq 6$ /Gleason grade group 1
- PSA  $< 10$  ng/mL

## Intermediate:<sup>f</sup>

- T2b-T2c or
- Gleason score 3+4=7/  
Gleason grade group 2 or
- Gleason score 4+3=7/  
Gleason grade group 3 or
- PSA 10–20 ng/mL

## High:<sup>f</sup>

- T3a or
- Gleason score 8/ Gleason grade group 4 or
- Gleason score 9–10/  
Gleason grade group 5
- PSA  $> 20$  ng/mL

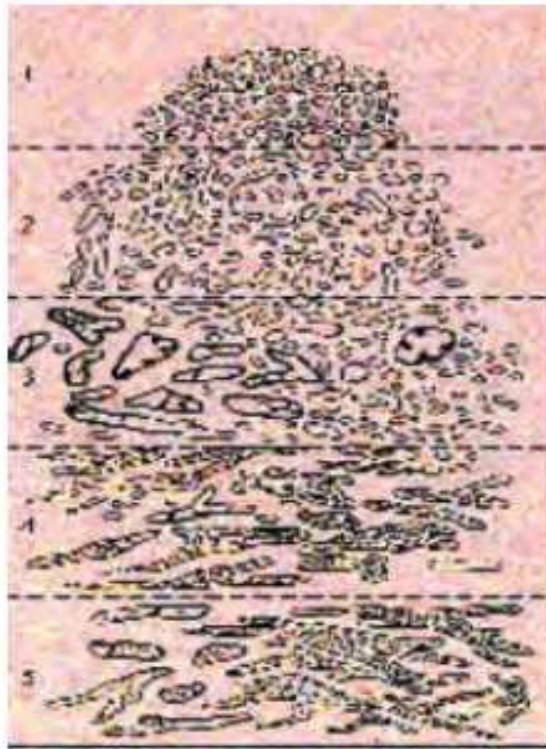
## Locally Advanced:

### Very high:

- T3b-T4 or
- Primary Gleason pattern 5/  
Gleason grade group 5 or
- $> 4$  cores with Gleason score 8–10/  
Gleason grade group 4 or 5

# Gleason scoring

## Gleason Pattern



1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Well differentiated



Moderately differentiated



Poorly differentiated/  
Anaplastic



# Prostate Specific Antigen (PSA)

- It is Organ specific, NOT Cancer specific
- Screening tool?
- Levels of PSA
- Midlife PSA
- PSA Density
- PSA Velocity
- Kallikreins (4)
- Free/ Total PSA

# Castration

- **Surgical orchidectomy**

(subcapsular)

- **Medical orchidectomy**

(LHRH agonists, LHRH antagonists, High Dose Antiandrogens)

- **Testosterone Level :**

The standard castrate level was  $< 50$  ng/dL (1.7 nmol/L).

It was defined more than 40 years ago, when testing was limited.

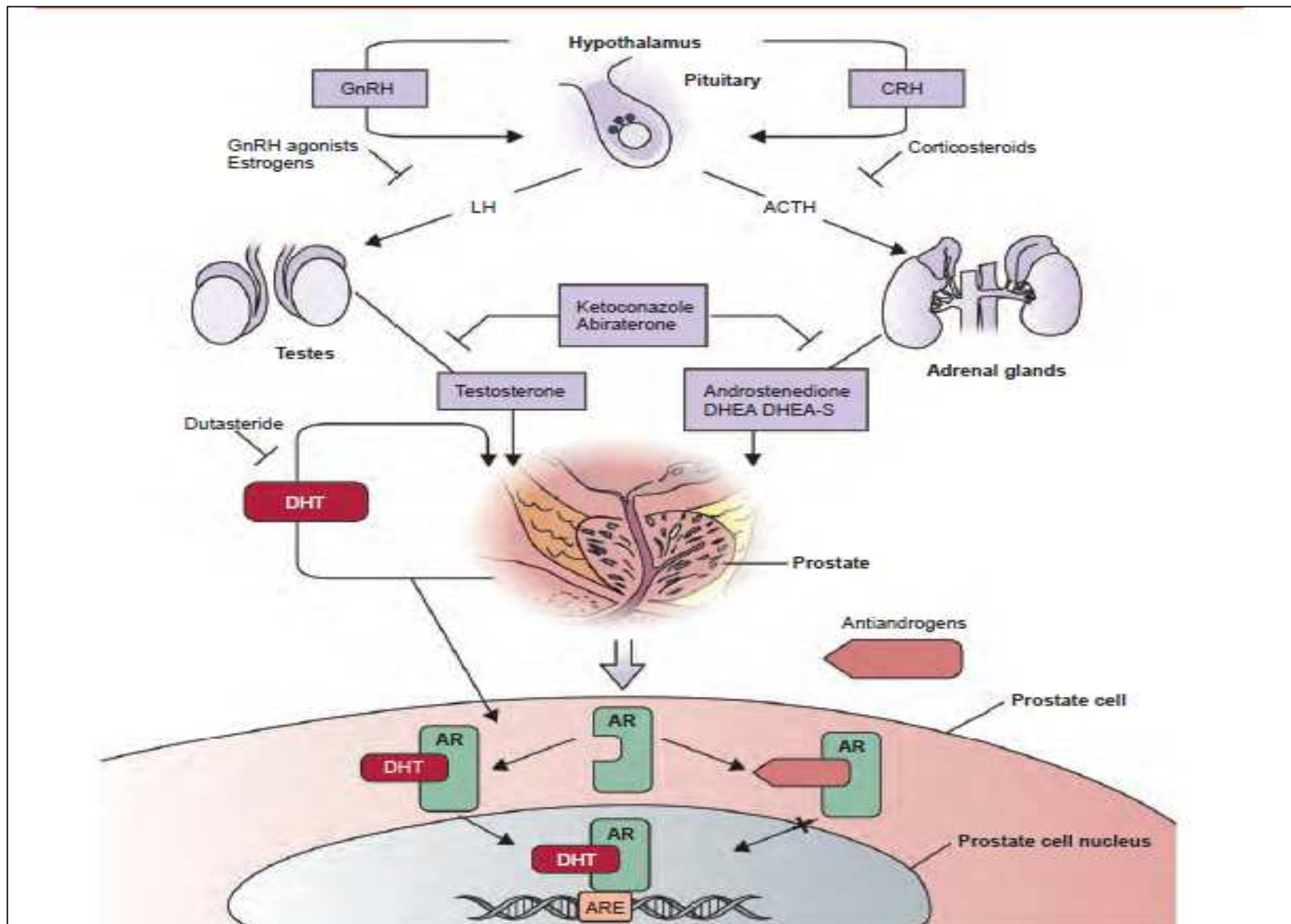
# Hormone Therapy

- Neoadjuvant Setting
- Adjuvant Setting – Duration of hormone therapy?
- Metastatic
- Castrate Resistant Prostate Cancer (CRPC)

# Hormonal Therapy - Options

- Bilateral Orchiectomy
- LHRH agonists and antagonists
- Anti androgens
- Combined Androgen Blockade
- Hormone Therapy for CRPC





# Hypothalamic Pituitary Gonadal Axis

- Hypothalamus → LHRH → Pituitary → FSH → Sertoli Cells  
→ LH → Leydig Cells

## Bilateral Orchiectomy ( Total or Subcapsular )

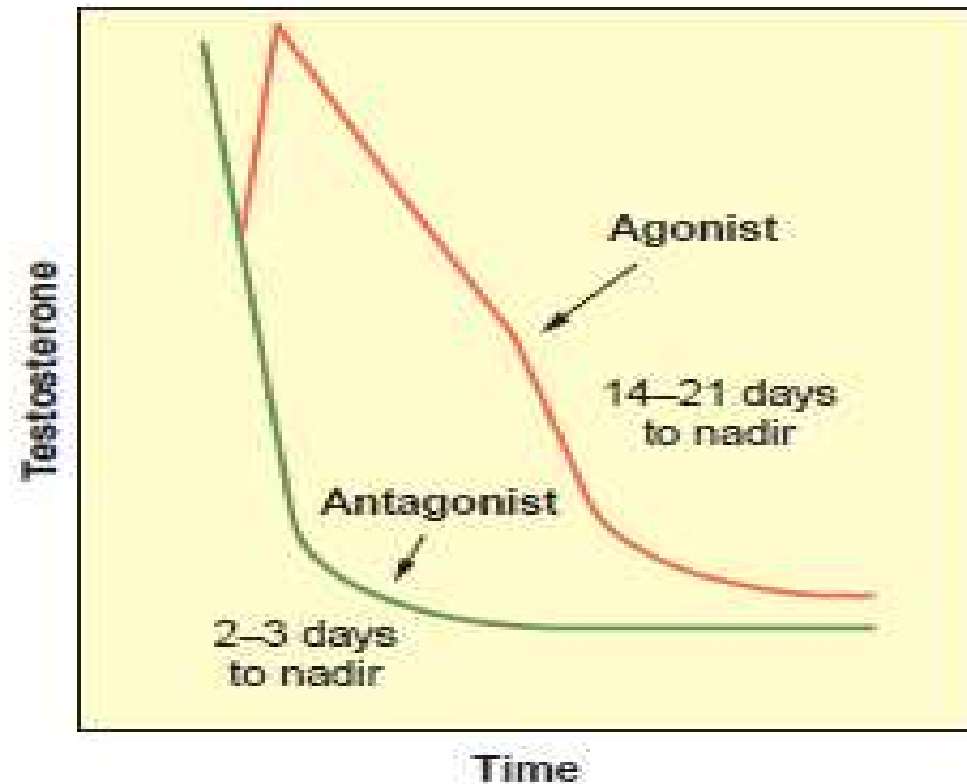
- Inexpensive
- Immediate castration without testicular surge
- Reduces testosterone levels to “castration levels”
- Out patient procedure
- Less than 12 hours
- Irreversible

# LHRH Agonists

- LHRH agonists produce an initial rise in LH that increases testosterone levels, followed 1 to 2 weeks later by down-regulation of LH receptors that results in a medical castration.
- Results in FLARE
- Antiandrogens to be given for 7 days along with LHRH agonists
- Approved : Leuprolide Acetate, Eligard, Viadur, Goserelin Acetate, Triptorelin Pamoate, Histrelin Acetate

# LHRH Antagonists

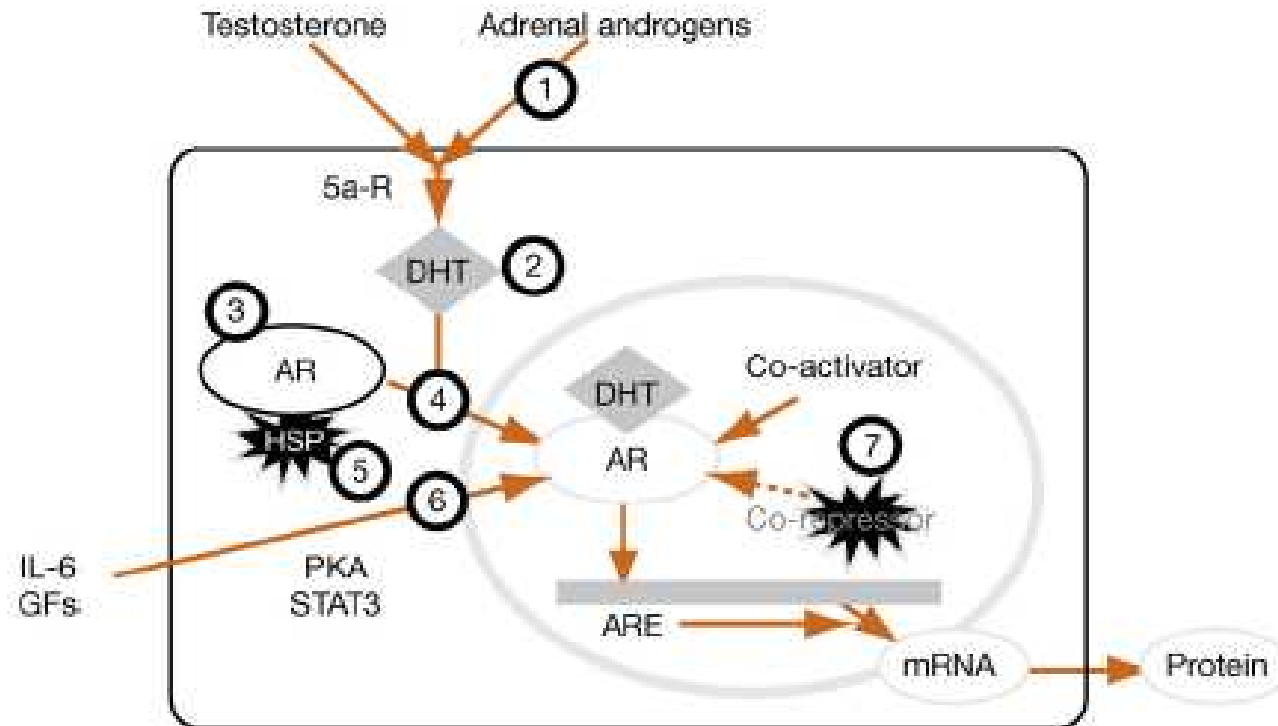
- Castration levels in 48 hours without initial flare
- Approved : Degarelix



# Antiandrogens

- Antiandrogens block the binding of testosterone to the AR
- **Steroidal agents (Type I) :**
  - Cyproterone acetate
  - Progestational properties that suppress LH levels
- **Nonsteroidal agents (Type II) :**
  - Bind to the AR and act as competitive antagonists for ligands
  - 1<sup>st</sup> generation : Flutamide, Bicalutamide and Nilutamide
  - 2<sup>nd</sup> generation : Enzalutamide (blocks the translocation of ligand bound AR complex to the nucleus and from binding to DNA)

# Mechanism of Action



1. Inhibition of adrenal androgens: androgen-supersensitive cells
2. Insufficient decline in tissue androgen level
3. Prevention of AR amplification
4. Inhibition of ligand binding to AR: different activity to mutant AR
5. Direct effect on AR function: inhibition of dissociation of HSP
6. Inhibition of ligand-independent activation of AR
7. Alteration of co-activator and co-repressor

# Toxicities of Androgen Deprivation Therapy

- Androgen Deprivation Syndrome :  
Hot flashes, decreased libido, erectile dysfunction, impotence, fatigue, anemia, weight gain, bone loss, depression, mood swings, personality changes, loss of muscle mass.
- Metabolic Changes – alteration in fat metabolism
- Osteopenia and Osteoporosis
- Cardiotoxicity

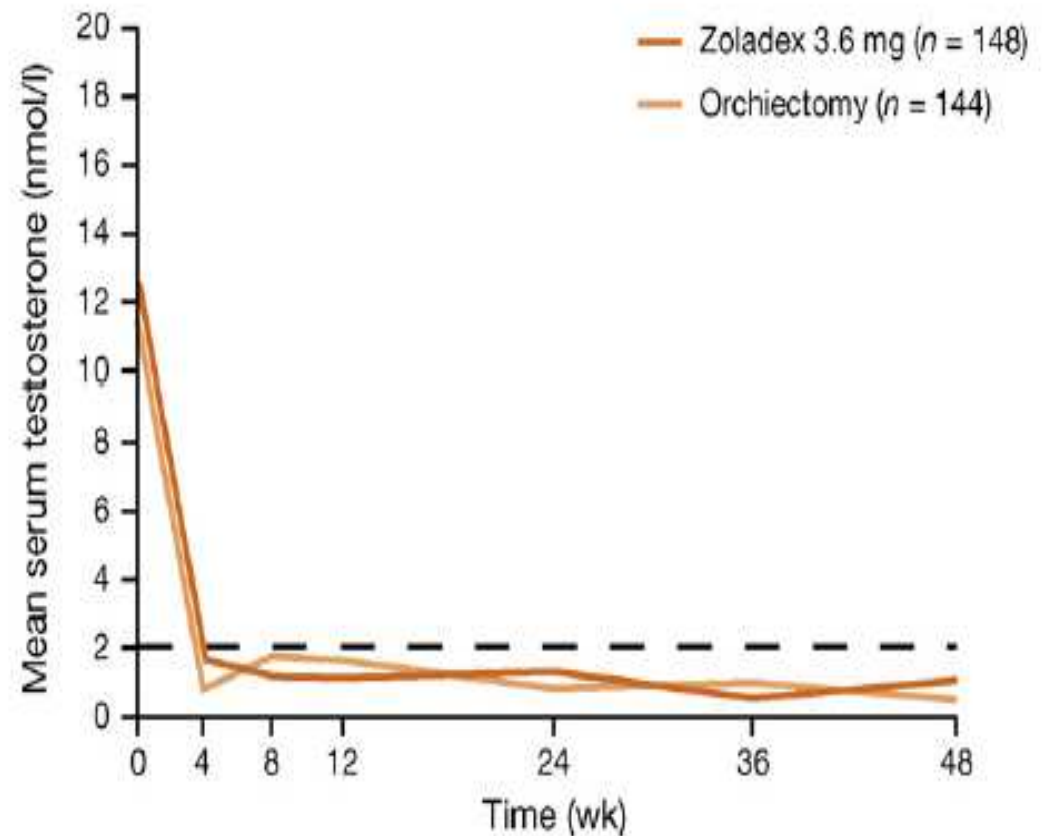
# Toxicities of Anti-androgens

- Antiandrogens do not lower serum androgens  
Less loss of libido, less hot flashes while muscle and bone mass retained.
- Elevations in hepatic enzymes, diarrhea.
- Gynecomastia/ severe breast tenderness.



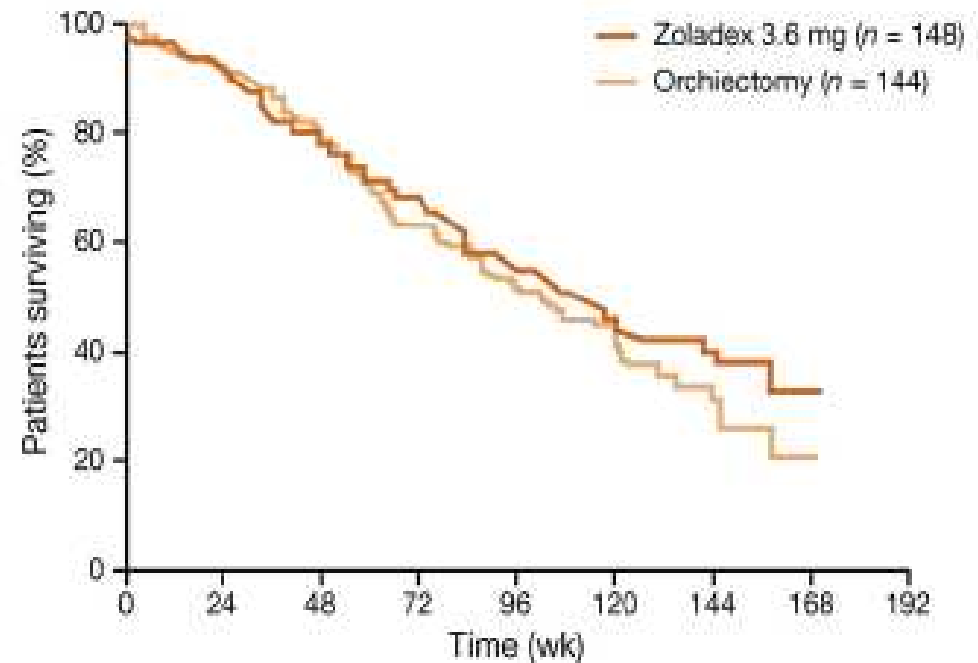
# Medical vs Surgical Castration

- Zoladex monotherapy achieves similar testosterone suppression to surgical castration, maintaining testosterone levels to below the castrate level.



# Medical vs Surgical Castration

- Zoladex monotherapy is as effective as castration in terms of overall survival



# Bicalutamide 150mg as monotherapy

- Bicalutamide 150 mg has shown equivalent efficacy to castration in M0 patients ( Iverson et al 2000 )
- Bicalutamide 150 mg may offer additional significant QoL advantages over castration
- None of these antiandrogens are approved as monotherapies in the United States though approved in European Union.
- Antiandrogen monotherapy is less effective than medical or surgical castration – NCCN Guidelines 2017

# Combined Androgen Blockade

- Original Rationale : Combine castration-based deprivation of testicular androgen with physiologic inhibition of adrenal androgens via an antiandrogen.
- Two populations of cell would survive following surgical or medical castration: androgen-independent cells (which may be responding to locally produced androgens) and androgen-supersensitive cells.
- Addition of an antiandrogen to castration therapy would be expected to target the androgen-supersensitive cells, thereby reducing the number of proliferating cancer cells.

# Evidence

- Prostate Cancer Trialists' Collaborative Group (PCTCG) conducted a metaanalysis 2001
- With Nonsteroidal antiandrogens, significant 8% **reduction** in risk of death. With steroidal antiandrogens, significant 13% **increase** in risk of death.
- Nonsignificant benefit for CAB over castration alone in terms of 5-yr overall survival (survival 25.4% vs. 23.6%, respectively).
- Difference in steroidal vs non steroidal drugs

# PCTCG meta analysis

5-year survival favoured CAB (25.4% vs 23.6%)

Outcome dependent on choice of antiandrogen

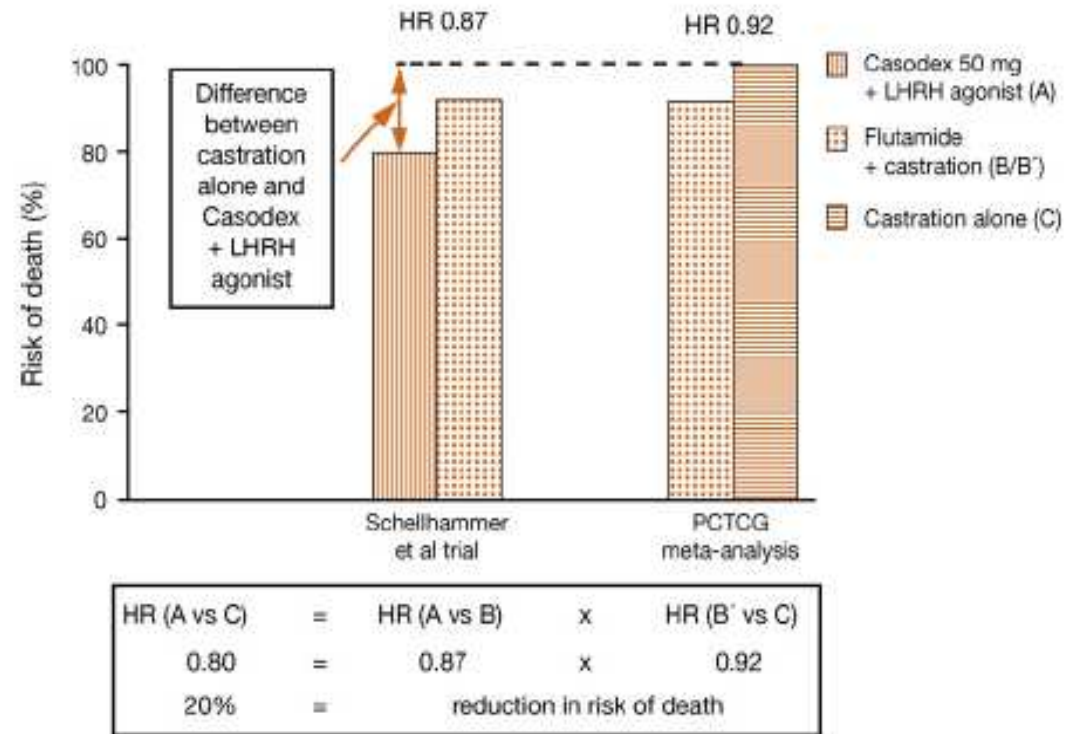
With NON-STEROIDAL antiandrogens\*, there was a significant 8% reduction in the risk of death (p=0.005)

With STEROIDAL antiandrogens, there was a significant 13% increase in the risk of death (p=0.04)

# Evidence

Combined androgen blockade is predicted to reduce mortality by 20% compared with surgical or medical castration.

Of the available nonsteroidal antiandrogens, Bicalutamide 50 mg is the best tolerated



HR, hazard ratio; LHRH, luteinising hormone-releasing hormone; PCTCG, Prostate Cancer Trialists' Collaborative Group

# Principles of ADT - NCCN 2017

## Clinically Localized

- Neoadjuvant ADT before RP is discouraged
- ADT should NOT be used as monotherapy in clinically localized prostate cancer
- Giving ADT before, during and after Radiation therapy in select patients prolongs SURVIVAL



# Principles of ADT - NCCN 2017

## Biochemical Failure without Metastasis

- The timing of ADT whose evidence is only rising PSA is influenced by PSA velocity, patient anxiety and side effects
- Patients with shorter PSADT and long life expectancy should receive early ADT administration
- Men with longer PSADT and who are older can be observed

# ADT in Low Risk Disease

- Common practice in community
- No survival benefit found after 15 years
- Placing patients with early prostate cancer on ADT SHOULD NOT be of routine practice ( NCCN 2017 )

# ADT in Intermediate Risk Disease

- Addition of short term ADT to radiation therapy improved OS
- EORTC 22991 : 6 months ADT improved biochemical DFS in intermediate risk group as compared to radiation alone

# ADT in High Risk Disease

- Long duration of ADT is preferred
- Evidence from following trials is available
  - RTOG 9202 trial
  - EORTC 22863 trial
  - DART 01/05 trial
  - RTOG 8531

# TOG 9202

## trial

- Group 1  
4 months ADT  
before and  
during RT
- Group 2  
4 months ADT  
before and during  
RT followed by  
2 years of ADT
- Subgroup :  
GS 8-10, OS benefit

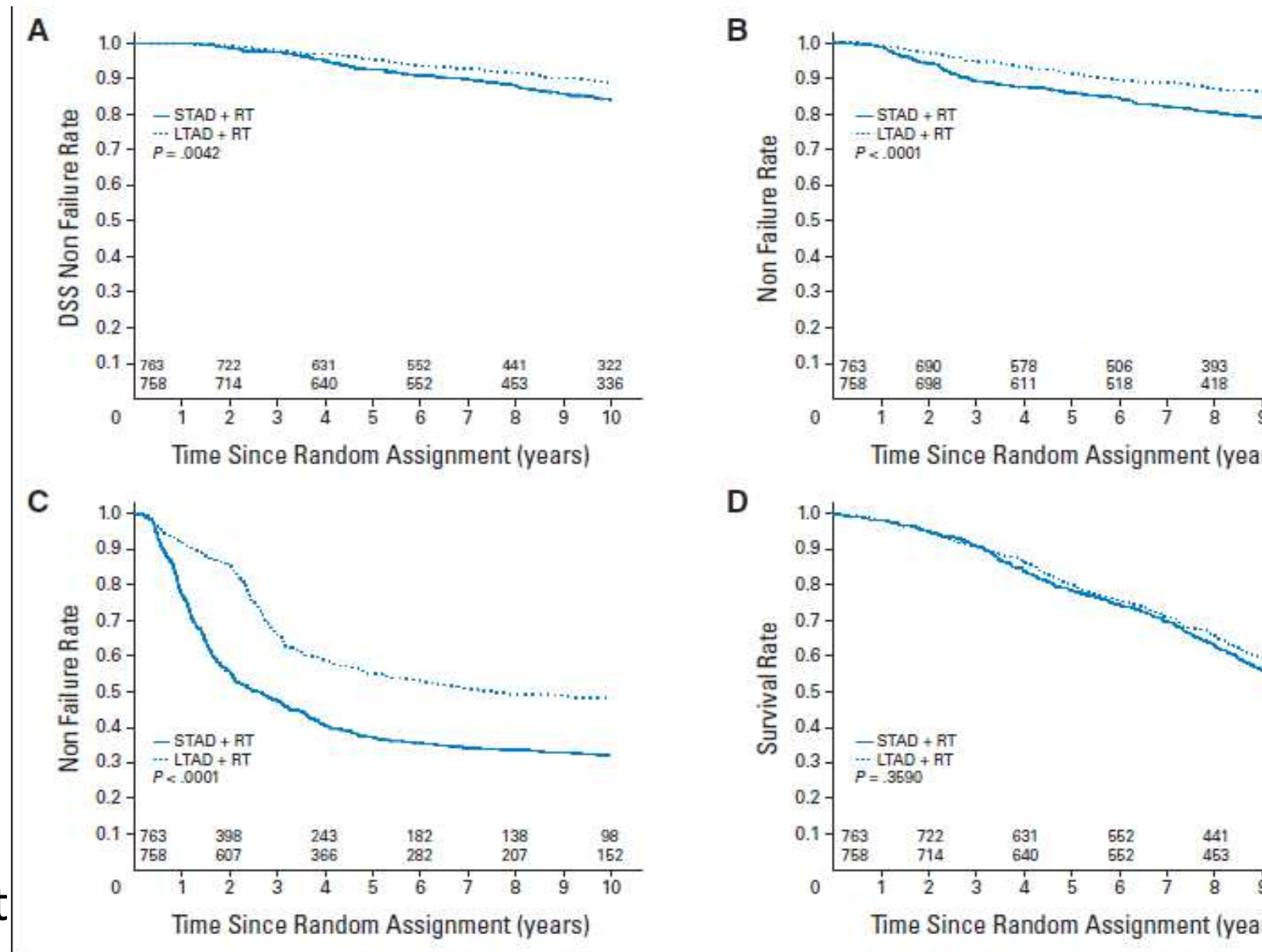


Fig 1. (A) Disease-specific survival, (B) distant metastasis failure, (C) biochemical failure, and (D) overall survival for all eligible patients. STAD, short-term androgen-deprivation therapy; LTAD, long-term androgen-deprivation therapy; RT, radiotherapy.

# EORTC 22863 trial

- Node-negative patients with clinical stage T3 disease or T1–T2 patients with high-grade disease
- Received adjuvant ADT on the first day of radiotherapy (prescribed dose of 70 Gy) and continued for 3 years.
- The 10-year overall survival was 58% versus 40% for patients treated with ADT plus EBRT and EBRT alone, respectively ( $p = 0.0004$ ).

# Role with Radical Prostatectomy

- No Role of Neoadjuvant ADT prior to Radical Prostatectomy
- Indication of Adjuvant ADT – lymph node positivity  
immediate ADT improved OS as compared to delayed ADT

# Continuous vs Intermittent ADT (M0)

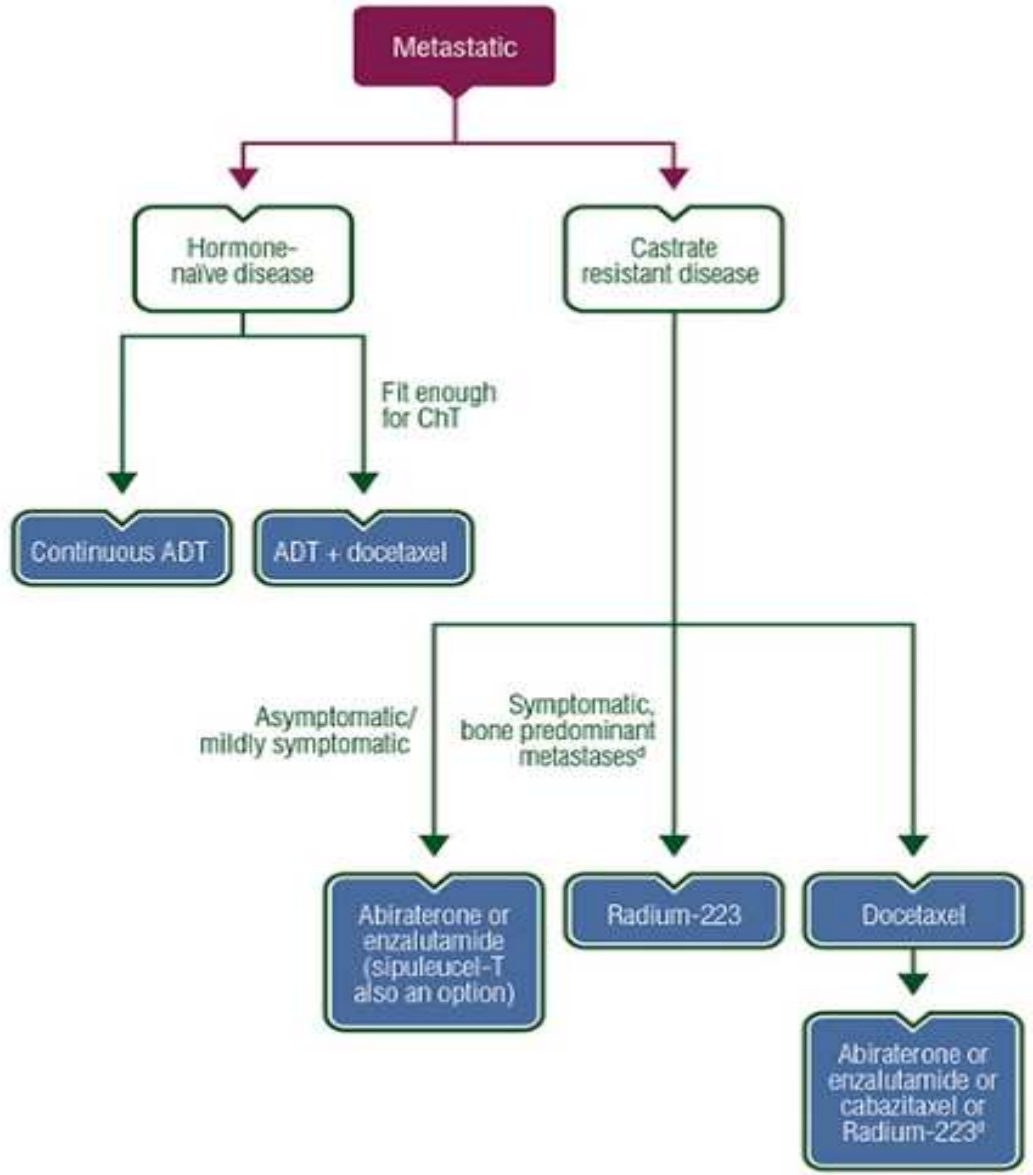
- Principle : Cycles of androgen deprivation followed by re exposure may delay androgen independence, reduce morbidity, improve QOL.
- Canadian PR7 trial: included patients with biochemical failure after RP  
Showed intermittent ADT is non inferior in terms of OS, better QOL.



## PSA level at 7 months (SWOG 9346 cohort)

- After starting ADT, the PSA level after 7 months of ADT may lead to 3 groups with very different survival expectancy.
- The median survival is
  - 75 months if the PSA level  $< 0.2$  ng/mL,
  - 44 months if the PSA  $< 4$  ng/mL,
  - 13 months if the PSA is  $> 4$  ng/mL.

# Metastatic Prostate Cancer



# Castration Resistant Prostate Cancer

- Definition : Disease progression despite ADT and may present either as RISE IN SERUM PSA LEVELS (despite castrate levels of testosterone), PROGRESSION OF PRE EXISTING DISEASE or APPEARANCE of NEW LESIONS
- Enhancement of autocrine or paracrine androgen synthesis in the tumor microenvironment

# First Step

- Document castration levels of testosterone
- Discontinue antiandrogen therapy and monitor the patient for withdrawal
- Onset of withdrawal response depends on half life of the drug being used.

# Types and Guidelines - M0

## NCCN 2017

- Maintain castration serum levels of testosterone <50mg/dL
- PSADT
- If < 10months then
  - Antiandrogen
  - Ketoconazole
  - Corticosteroid
- If > 10months then observe

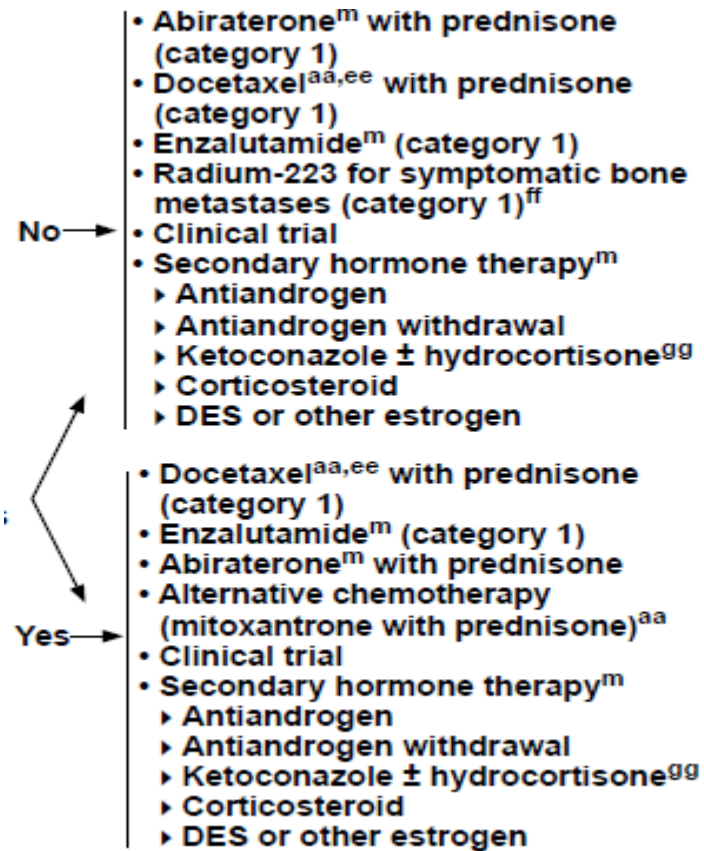
# Types and Guidelines - M1

## NCCN 2017

- Maintain castrations levels of testosterone < 50mg/dL
- Consider Denosumab/ Zolidronic Acid
- Sipuleucel T ( if asymptomatic, no liver metastasis, PS 0-1 and life expectancy > 6 months )
- Site of Metastasis
  - Bone
  - Nodal
  - Soft Tissue
  - Visceral

# Visceral Metastasis in CRPC

## NCCN 2017



# Estrogen

- Diethylstilbesterol
- 1mg/d – 3mg/d
- Provided PSA decline rates in the 24% to 42% range, although durable responses were rare
- Transdermal estrogen delivery systems have been made; however, efficacy in these trials has generally been less than anticipated.



# Ketoconazole

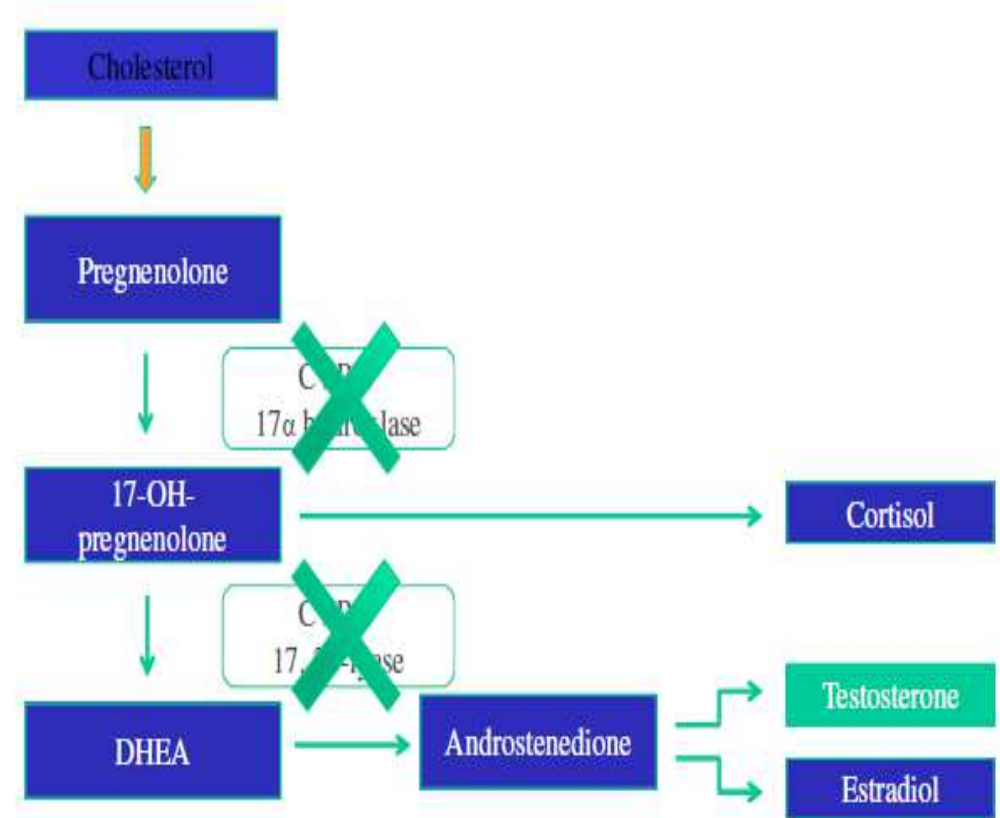
- Ketoconazole, 600 to 1,200 mg/d in combination with hydrocortisone
- To minimize adrenal insufficiency,
- Produces PSA decline by  $\geq 50\%$  in up to 71% of patients.
- Caution is urged with ketoconazole use as it is a potent inhibitor of CYP3A4.
- Cancer progression is associated with rises in androstenedione and DHEA sulphate, implying that steroidogenic compensatory mechanisms contribute to escape from ketoconazole.

# Prednisolone

- Prednisone 10 mg daily was shown to palliate symptoms of the disease in one-third of patients by Tannock et al.
- Similar results have been reported with hydrocortisone 30 mg/d to 40 mg/d and low-dose dexamethasone 0.5 mg to 2 mg daily in the PSA era, with reported decline rates ranging from 16% to 59% of patients.
- These agents also lower serum androgen levels and increase median survival times

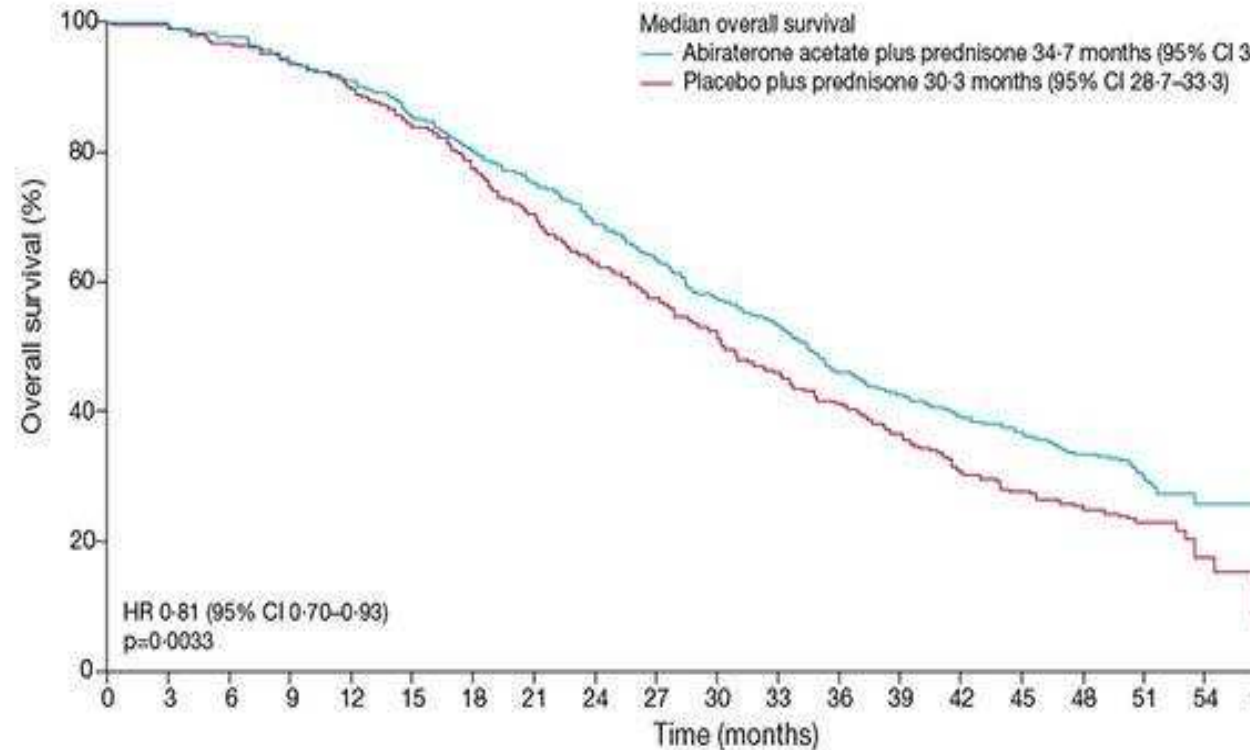
# Abiraterone Acetate (AA) – Mechanism

- It is an inhibitor of the  $17\alpha$ -hydroxylase and  $17,20$ -lyase.
- AA is administered with 2 x 5 mg prednisone to counteract side effects.



# Abiraterone Acetate

- The COU-302 trial found, in chemotherapy-naïve patients, that AA significantly improved radiographic progression-free survival and mOS vs P alone.



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Abiraterone acetate plus prednisone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15
Placebo plus prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10

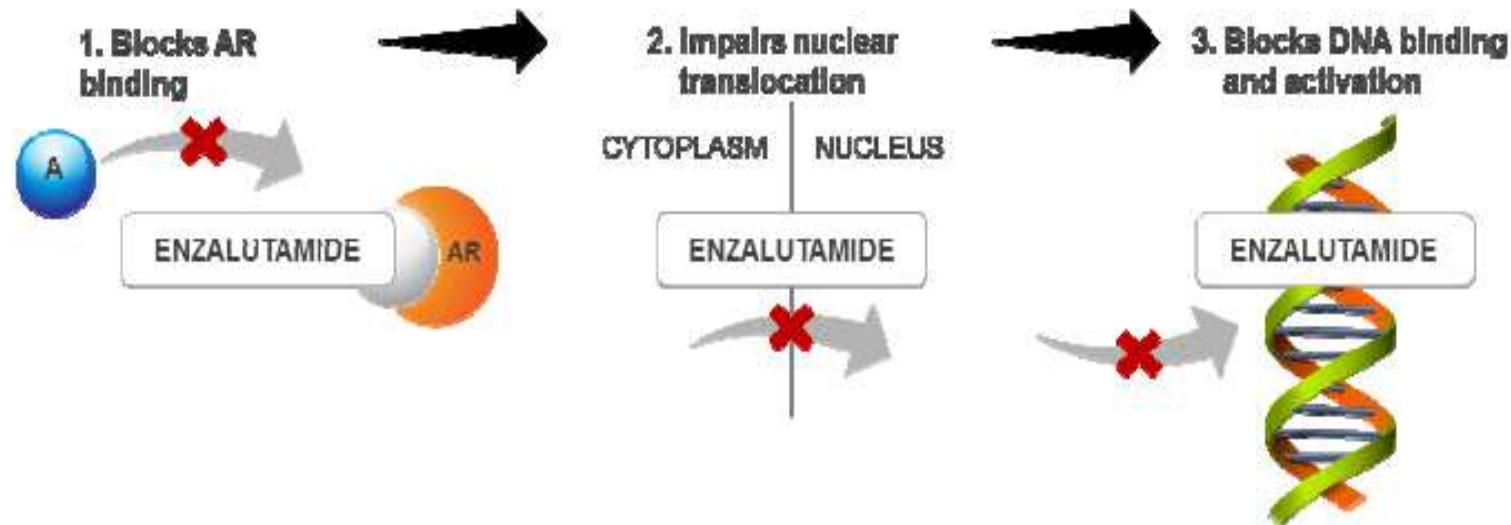
- Pre docetaxel

# Side effects

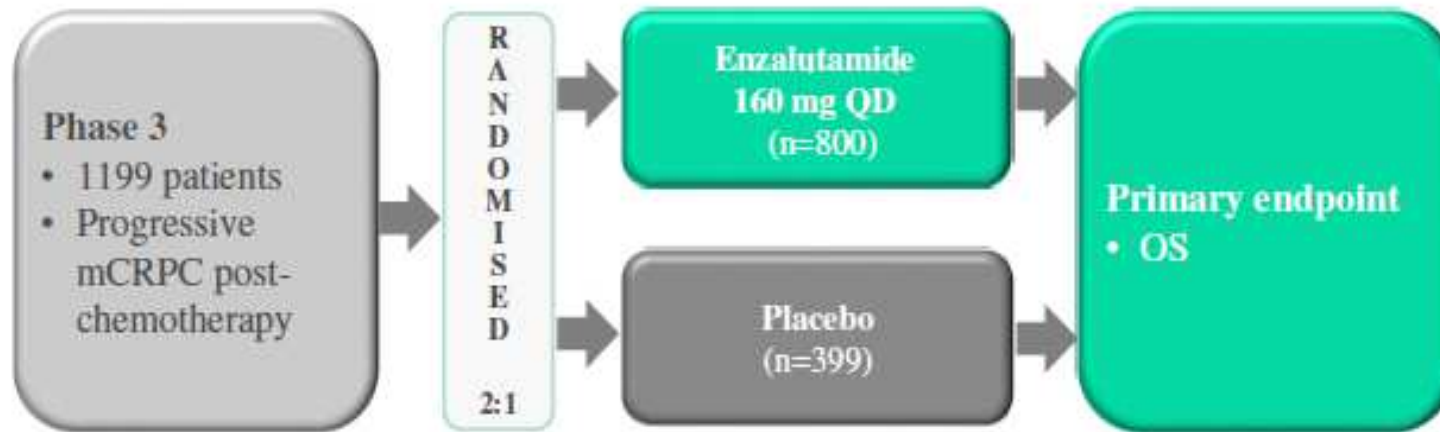
- Fluid retention or edema
- Hypokalemia
- Cardiac Disorders
- Hypertension
- Elevated Liver Enzymes

# Enzalutamide

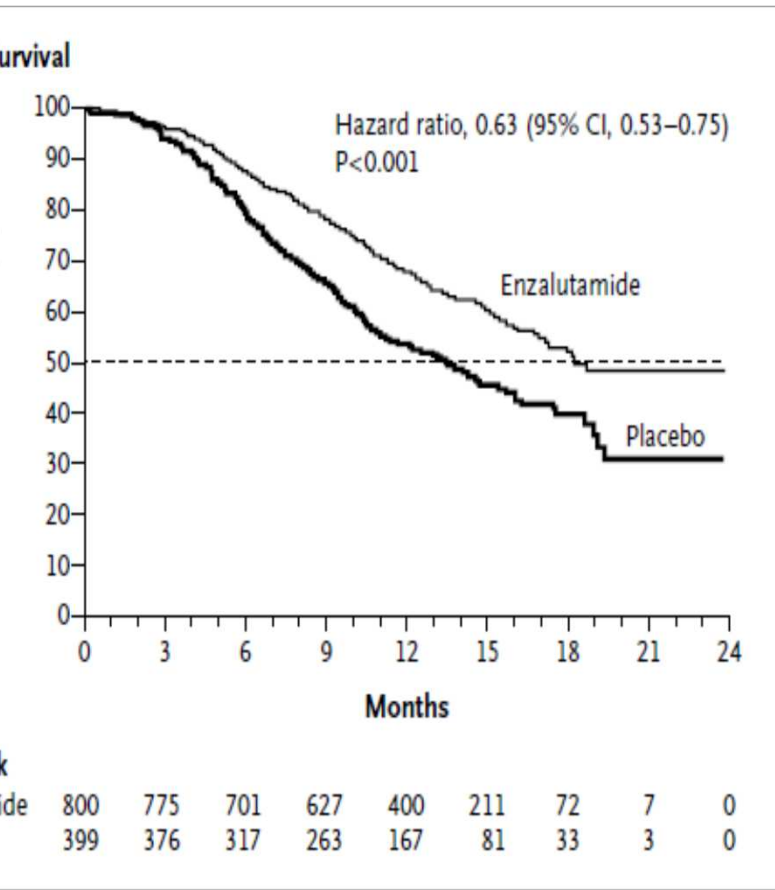
- Enzalutamide is an AR signalling inhibitor that directly targets three stages of the AR signalling pathway.
- The most common side effects of enzalutamide are fatigue, hypertension, and hot flushes. In <1% of patients on enzalutamide, seizures occurred.



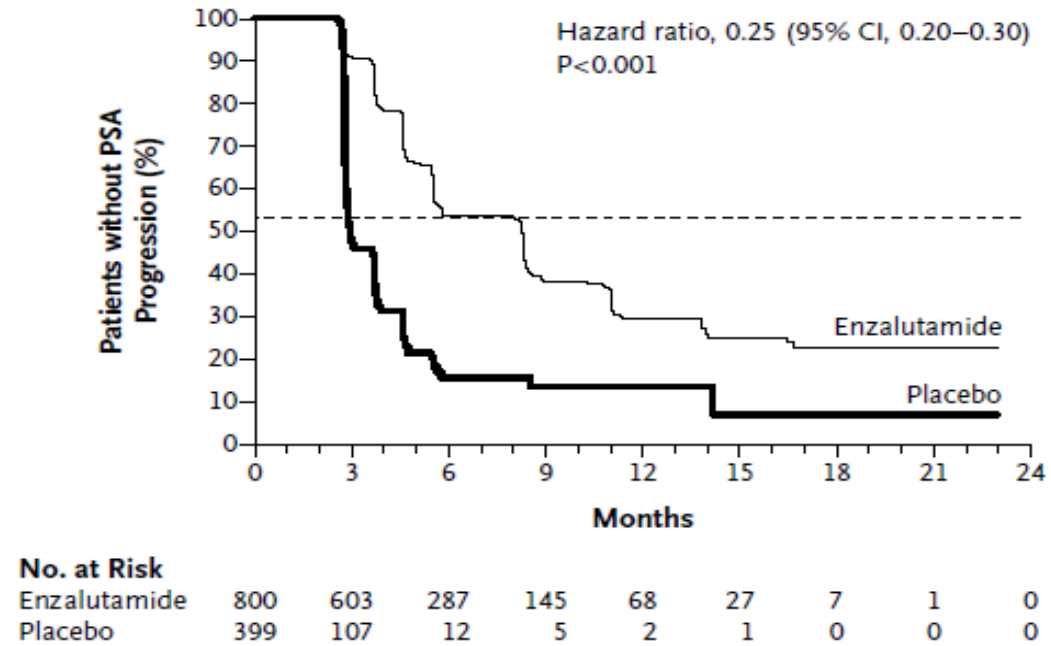
# Evidence : AFFIRM trial



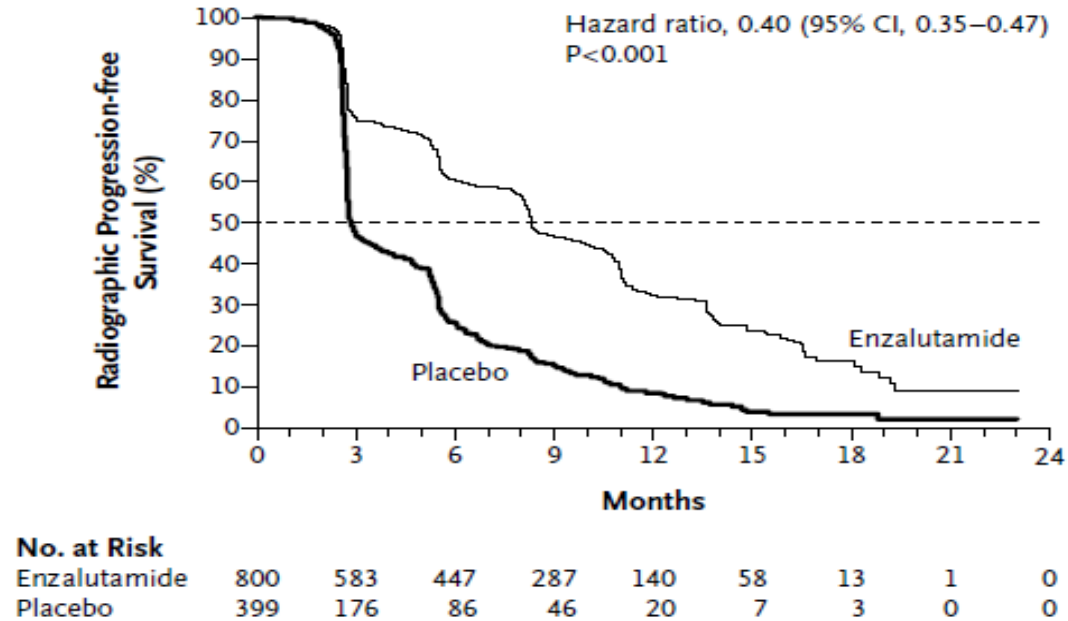
# Results



## B Time to PSA Progression

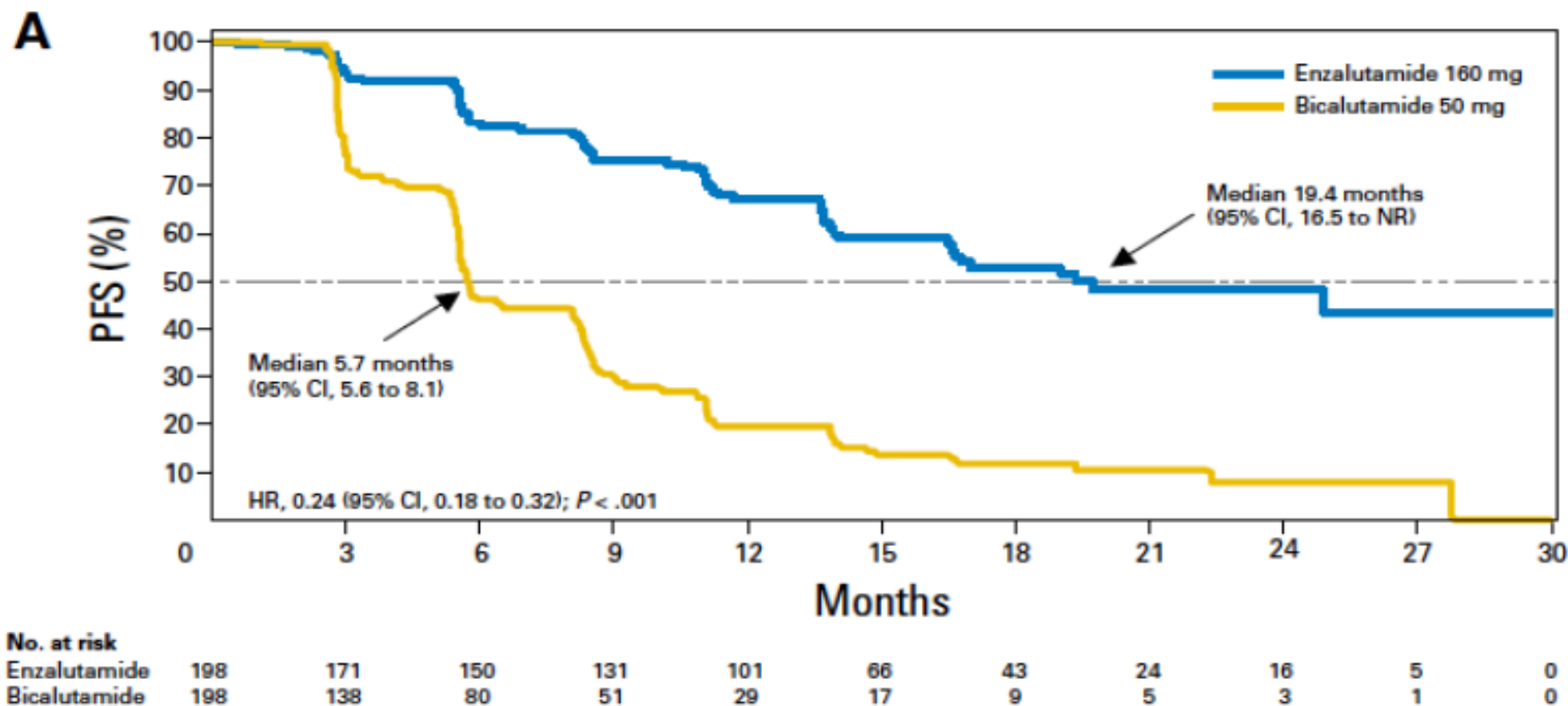


## C Radiographic Progression-free Survival





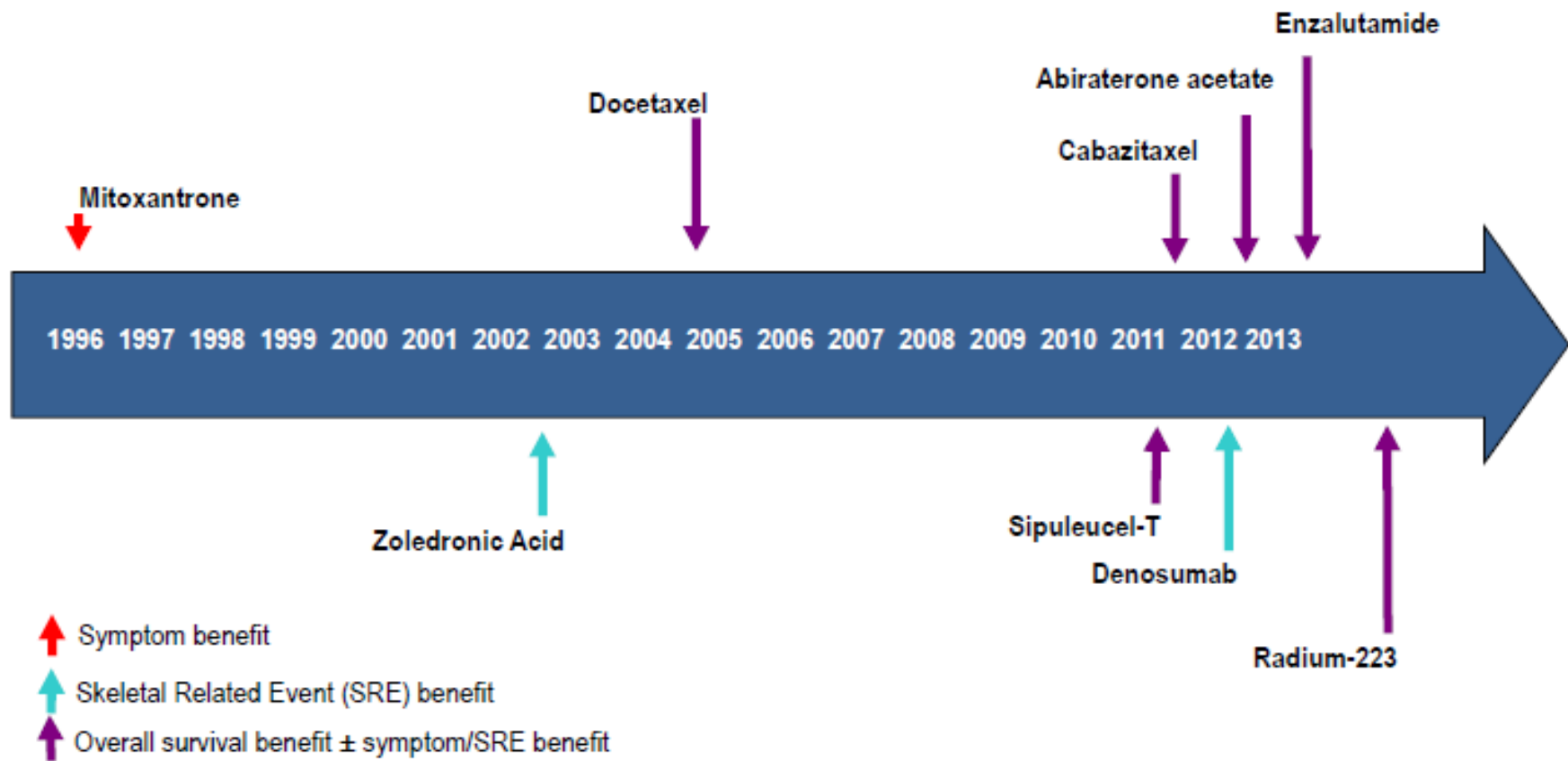
# Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial



# Data on Sequencing

Scenario	N	Outcome	Reference
A after D and E	38	8% PSA ↓ ≥50% 18% PSA ↓ ≥30% PFS 2.7 mo	Loriot 2013
A after D and E	30	No responses	Noonan 2013
E after D and A	35	45.7% PSA ↓ ≥50% PFS 4.0 mo	Schrader 2013
E after D and A	39	41% PSA ↓ ≥30% 13% PSA ↓ ≥50%	Bianchini 2013
CBZ after D and E/A	59	RR 14% Palliative benefit 24% 39% PSA ↓ ≥50%	Pezaro 2013
D after A	35	26% PSA ↓ ≥50% 37% PSA ↓ ≥30% All who failed A also failed D	Mezynski 2012

# Shifting Landscape



# Emerging Drugs in CRPC

- PARP
- PI3K/Akt
- AR (non-ligand binding domain)
- Prostate-specific membrane antigen (PSMA)
- Immune checkpoints

**THANK YOU**