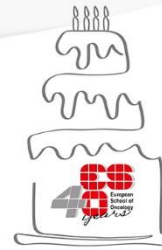




**40 years** of Learning to Care,  
a lot more to come,  
a lot more to Learn.

1982  
2022



www.ESO.net



# Basic principles of endocrine therapy (ET) with toxicity

**Assoc. Prof. Boštjan Šeruga, MD, PhD**

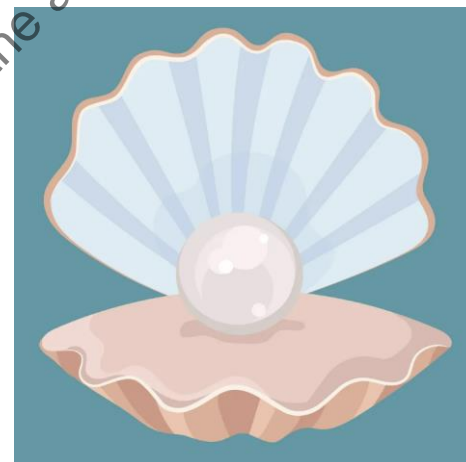
**Division of Medical Oncology, Institute of  
Oncology Ljubljana and University of Ljubljana**

**ESO Basic Principles in Oncology Course  
Ljubljana, October 27-30, 2022**



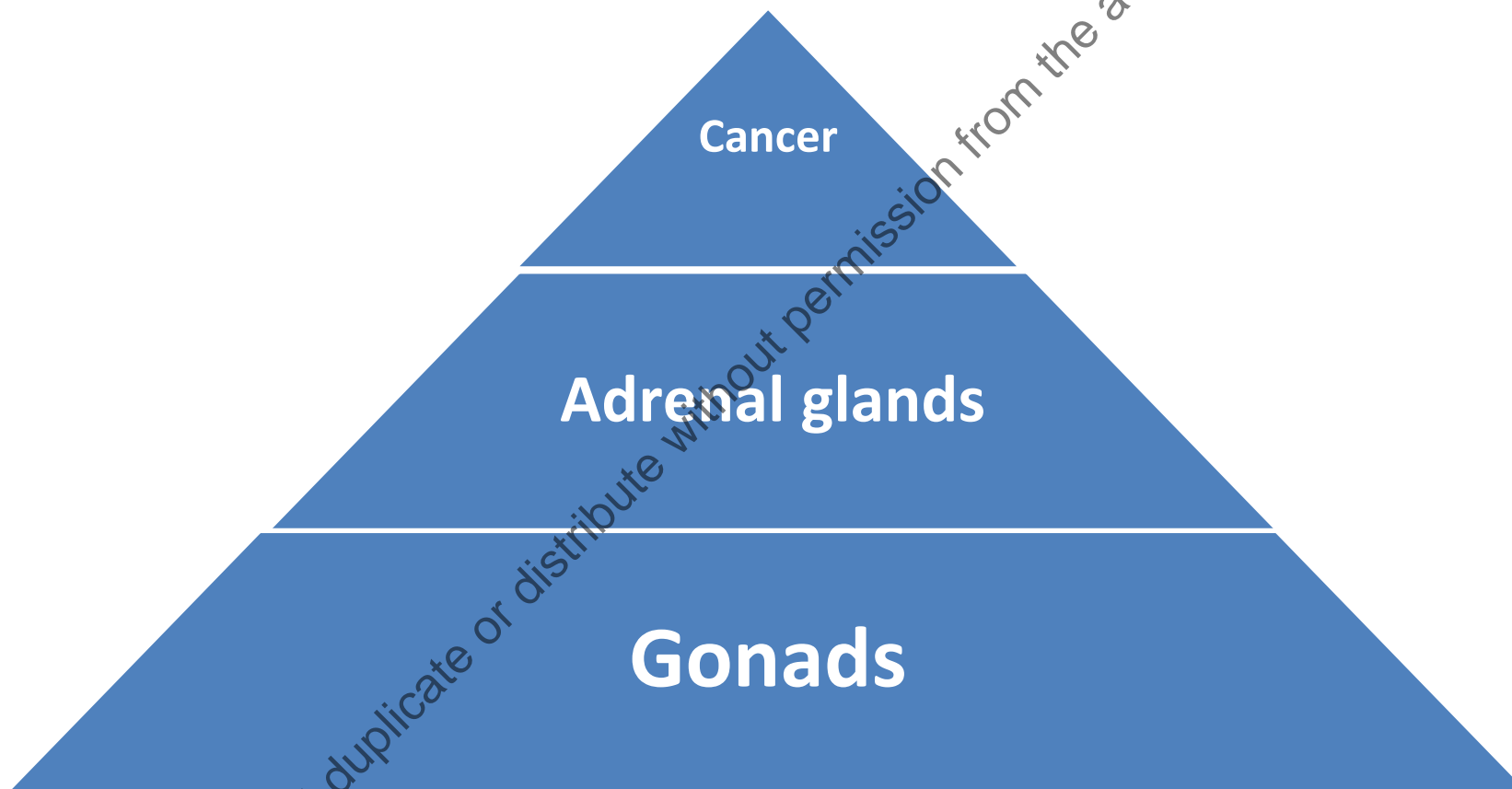
# Outline

- **What are sources of sex hormones?**
- **What are sex hormone receptors?**
- **How does ET work?**
- **When and what to test?**
- **When and how to treat with ET?**
- **What is toxicity of ET?**



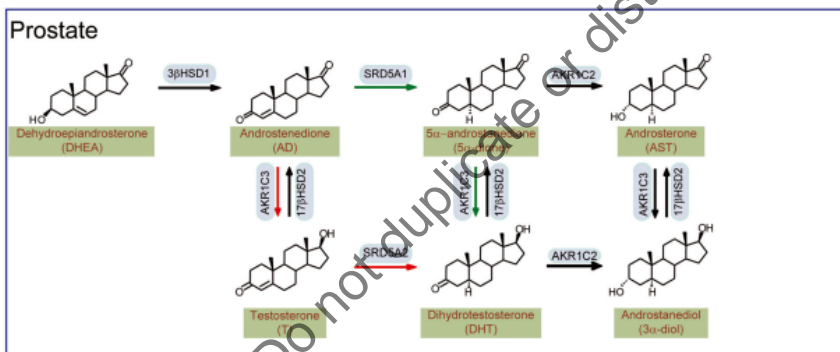
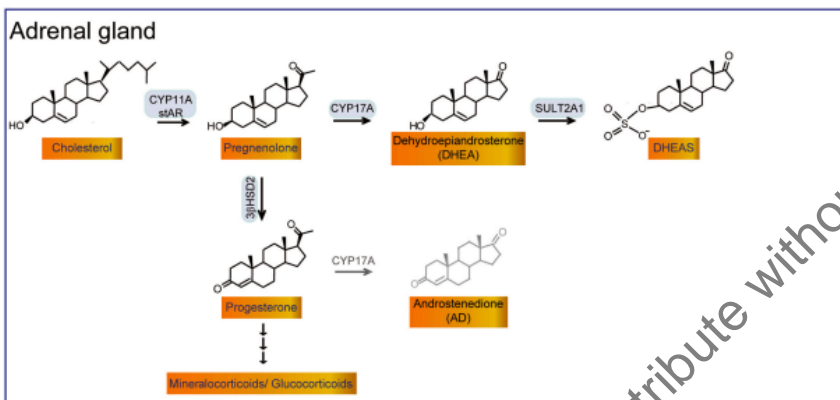
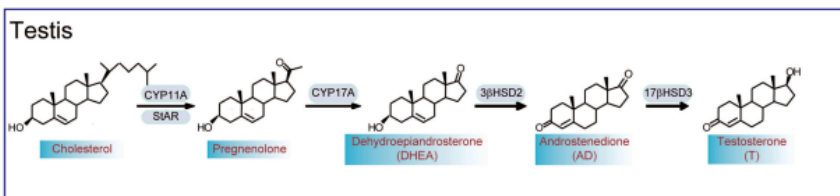


# Steroidogenesis of sex hormones



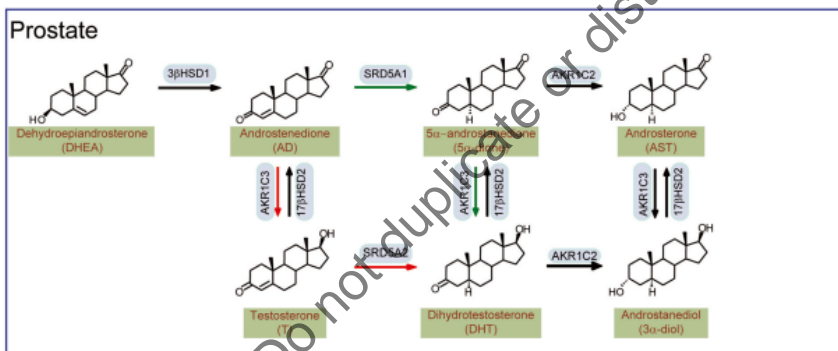
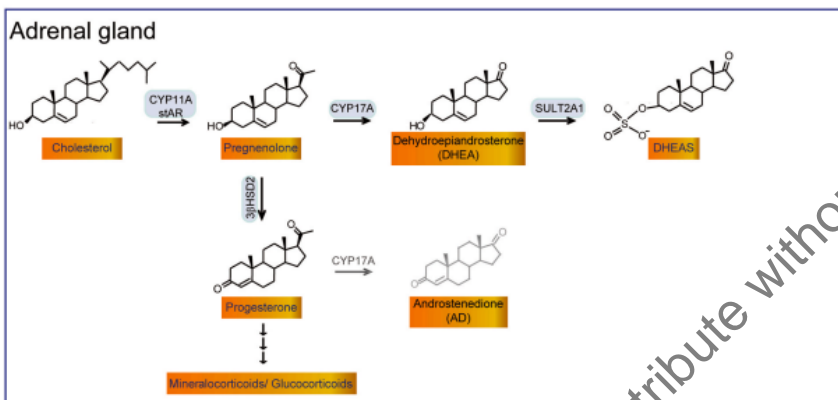
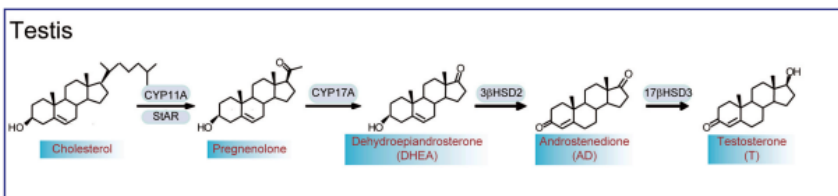


# Steroidogenesis in men

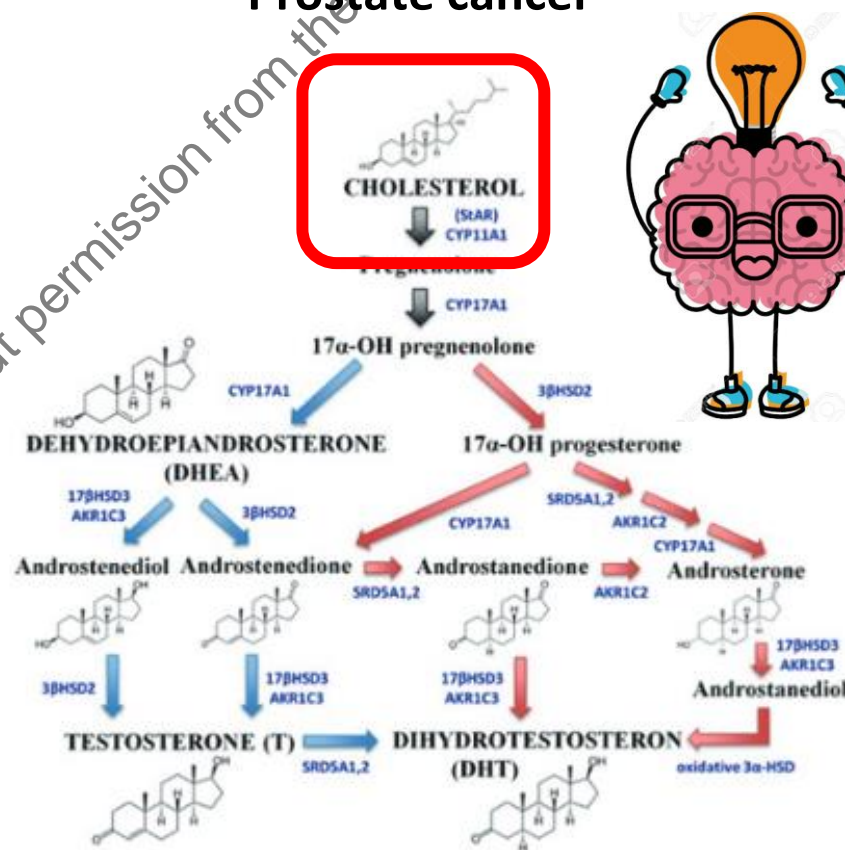
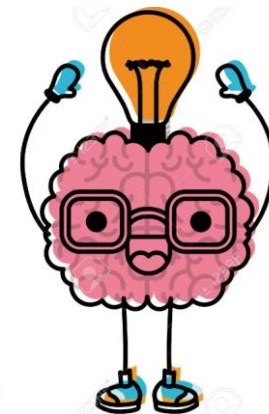




# Steroidogenesis in men with prostate cancer

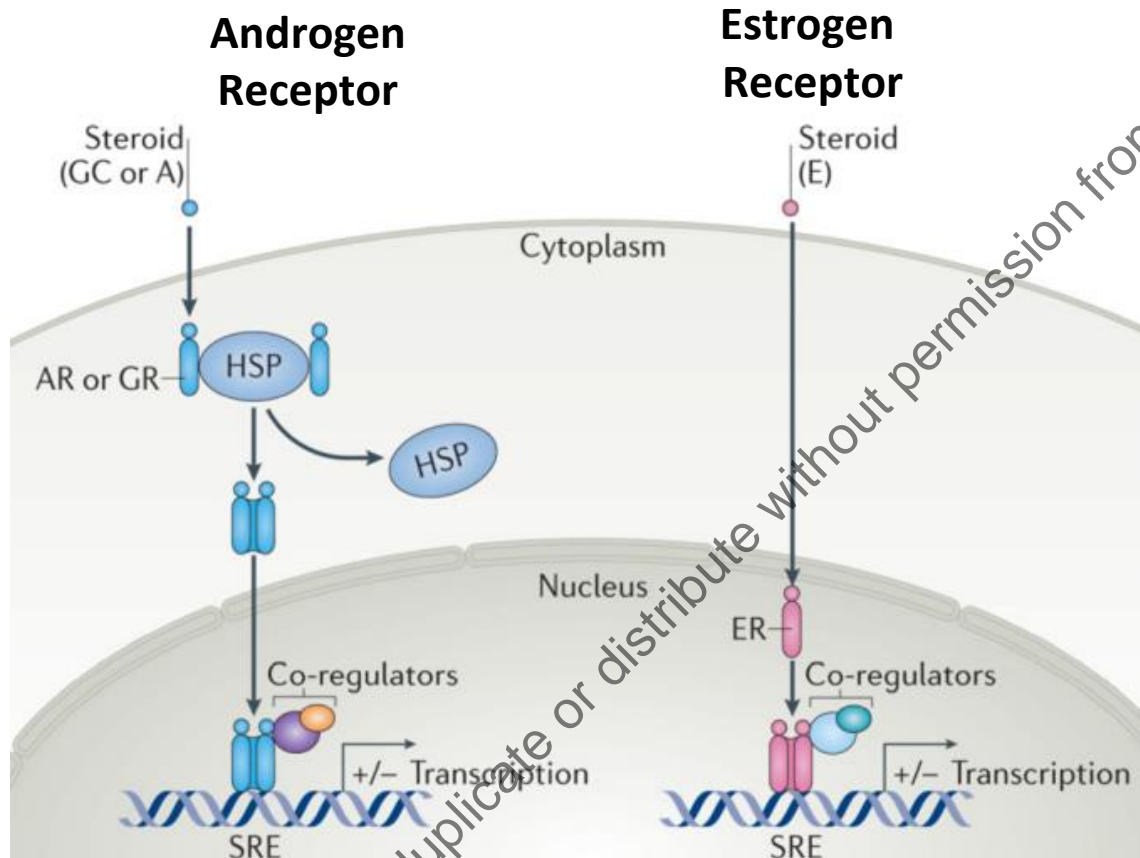


## Prostate cancer





# Steroid receptors superfamily signalling

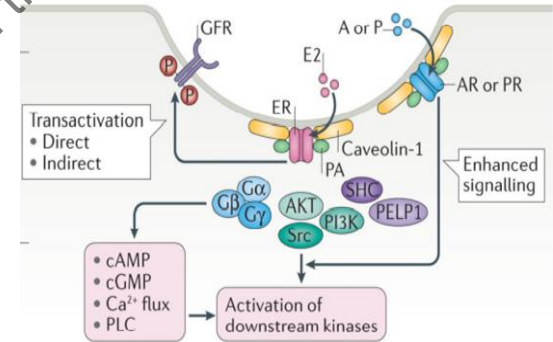
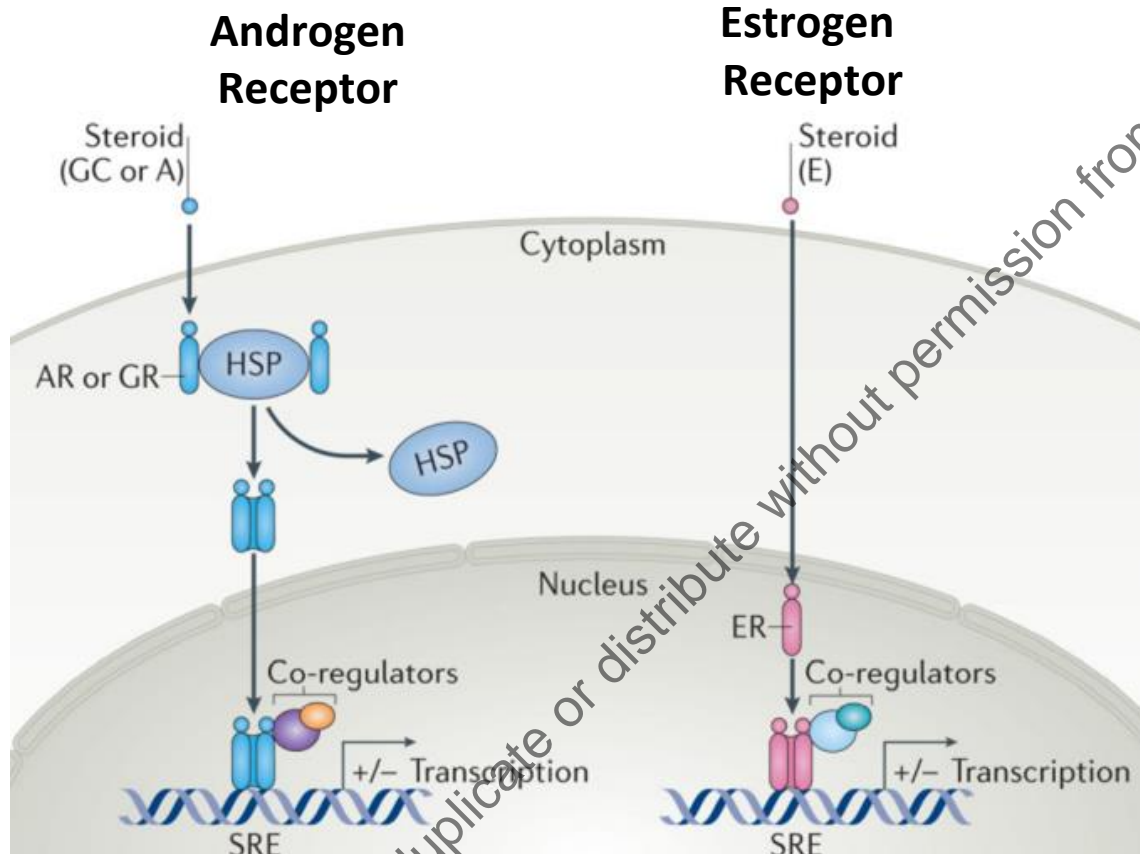


AR monomers primarily  
in the cytoplasm

ER monomers primarily  
in the nucleus



# Steroid receptors superfamily signalling



Part of the signalosome:

- Interaction with G protein, kinases
- Interaction with growth factor receptors
- Association with other steroid receptors

AR monomers primarily  
in the cytoplasm

ER monomers primarily  
in the nucleus

~ 5% of steroid receptors  
at plasma membrane



# What are sources of sex hormones?

<b>Breast cancer</b> Estrogen	<b>Prostate cancer</b> Androgens
<b><i>Premenopausal</i></b> <ul style="list-style-type: none"> <li>• Ovaries</li> <li>• Peripheral tissues <i>(by aromatase)</i></li> </ul>	<b><i>Castrate-responsive disease</i></b> <ul style="list-style-type: none"> <li>• Testicles</li> <li>• Adrenal glands</li> </ul>
<b><i>Postmenopausal</i></b> <ul style="list-style-type: none"> <li>• Peripheral tissues <i>(by aromatase)</i></li> </ul>	<b><i>Castrate-resistant disease</i></b> <ul style="list-style-type: none"> <li>• Adrenal glands</li> <li>• Prostate cancer</li> </ul>

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# Almost 60 years ago...

## Two Principles in Endocrine Therapy of Cancers: Hormone Deprivation and Hormone Interference<sup>1</sup>

CHARLES HUGGINS

*(The Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois)*

### SUMMARY

Hormones, or synthetic substances exerting physiologic effects similar thereto, are of crucial significance for growth of 7 hormone-dependent cancers of man and the animals. Two opposite sorts of change of the hormonal status can induce regression of such cancers: (a) deprivation of essential hormones; (b) hormone interference

*Cancer Research*

Vol. 25, August 1965

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Deprivation of sex  
Hormones

Blockage/  
degradation of  
receptors

2022

2022

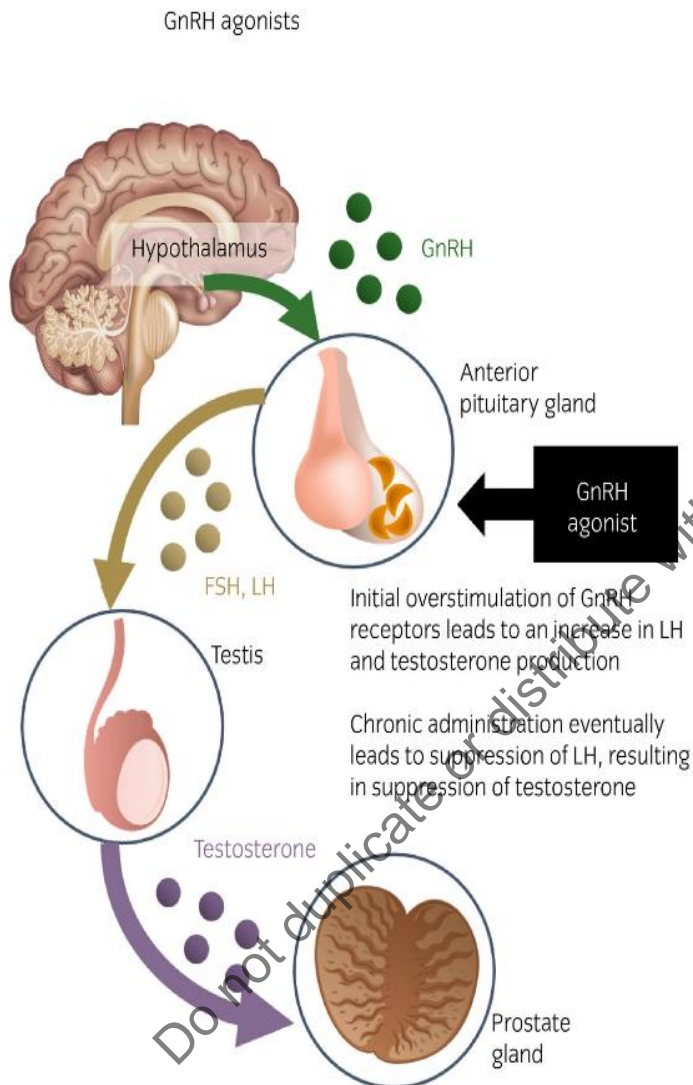


# How does ET work?

	Breast cancer	Prostate cancer
<b>Deprivation of sex hormones</b>	<p><b>LHRH analogues/Ovariectomy</b></p> <ul style="list-style-type: none"> <li>only in premenopausal w.</li> </ul> <p><b>Inhibition of aromatase (CYP19A1)</b></p> <ul style="list-style-type: none"> <li><b>Aromatase inhibitors</b> (anastrozole, letrozole, exemestane)</li> </ul>	<p><b>LHRH analogues/antagonists or Orchiectomy</b></p> <p><b>Inhibition of CYP 17A</b></p> <ul style="list-style-type: none"> <li>Abiraterone acetate (2nd gen.)</li> </ul>
<b>Blockage/ Degradation of hormone receptors</b>	<p><b>Antiestrogens</b></p> <ul style="list-style-type: none"> <li><b>Tamoxifen</b> (Selective Estrogen Receptor Modulator - SERM)</li> <li><b>Fulvestrant</b> (Selective Estrogen Receptor Downregulator - SERD)</li> </ul>	<p><b>Antiandrogens</b></p> <ul style="list-style-type: none"> <li><b>Apalutamide</b> (2nd gen.)</li> <li><b>Enzalutamid</b> (2nd gen.)</li> <li><b>Darolutamide</b> (2nd gen.)</li> </ul>



# LHRH analogues and antagonists

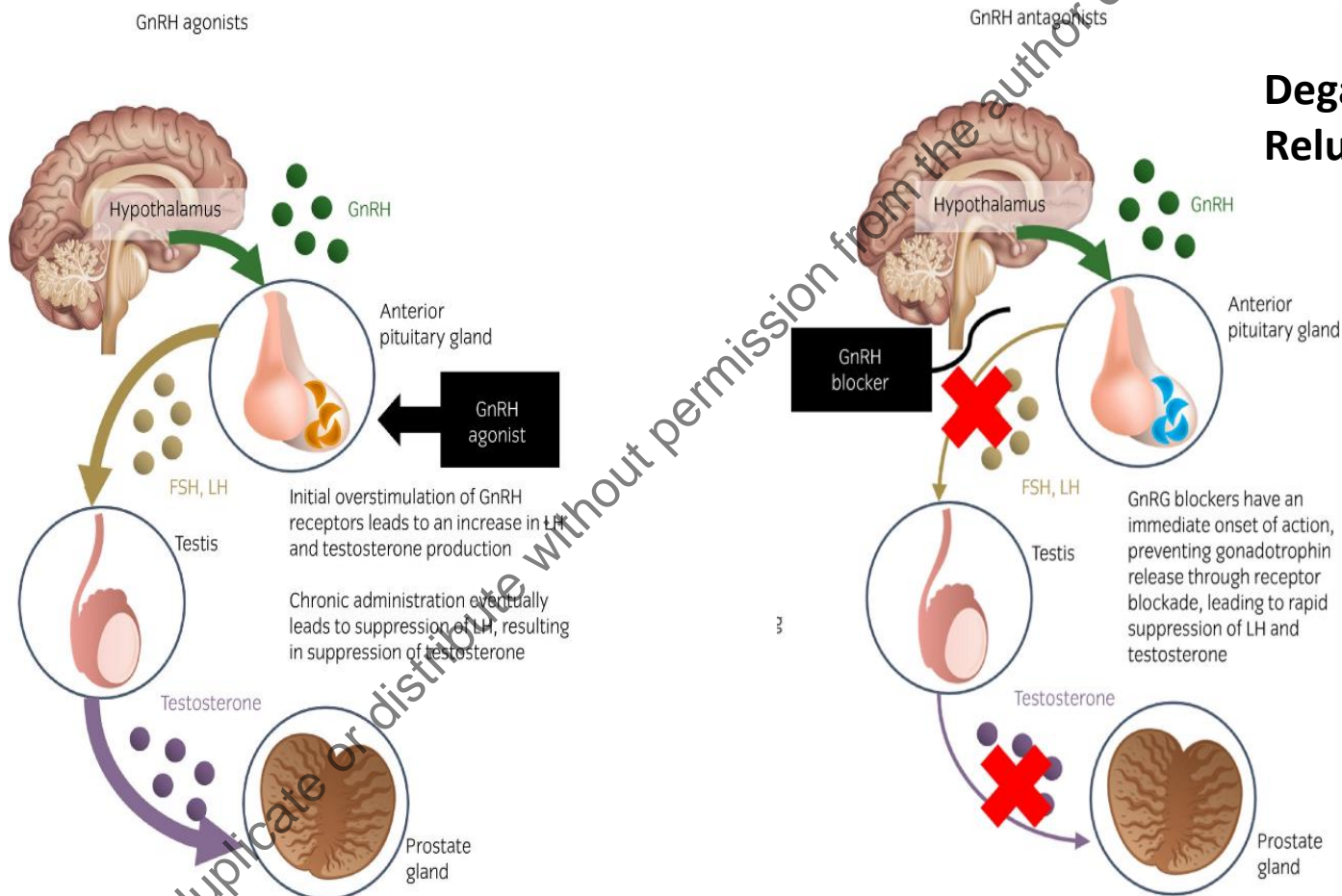


**Gosereline**  
**Leuproreline**  
**Triptoreline**

**Can preserve fertility in women with breast cancer undergoing adjuvant ChT**



# LHRH analogues and antagonists



**Degarelix**  
**Relugolix**

**Castrate level of testosterone: < 1.7 nmol/l (< 50 ng/dl)** (a more appropriate level, which is in accordance with surgical castration should be defined as < 20 ng/dL (1 nmol/L))



# Can LHRH analogues fail?

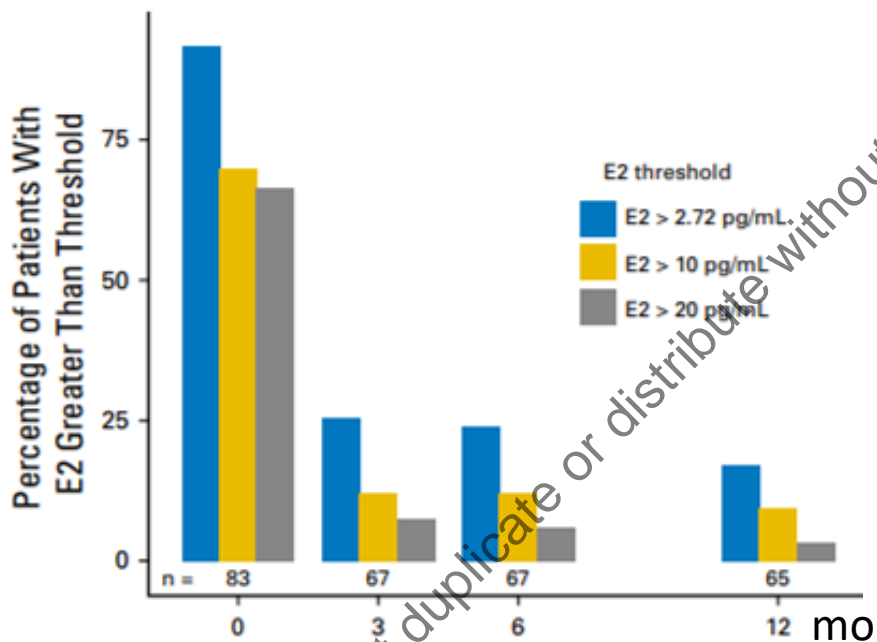
**YES!**

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# Can LHRH analogues fail?

## SOFT-EST substudy N=83 (Triptorelin+Exemestane)



E2 > 2.72 pg/ml at 12 mo: 17%

E2 > 20 pg/ml: 8%

Bellet et al, JCO, 2016

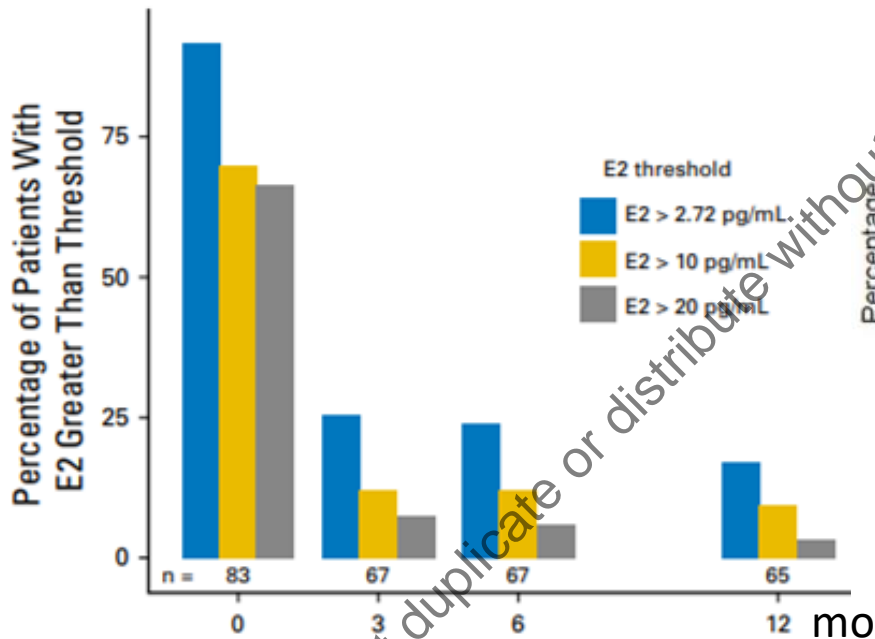




# Can LHRH analogues fail?

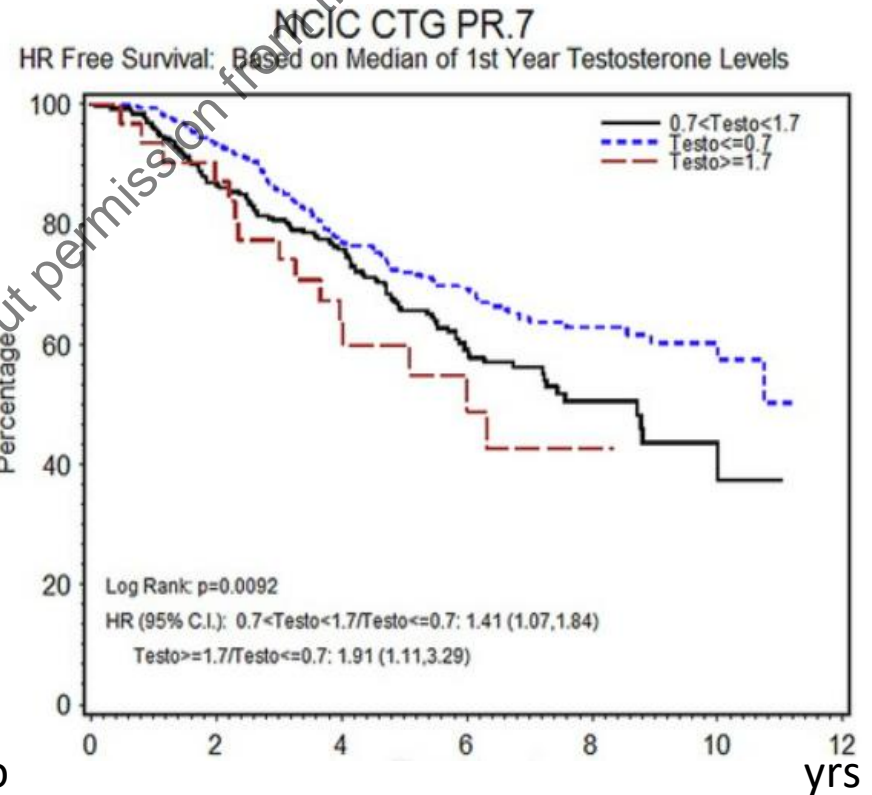
## SOFT-EST substudy

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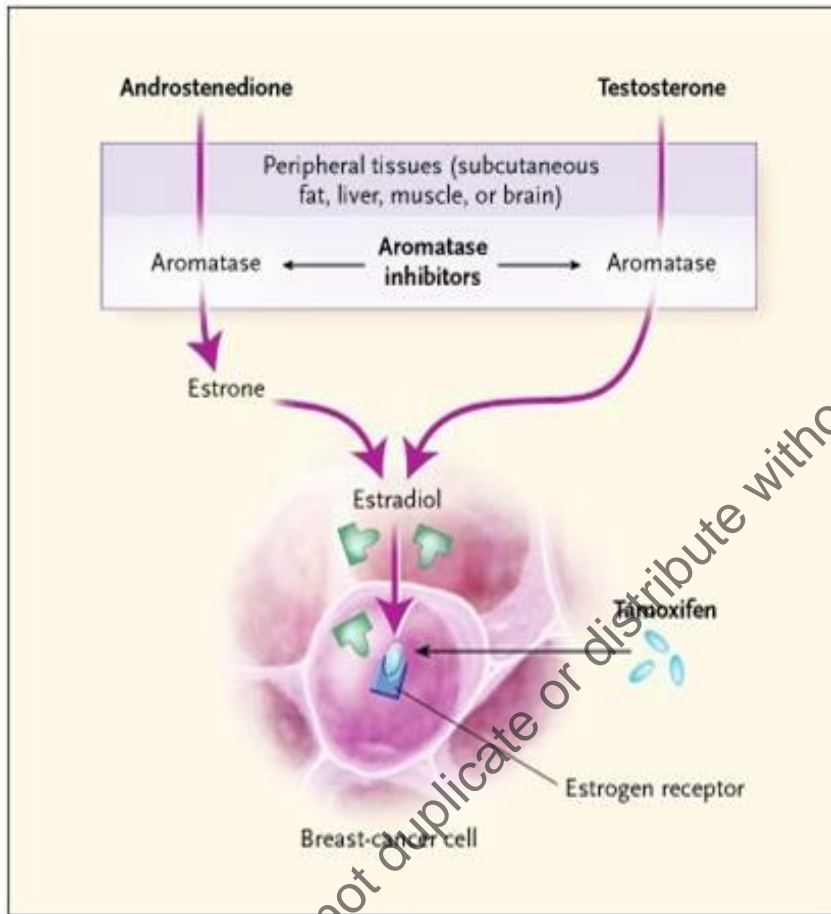
Testost. ≥ 1.7 nmol/L: 4.9%  
 0.7 nmol/l < Test. < 1.7 nmol/l: 37.6%

Klozt et al, J Urol, 2014





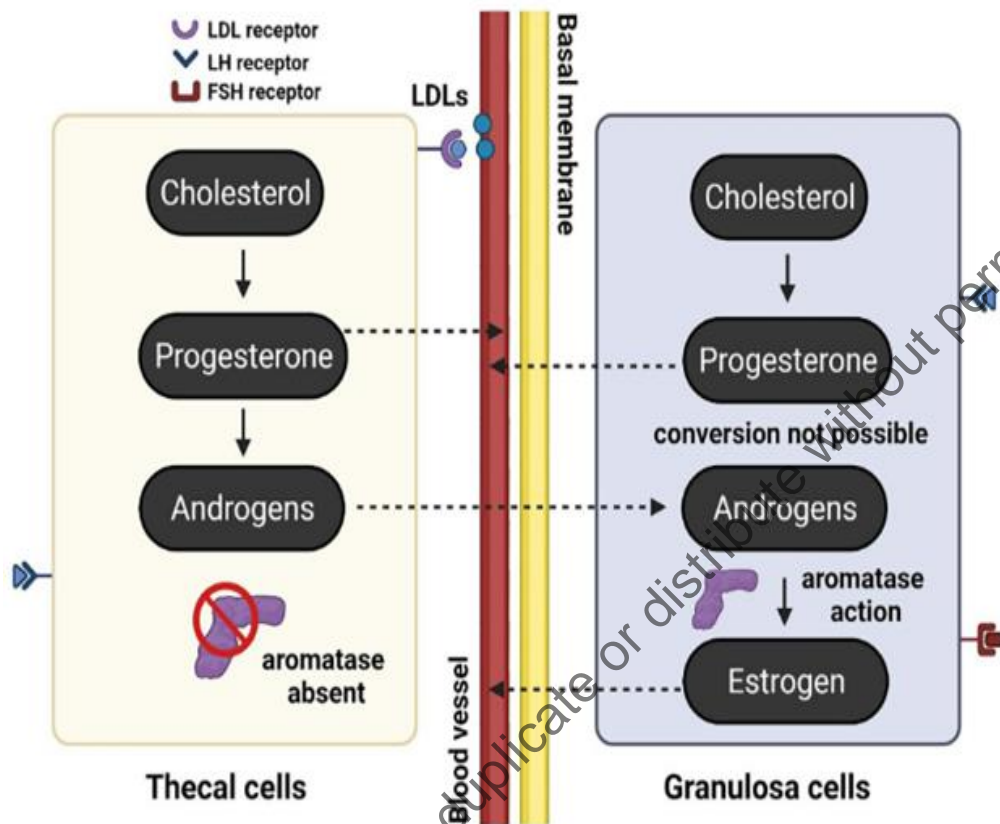
# How do AIs work?



- **Aromatase CYP19A1 or estrogenic synthetase is responsible for the aromatization of androgens to estrogens**
- **Concentrations of estrogen much higher in peripheral tissues than in the circulation**
  - **Circulating levels reflect rather than direct estrogen action in postmenopausal women and in men**



# Why AIs alone are not effective in premenopausal women?



- In thecal cells cholesterol is converted to androgens, granulosa cells convert androgens to estrogens
- Without ovarian suppression compensatory physiological responses induce ovarian oestrogen production

↓ Estrogen → ↑ LH and FSH → ↑ Estrogen

# Adjuvant Aromatase Inhibitors for Early Breast Cancer After Chemotherapy-Induced Amenorrhoea: Caution and Suggested Guidelines



- **45 women** of median age **47 yrs (39-53 yrs)** with **ER+ early BC** and **ChT-induced amenorhea** treated with **Als**
- **12 (27%) women** showed a **return of ovarian function**, median age **44 yrs (40-50 yrs)**
  - **10 renewed menses**
  - **1 pregnancy**
  - **1 Biochemically premenopausal**

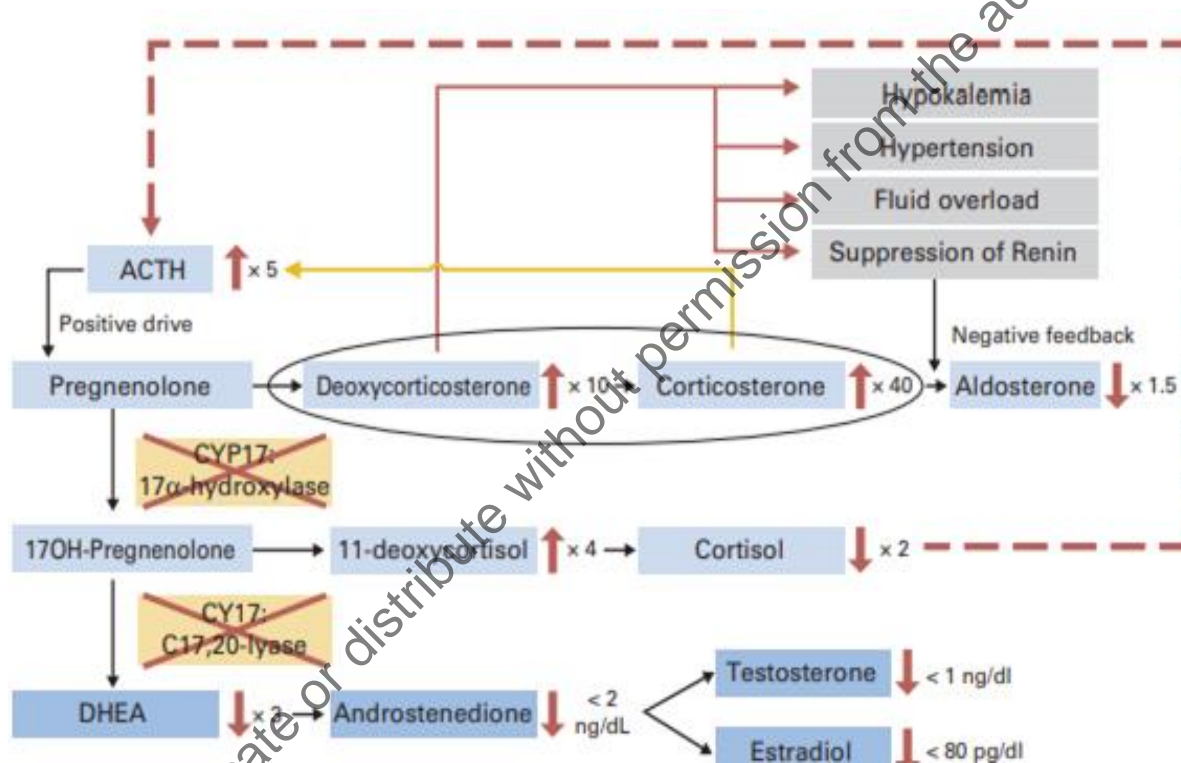


# Definition of menopause

- **Prior bilateral oophorectomy**
- **Age  $\geq 60$  years**
- **Age  $< 60$  years**
  - **With amenorrhea for  $\geq 12$  months in the absence of prior ChT, receipt of tamoxifen, ovarian suppression and estradiol and FSH in the postmenopausal range**
  - **ChT induced amenorrhea for  $\geq 12$  months with FSH and estradiol in the postmenopausal range on serial assessments**
  - **On tamoxifen and with FSH and estradiol in the postmenopausal range**



# How does abiraterone acetate work?



**Always combine with glucocorticoids!!!**



# When to test for sex hormone receptors?

	<b>Breast cancer</b> <i>ER and PR</i>	<b>Prostate cancer</b> <i>AR</i>
<b>Early</b>	<b>Always</b>	<b>Never</b>
<b>Metastatic</b>	<b>At least once in metastatic setting</b>	<b>Optional when small cell/neuroendocrine prostate cancer suspected</b>

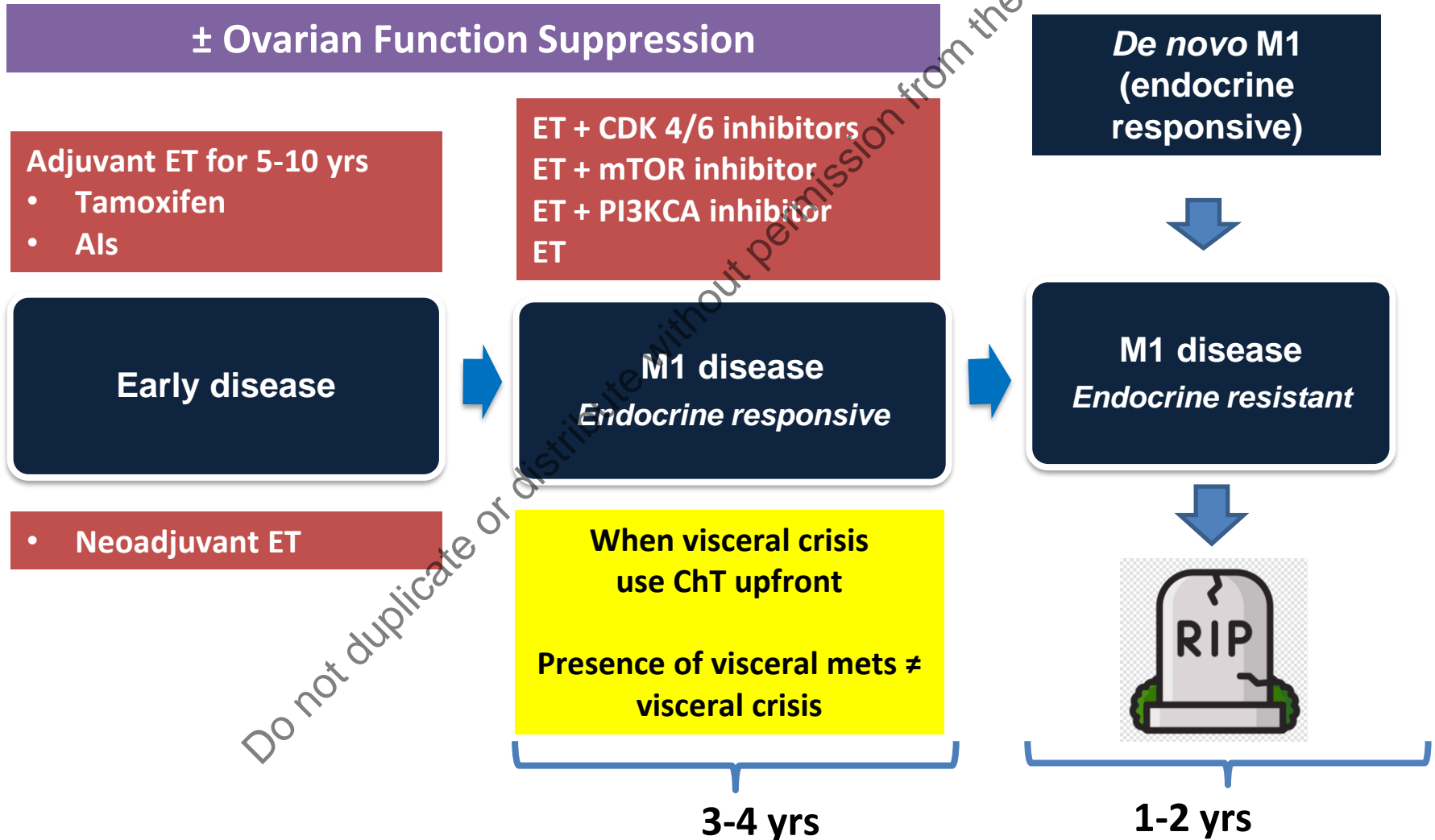
Learning  care

# Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

- **ER testing and assessment by validated immunochemistry (IHC) testing**
  - Adequate sample
  - Preanalytical requirements met
  - External and internal controls
- **Breast cancer samples are:**
  - **POSITIVE: 1% to 100% of tumor nuclei reactive**
    - **LOW POSITIVE: 1-10% of tumor nuclei reactive**
  - **NEGATIVE: <1% or 0% of tumor cell nuclei reactive**
- **PR testing is used primarily for prognostic purposes**



# When to use ET in breast cancer?



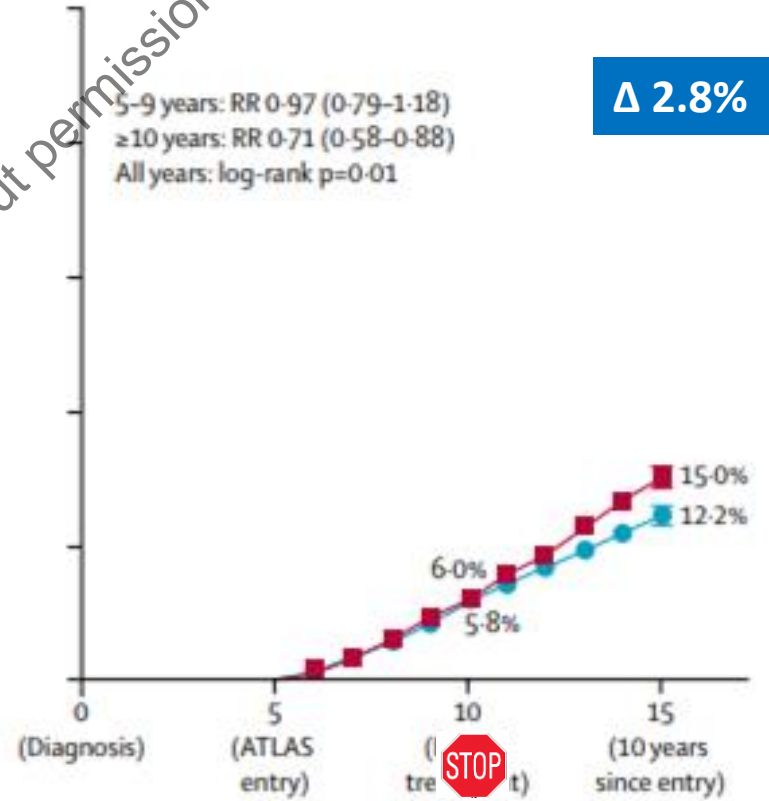
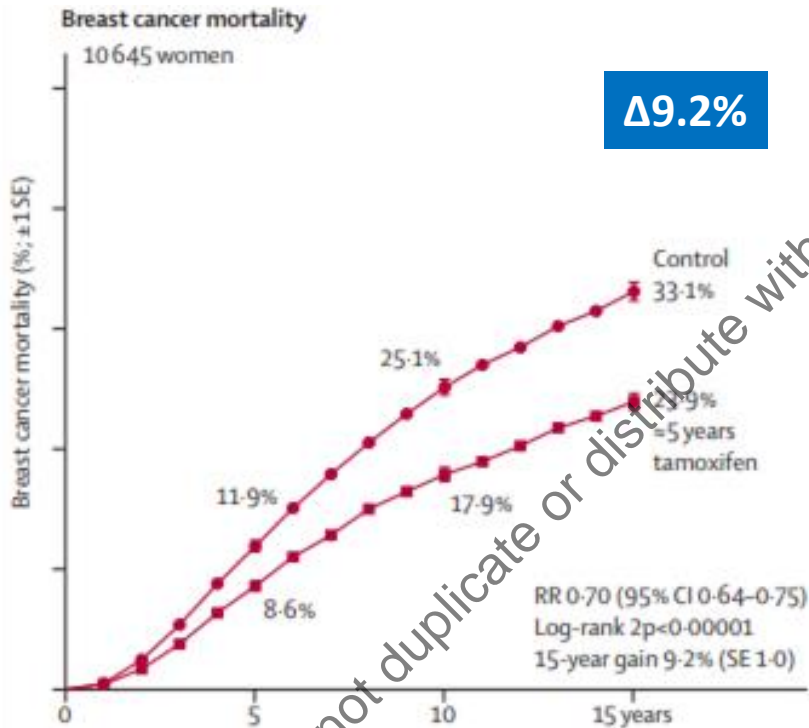




# How long is long enough?

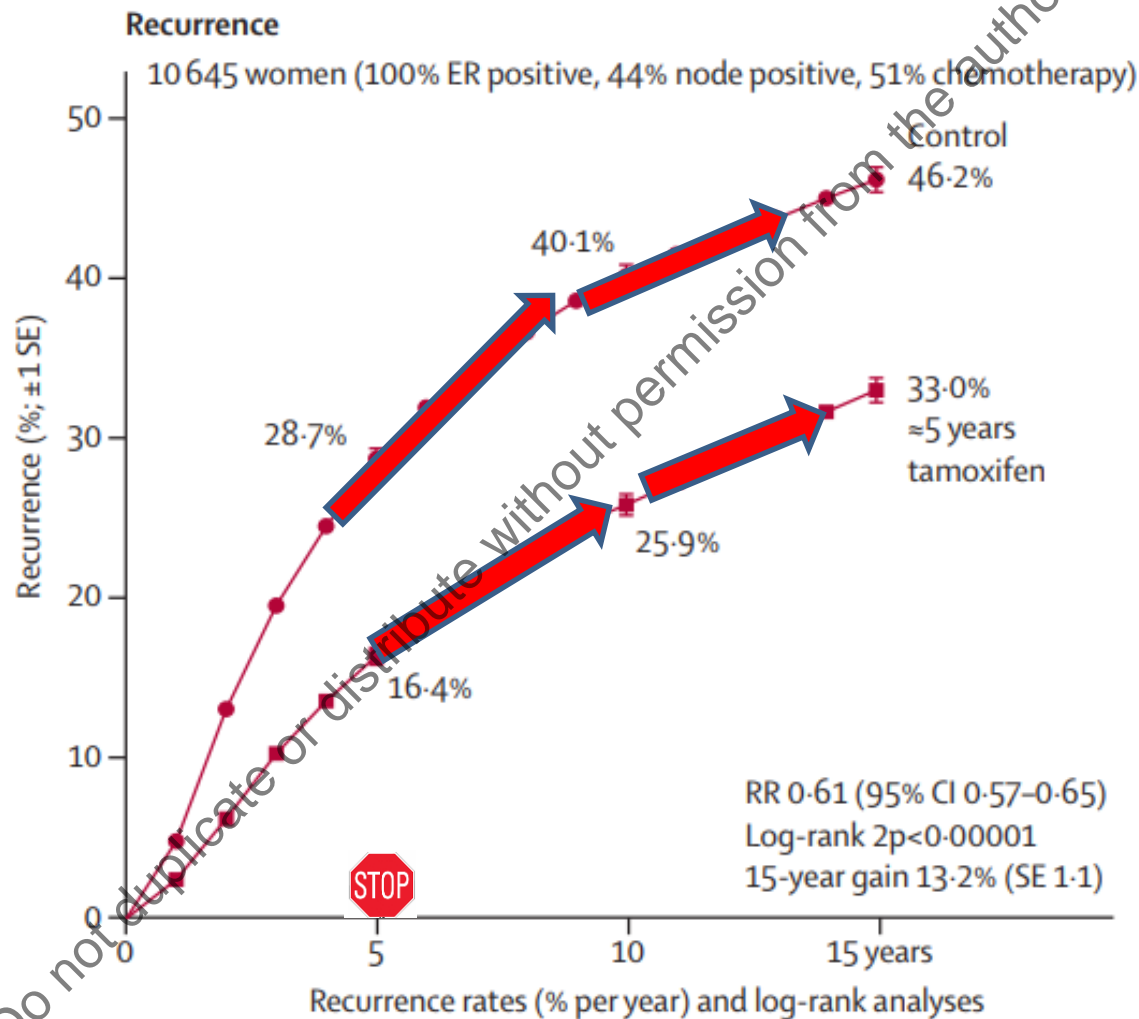
5 yrs of tamoxifen is much better than nil  
(and better than 1 or 2 yrs of tamoxifen)

10 yrs of tamoxifen is better than  
5 yrs of tamoxifen



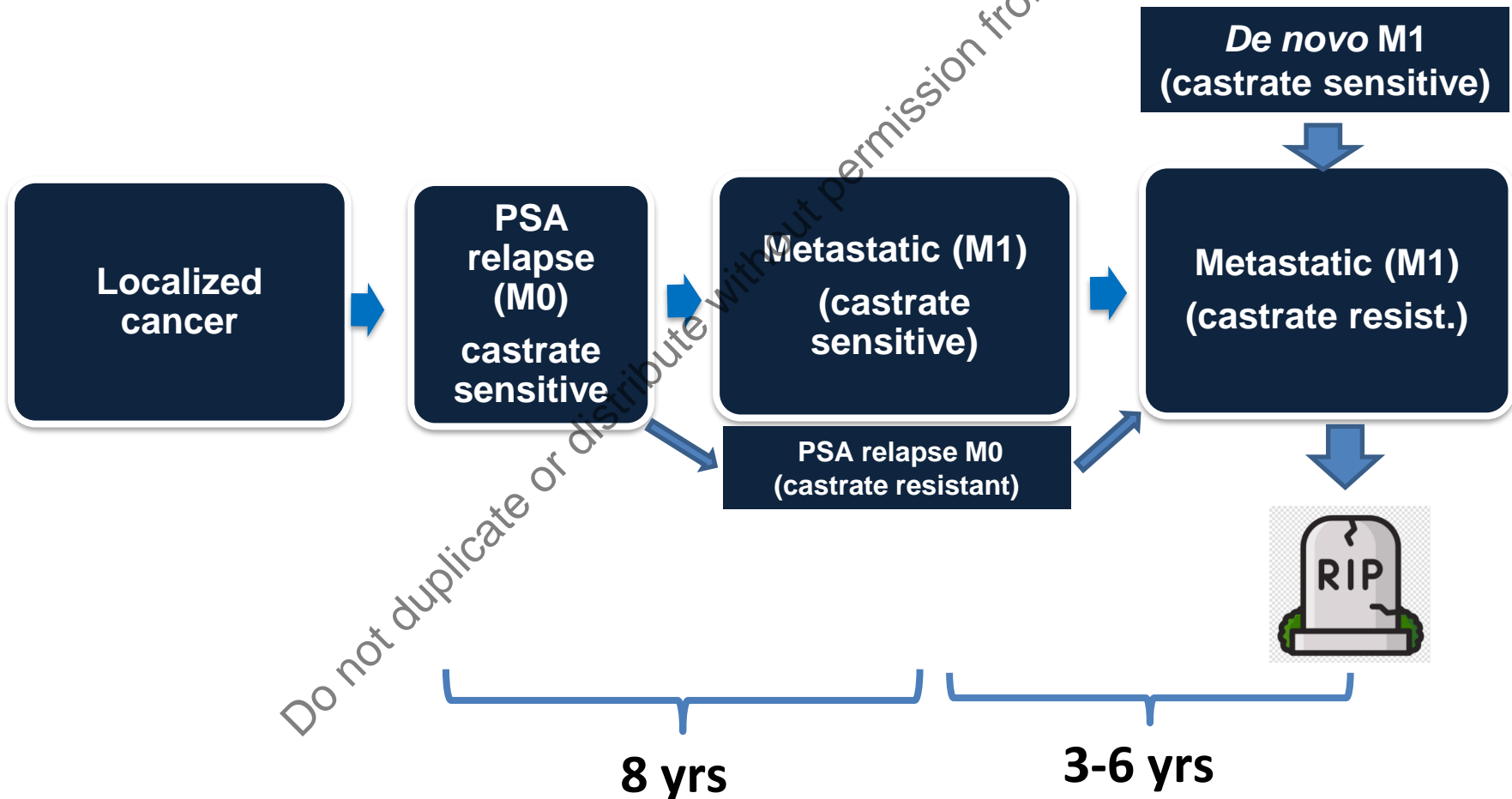


# What is carryover effect?



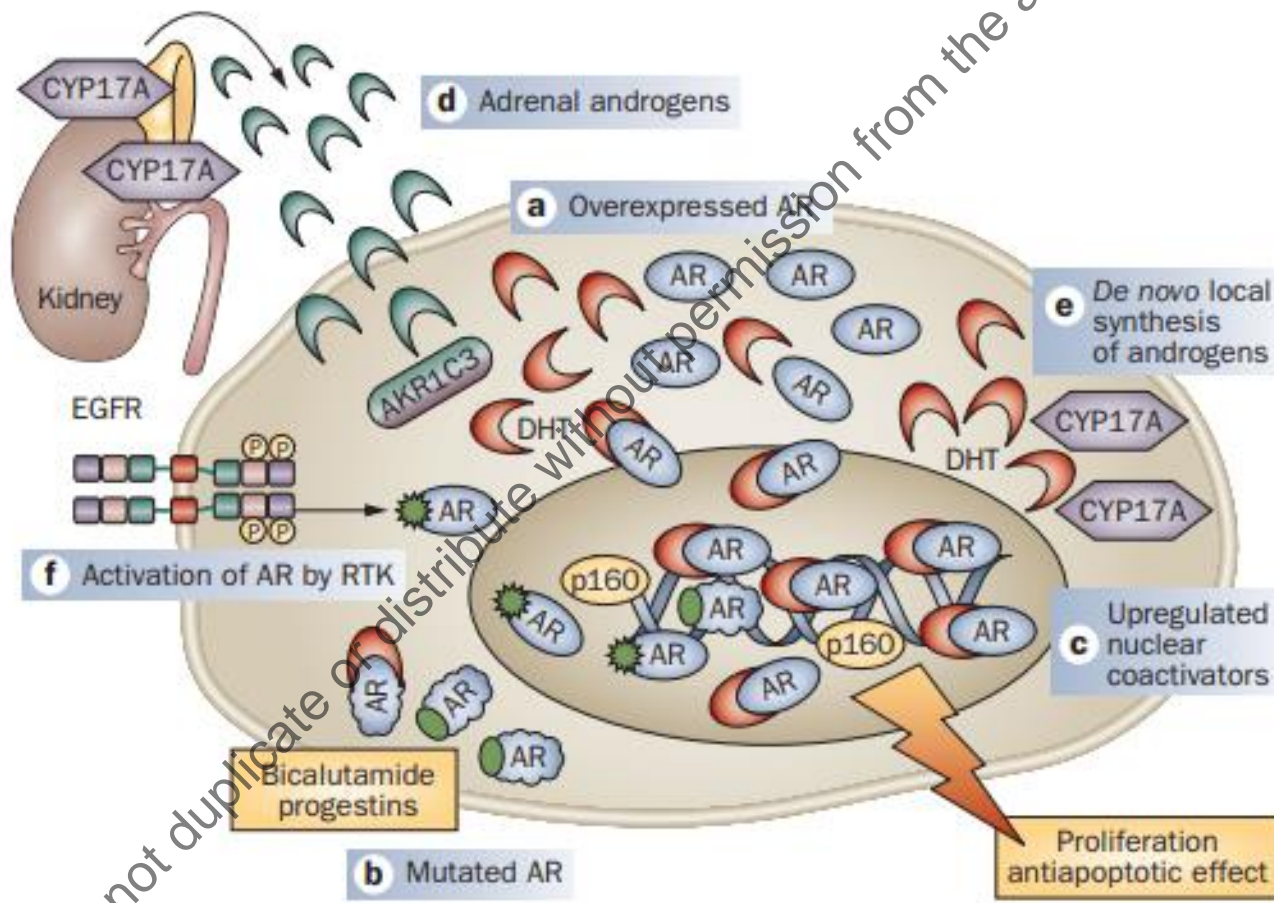


# From early to advanced prostate cancer



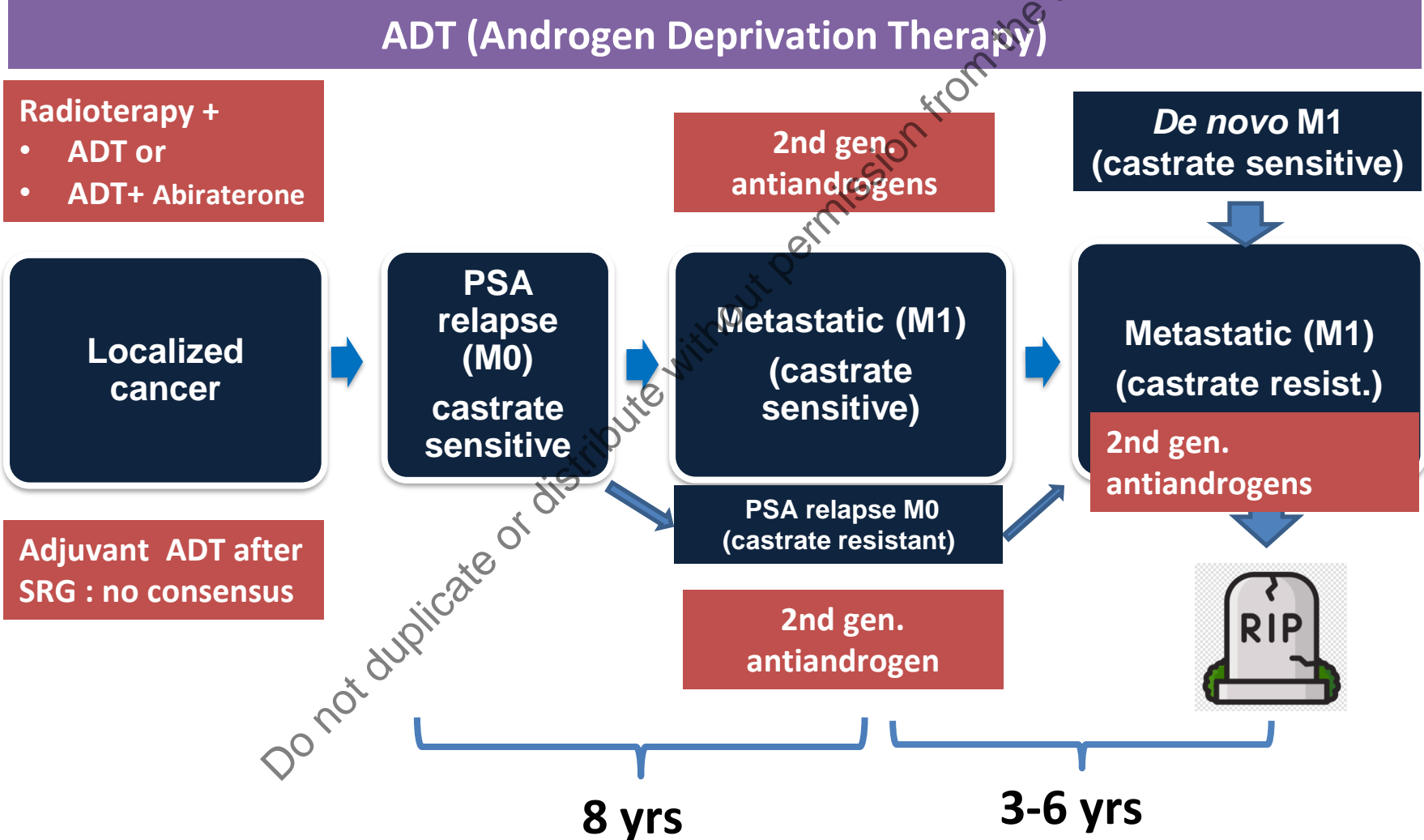


# AR signalling in prostate cancer: a tale that never ends



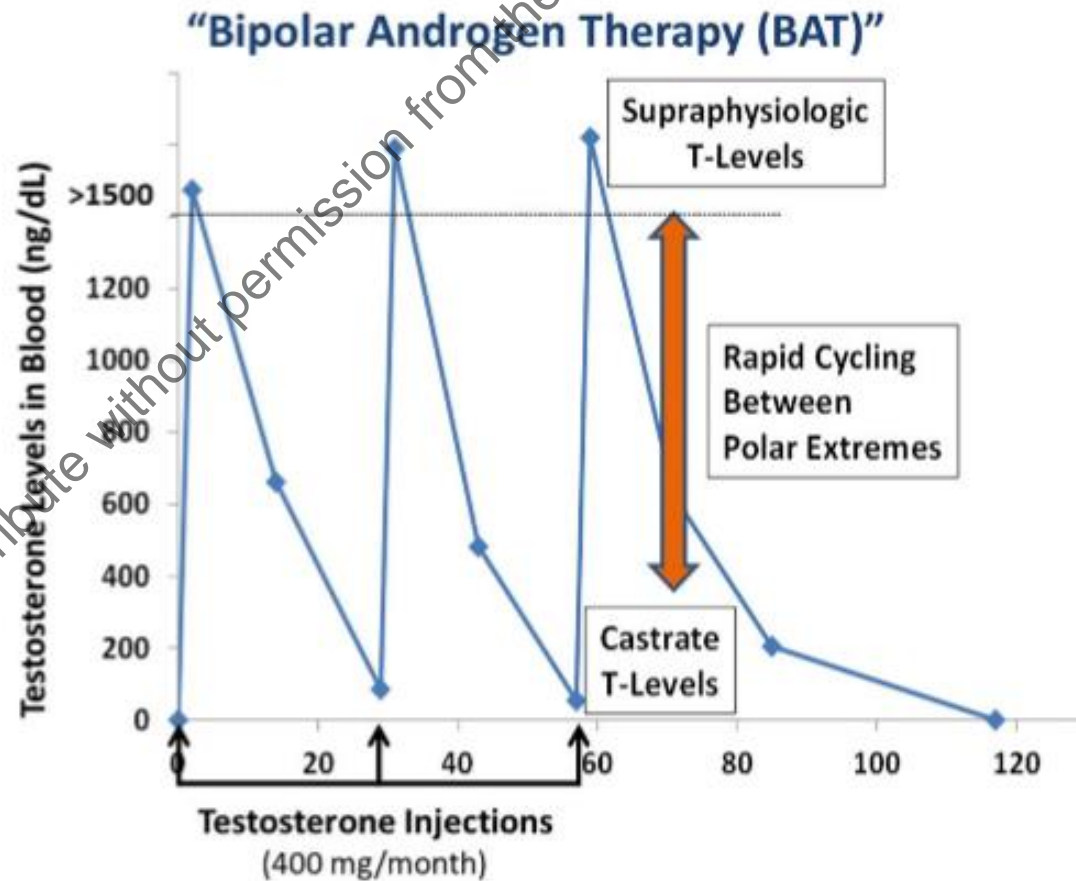
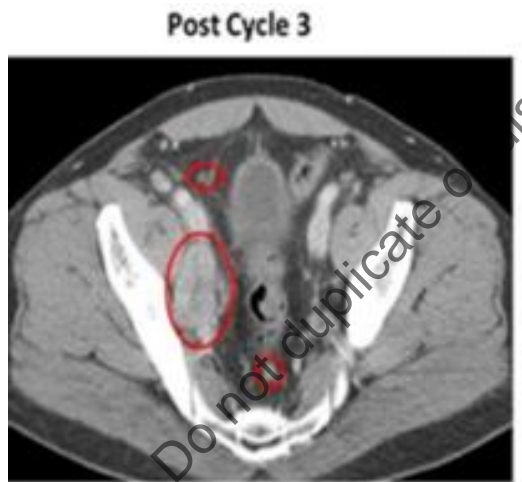


# When to use ET in prostate cancer?





# Bipolar Androgen Therapy







# What are consequences of the deprivation of sex hormones?



- **Hot flashes**
- **Musculoskeletal**
  - Osteoporosis
  - Sarcopenia (sarcopenic obesity)
- **Sexual**
  - Erectile dysfunction, loss of libido, gynecomastia, thinning of body hair
  - Vaginal dryness
- **Metabolic**
  - weight gain, hyperlipidemia, diabetes
- **Cardiovascular**
  - Ischemic heart disease
- **Neurocognitive**
  - Depression, memory loss



# Toxicity of tamoxifen and AIs

Tamoxifen	AIs
<b>Hot flashes</b> <b>Night sweats</b>	<b>Hot flushes</b> <b>Night sweats</b>
<b>Loss of libido</b> <b>Vaginal dryness</b>	<b>Loss of libido</b> <b>Vaginal dryness</b>
<b>Venous thrombembolisms</b> <b>Ischemic stroke</b>	<b>Ischemic heart disease</b>
<b>Uterine cancer</b>	<b>Joint pain</b> <b>Muscle pain</b>
<b>Hypertriglyceridemia</b>	<b>Hypercholesterolemia</b>
	<b>Loss of bone mineral density</b> <b>Bone fractures</b>





# Intensification of ET in premenopausal patients with BC

N=5648*	Tamoxifen (%)	Tamoxifen + OS (%)	Exemestane + OS (%)
Hot flashes	80.4	93.5	92.4
Insomnia	46.8	59.5	59.3
Thrombosis/ Embolism	2.2	2.3	1.2
Fracture	5.3	6.0	7.7
Vaginal drynes	42.4	49.2	53.7
Diabetes	2.0	4.0	3.1

\*All grades toxicities; OS: Ovarian Supression



# Inhibitors of the AR signalling

<b>Apalutamide, Enzalutamide Darolutamide</b>	<b>Abiraterone acetate</b>
<b>Fatigue</b>	<b>Hypokalemia</b>
<b>Falls and fractures</b>	<b>Fluid overload</b>
<b>Arterial hypertension</b>	<b>Hepatotoxicity</b>
<b>Seizures</b>	
<b>Ischemic heart and cerebrovascular disease</b>	

# Factors influencing five-year adherence to adjuvant endocrine therapy in breast cancer patients: A systematic review

- **26 studies were included into the systematic review**
- **Mean rate of adherence at five-year was 66.2%**
- **Older age, younger age, higher co-morbidity index, depression and adverse effects were associated with lower adherence**



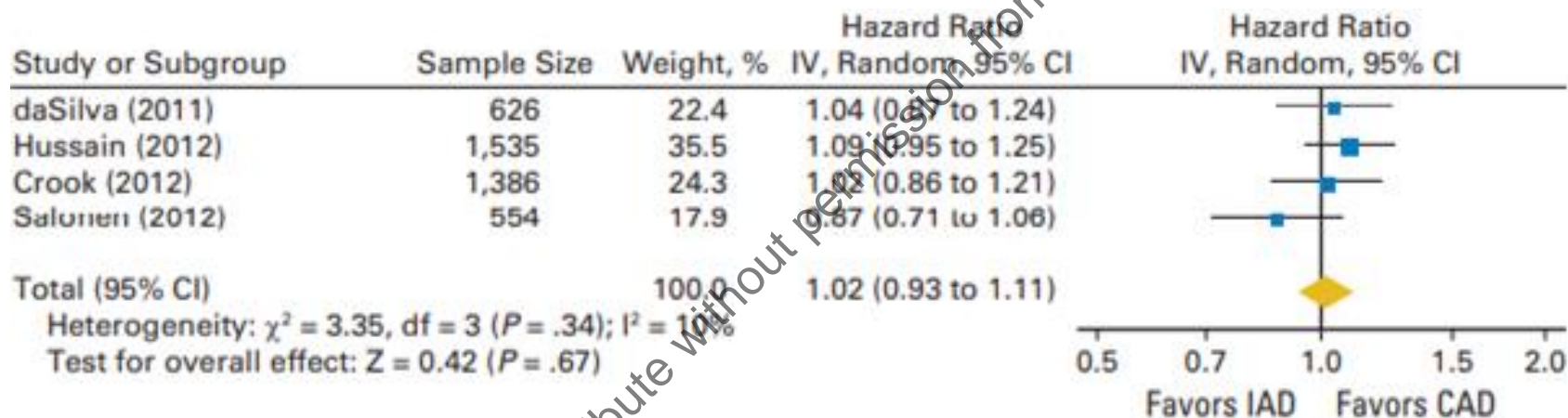
# How can we prevent or mitigate toxicity of ET?

- **Do not overtreat with ET**
- **Use alternative regimens of ET (if available)**
  - e.g. intermittent ET
- **Manage toxic effects of ET**

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# Intermittent ADT in advanced prostate cancer



**When ADT is poorly tolerated intermittent ADT is a treatment option in men with advanced prostate cancer**



# Aerobic and resistance training



- **Fatigue/Hot flushes**
- **Bone loss**
- **Sarcopenia**
- **Depression**
- **Cardiovascular health**

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# Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer

Maria Alice Franzoi, Elisa Agostinetti, Marta Perachino, Lucia Del Mastro, Evandro de Azambuja, Ines Vaz, Ann H Partridge, Matteo Lambertini

	Hot flashes	Sexual dysfunction	Weight gain	Musculo-skeletal symptoms	Fatigue
SSRIs and SNRIs	√√√	√√	--	√√√	--
Anticonvulsants	√√√	√	--	--	--
Oxybutynin	√√√	--	--	--	--
Aromatase inhibitor switch	--	--	--	√√	--
Vaginal lubricants or moisturisers	√√√	√√√	--	--	--
Vaginal CO <sub>2</sub> laser	--	√	--	--	--
Stellate ganglion block	√√	--	--	--	--
Cognitive behavioural therapy	√√√	√√√	√√√	√√√	√√√
Physical exercise	--	--	√√√	√√√	√√√
Acupuncture	√√	--	--	√√√	√√
Hypnosis	√√	--	--	--	--
Yoga and mindfulness	√√	--	√	√√	√√



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Anticonvulsants	√√√	..	..	..	..
Oxybutynin	√√√	..	..	..	..
Aromatase inhibitor switch	..	..	..	√√	..
Vaginal lubricants or moisturisers	..	√√√	..	..	..
Vaginal CO <sub>2</sub> laser	..	√	..	..	..
Stellate ganglion block	√√	..	..	..	..
Cognitive behavioural therapy	√√√	√√√	√√√	√√√	√√√
Physical exercise	..	..	√√√	√√√	√√√
Acupuncture	√√	..	..	√√√	√√
Hypnosis	√√	..	..	..	..
Yoga and mindfulness	√√	..	√	√√	√√



**Thank you for your attention**

*Be curious, ask questions and share what you learn.*

**ASK. LEARN. SHARE.**

[mike-taylor.org](http://mike-taylor.org)

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