

NASPPC: ABCs of Androgen Deprivation Therapy (ADT)



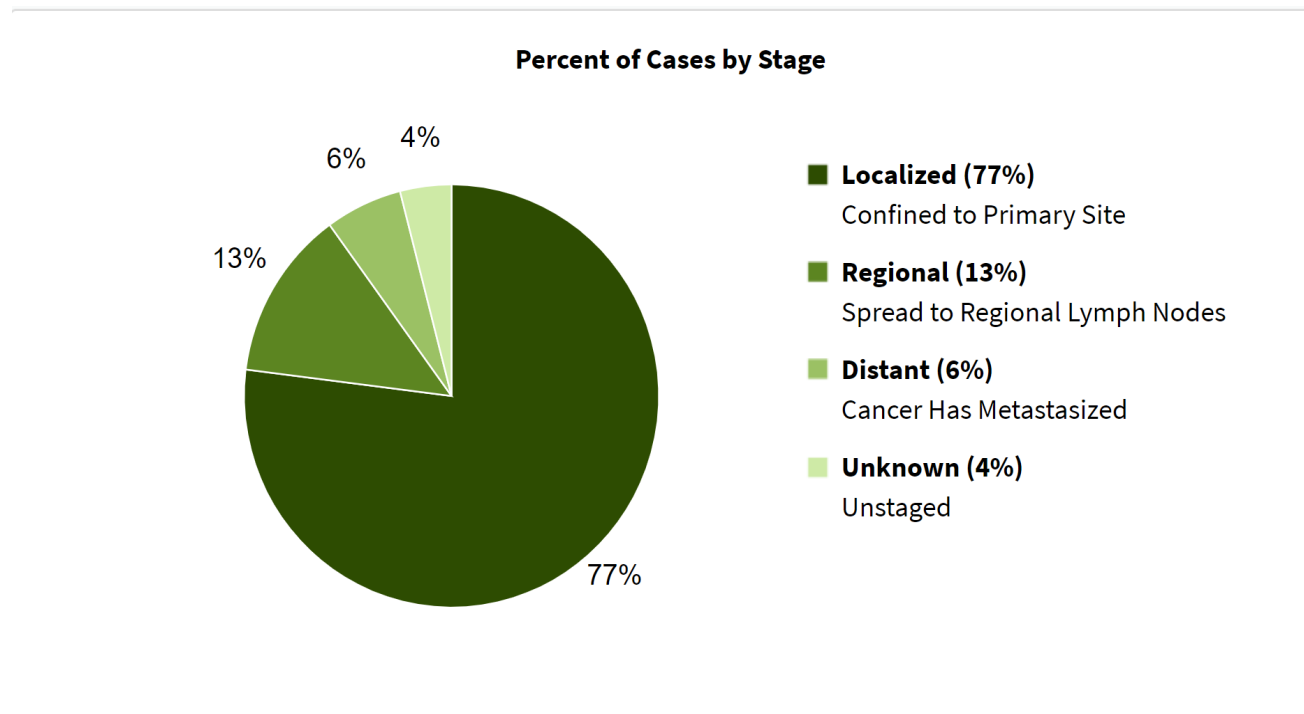
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- Median age: 66 y/o
- About 11.6% will be diagnosed in lifetime
- Risk Factors: Age; Race: AA>W>Asian; Family History



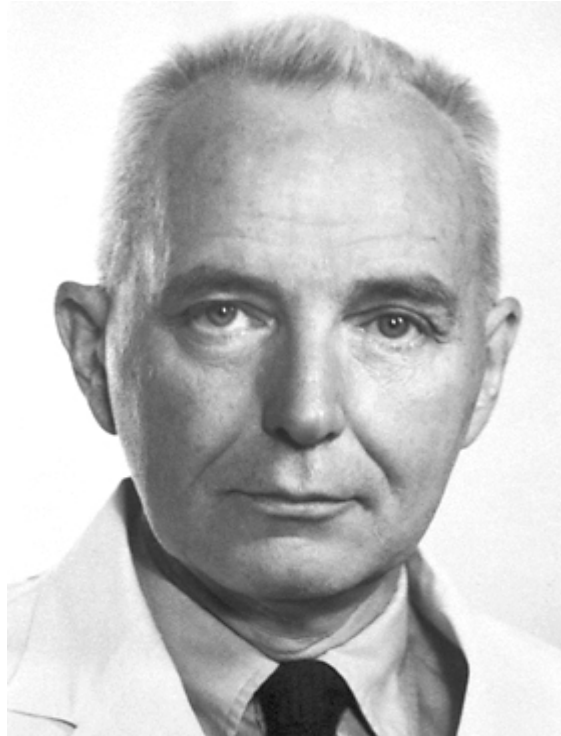
- ADT is “hormonal” therapy or Androgen “suppression” therapy
- Suppression of hormones (androgen/testosterone) to achieve “castrate” levels
- Achieved surgically or chemically¹
- Definition of “castrate” levels of testosterone < 50 ng/dl or < 20 ng/dl ^{2, 3}

1. Seidenfeld J. Ann. Intern. Med. 2000 Apr 4;132(7):566-77.

2. Cookson, M. S., et al. American Urological Association. 2018;

3. Cornford, P., et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Eur Urol 2017; 71: 630-642.

- ADT is a cornerstone of treatment for advanced or metastatic disease
- ADT is used in patients with biochemical/PSA recurrence
- Used in conjunction with radiation in early intermediate- or high-risk disease localized or locally advanced prostate cancer or as adjuvant therapy with radiation



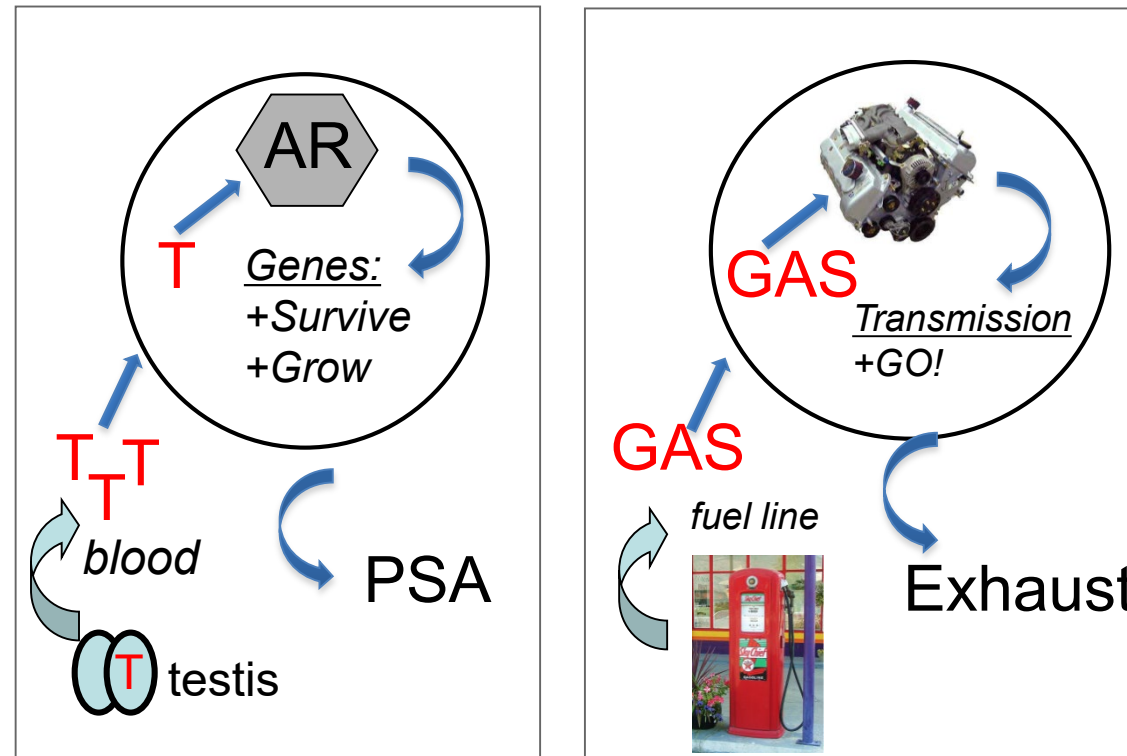
Nobel Prize 1966

for “his discoveries concerning hormonal treatment of prostatic cancer”

- Huggins and Hodges first treated men with prostate cancer with either orchiectomy or estrogen
- Huggins and Bergenstal used adrenalectomy for the “immediate and persistent relief of crippling bone pain”

1. Huggins C, Hodges. J Urol. 2002 Jul; 168(1):9-12
2. Huggins C, Bergenstal DM. Proc Natl Acad Sci U S A. 1952 Jan; 38(1):73-6.

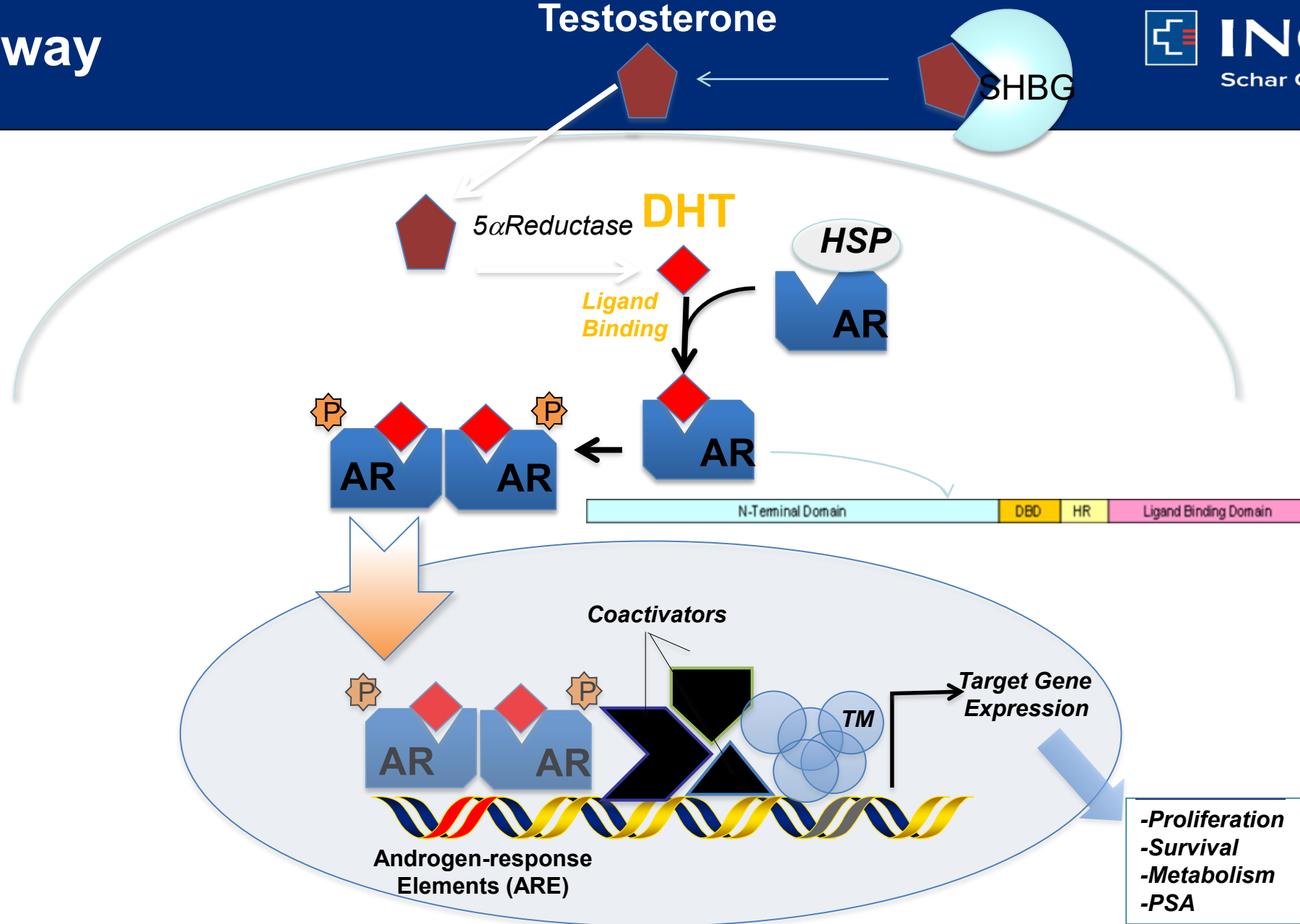
Androgen Receptor (AR): Engine Analogy



T= testosterone

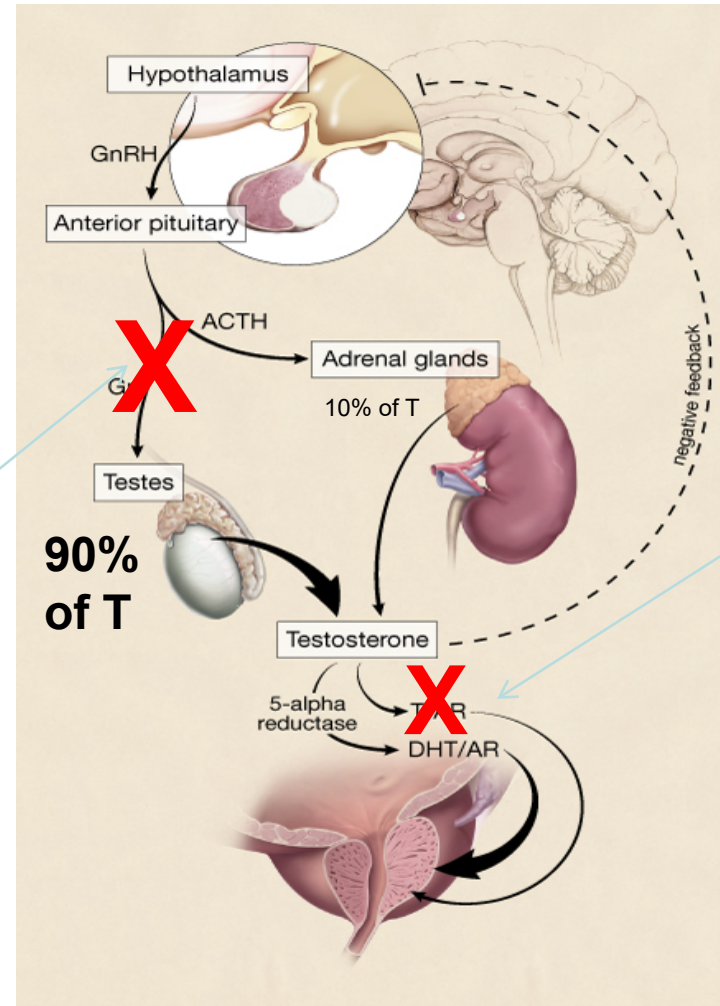
AR Pathway

Testosterone



Hypothalamic Pituitary Gonadotropin-axis: Androgen Deprivation Therapy

**GnRH-
Agonist
or
Antagonist**
(immediate
testosterone
suppression)



**Anti-
androgens**
(combined
androgen
blockade –
CAB*)

*Prostate Cancer Trialists' Collaborative Group. Lancet: 2000;

Hormonal Therapy Medications

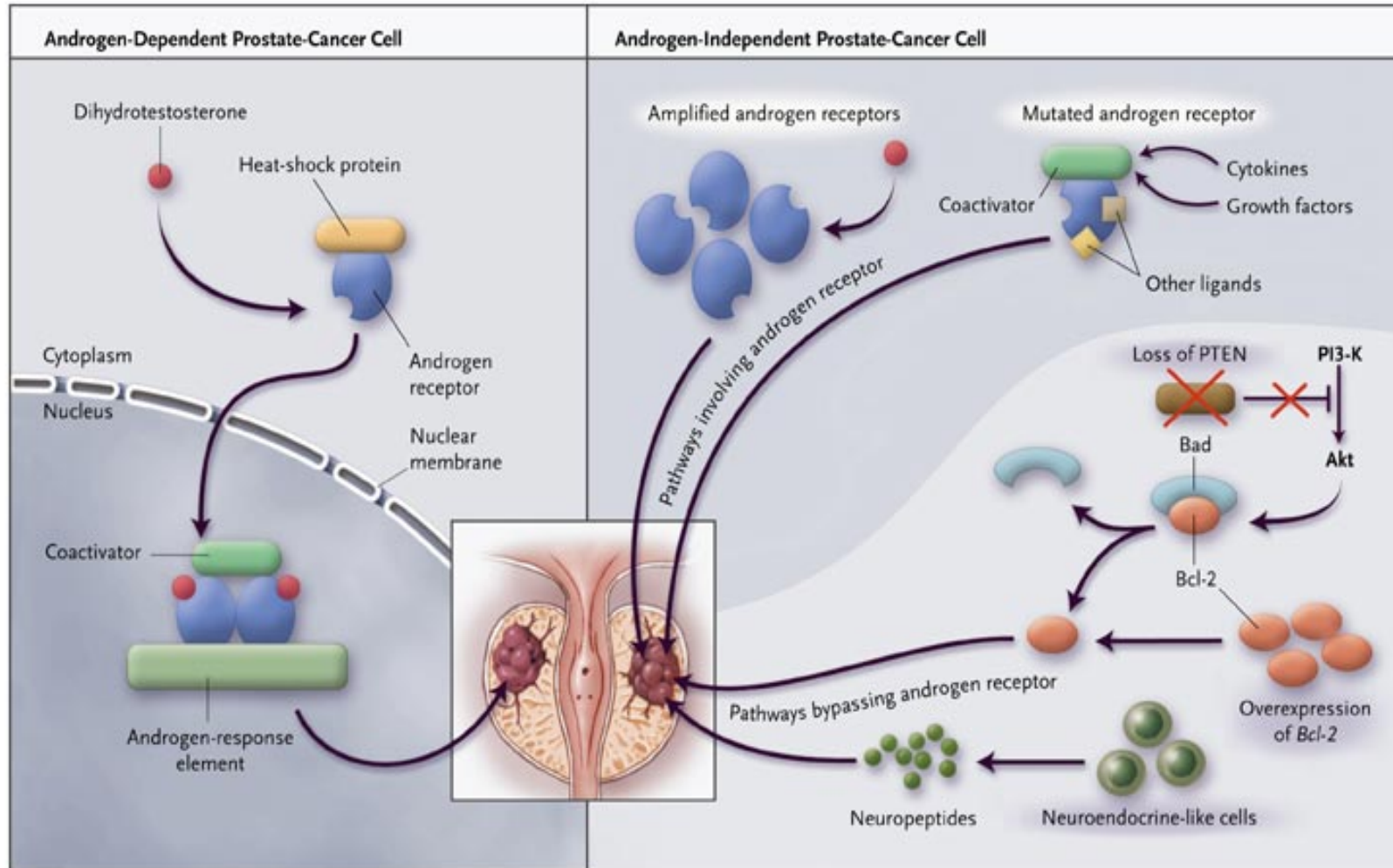
Hormonal Therapy	Dosing	Manufacturer
GnRH agonists		
Lupron Depot [®] or Eligard [®] (leuprolide acetate for depot suspension)	7.5 mg IM or s.c. q mo 22.5 mg IM or sc q 3 mos 30 mg IM or sc q 4 mos 45 mg IM or sc q 6 mos	Abbott Sanofi-Aventis
Zoladex [®] (goserelin acetate implant)	3.6 mg s.c. q mo 10.8 mg s.c. q 3 mos	Astra-Zeneca Pharmaceuticals
Viadur [®] (leuprolide acetate implant)	yearly implant	ALZA Corporation under license to Bayer Corporation
GnRH antagonist		
Firmagon [®] (degarelix)	240 mg sc. days 1 then 80 mg sc q 4 wks thereafter	Ferring Pharmaceuticals
Antiandrogens		
Casodex [®] (bicalutamide) tablets	50 mg daily	Astra-Zeneca Pharmaceuticals
Nilandron [®] (nilutamide) tablets	150 mg po daily	Sanofi-Aventis
Eulexin [®] (flutamide) capsule	250 mg po t.i.d.	Schering-Plough Pharmaceuticals
Xtandi [®] (Enzalutamide) tablets	160 mg p.o. daily	Astellas/Medivation
Erleada [®] (Apalutamide) tablets	240 mg po daily	Janssen
Nubeqa [®] (Darolutamide) tablets	300 mg po b.i.d.	Bayer
CYP17 Inhibitors		
Abiraterone acetate	1000 mg po daily	Janssen, Yonsarix

Emergence of castration-resistant disease or hormone-resistance

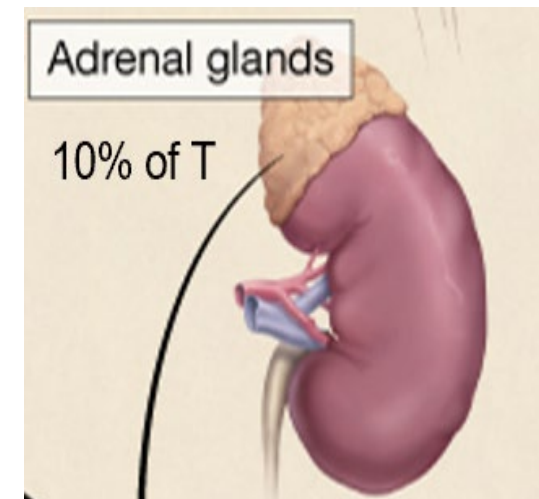


Castrate-resistant disease = PSA rising despite very low levels of testosterone (even while ADT is given)

Mechanisms of Castration-Resistant Prostate Cancer (CRPC)

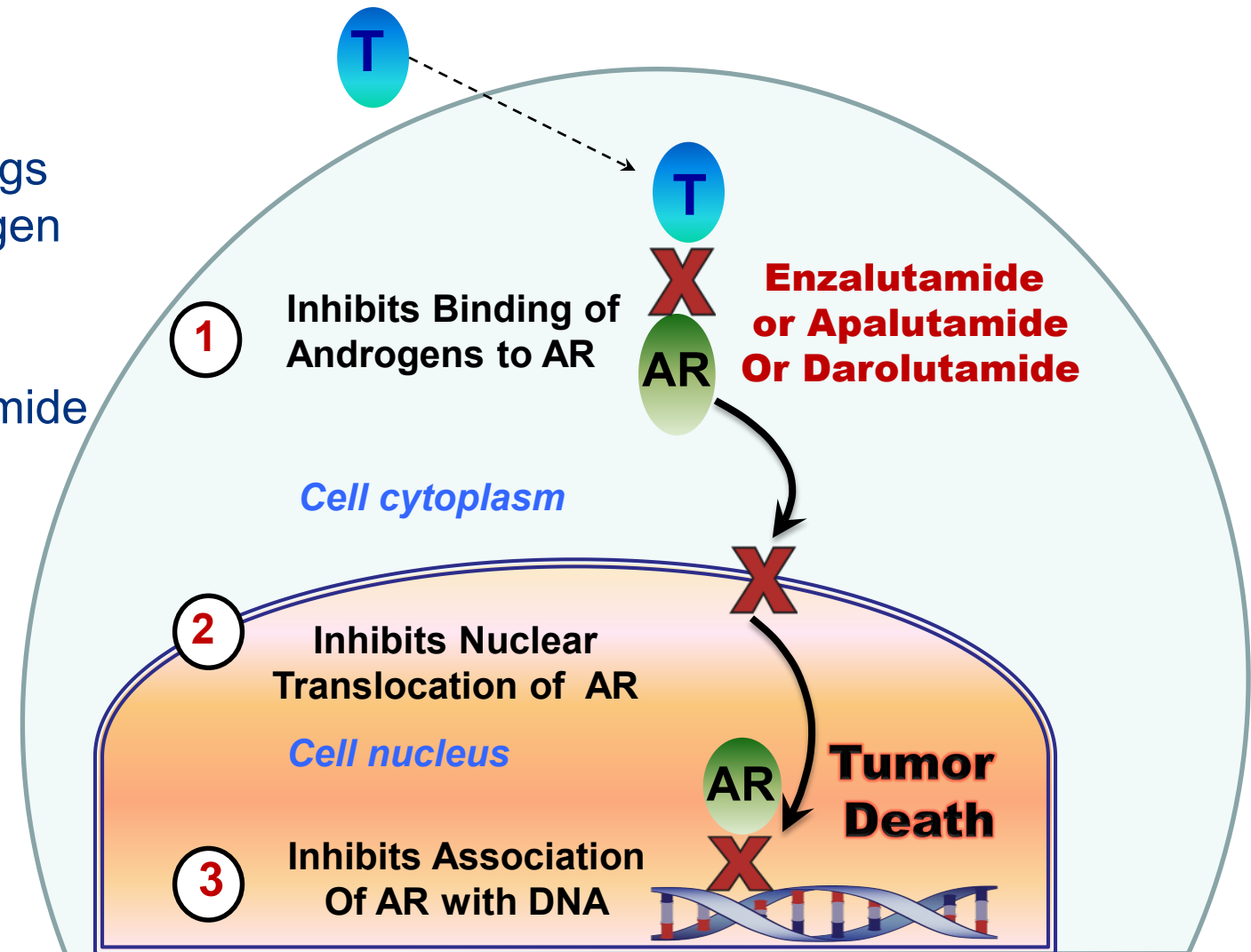


- Oral irreversible inhibitor of CYP17 (P450c17)
 - 17 α –hydroxylase
 - C17,20-lyase
- Inhibits testosterone production in testis, adrenal glands, prostate and tumor

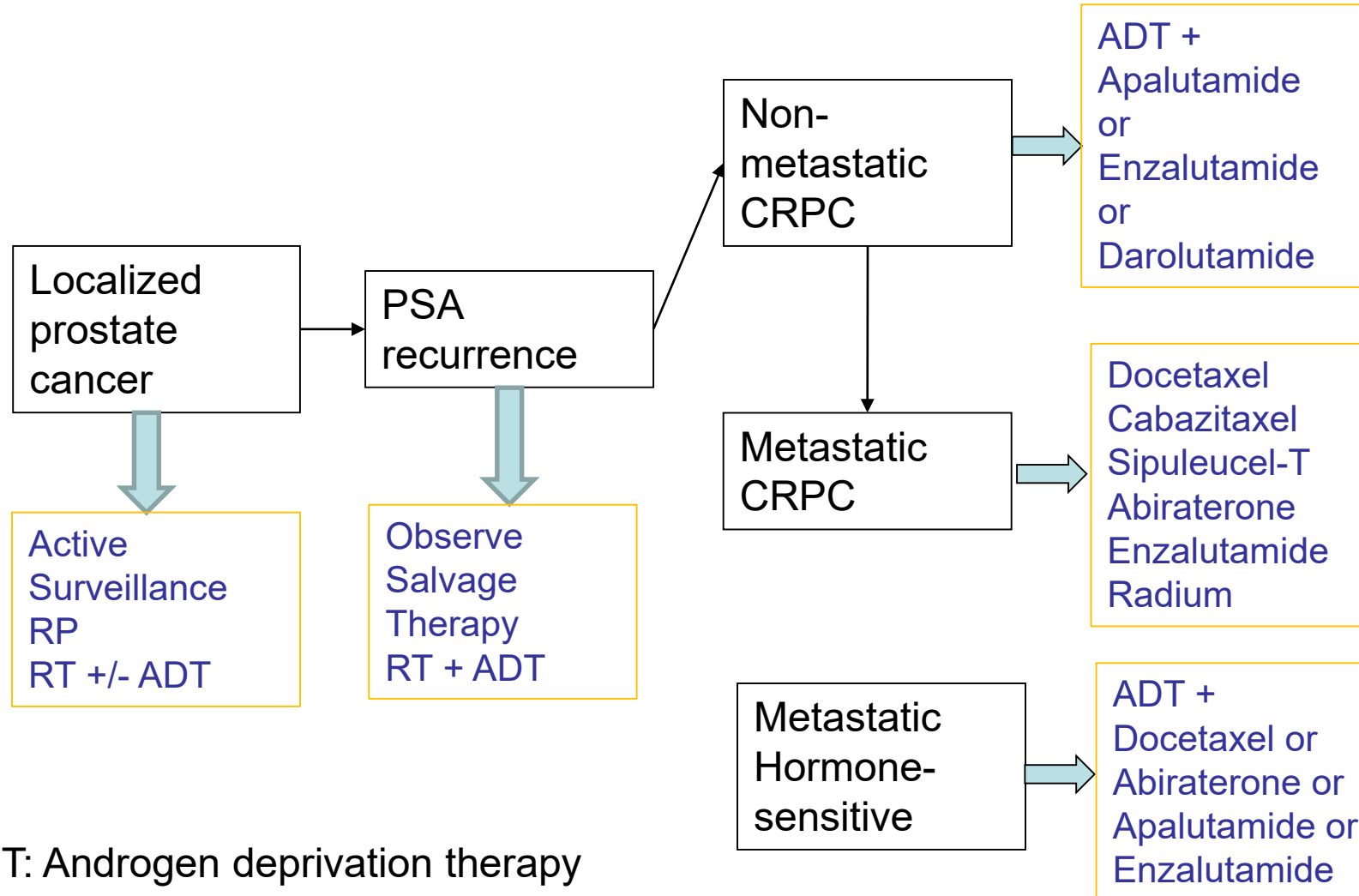


Apalutamide or Enzalutamide or Darolutamide mechanism of action

1. Apalutamide and enzalutamide and darolutamide are oral drugs designed to target androgen receptor (AR) signaling
2. Apalutamide or Enzalutamide or Darolutamide affects multiple steps in the androgen receptor (AR) signaling pathway.
T = testosterone

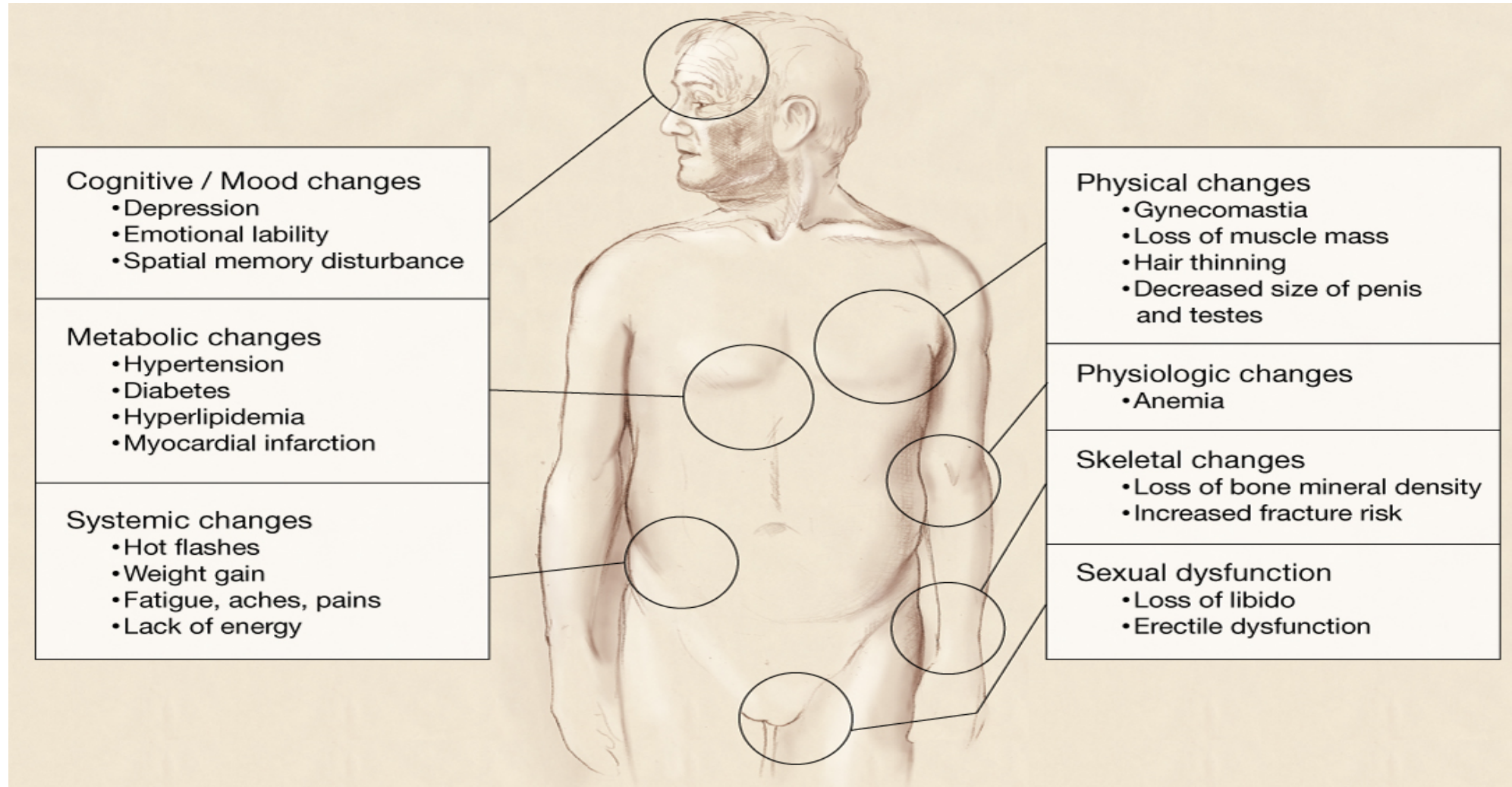


Different phases of prostate cancer and treatment



ADT: Androgen deprivation therapy
Rx: Treatment

ADT Side-effects



American Cancer Society Prostate Cancer Survivorship Care Guidelines

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Guidelines in the management of ADT side-effects

GUIDELINE	LEVEL OF EVIDENCE ^a
<p>Distress/depression/PSA anxiety</p> <ul style="list-style-type: none">• Assess for distress/depression/PSA anxiety periodically (at least annually) using a simple screening tool, such as the Distress Thermometer.• Manage distress/depression using in-office counseling resources or pharmacotherapy as appropriate.• If office-based counseling and treatment are insufficient, refer survivors experiencing distress/depression for further evaluation and or treatment by appropriate specialists.	0
<p>Fracture risk/osteoporosis: specific risk for men receiving ADT</p> <ul style="list-style-type: none">• Assess risk of fracture for men treated with ADT or older radiation techniques through baseline DEXA scan and calculation of a FRAX score.• For men determined to be high risk, prescribe weekly bisphosphonate therapy (oral alendronate at a dose of 70 mg) or annual intravenous zoledronic acid at a dose of 5 mg to increase bone density. Denosumab is also approved by the FDA to treat men at increased risk of osteoporosis.	2A ^c

Guidelines in the management of ADT side-effects

GUIDELINE	LEVEL OF EVIDENCE ^a
<p>Anemia: specific risk for men receiving ADT</p> <ul style="list-style-type: none">• Perform annual CBC to monitor hemoglobin levels.	0
<p>Cardiovascular and metabolic effects: specific risk for men receiving ADT</p> <ul style="list-style-type: none">• Follow USPSTF guidelines for evaluation and screening for cardiovascular risk factors, blood pressure monitoring, lipid profiles, and serum glucose (uspreventiveservicestaskforce.org/uspsttopics.htm).	A: hypertension ^b B, I: type II diabetes ^b A, B: lipid disorders ^b
<p>Vasomotor symptoms (eg, hot flushes): specific risk for men receiving ADT</p> <ul style="list-style-type: none">• Although not approved by the FDA for this indication, prescription of selective serotonin or noradrenergic reuptake inhibitors or gabapentin may offer symptom relief.	0/I (gabapentin trial)

Guidelines in the management of ADT side-effects

GUIDELINE	LEVEL OF EVIDENCE ^a
<p>Sexual dysfunction/body image</p> <ul style="list-style-type: none">• Discuss sexual function with survivors.• Use validated tools, such as the SHIM, to monitor erectile function over time.• Erectile dysfunction may be addressed through a variety of options, including penile rehabilitation or prescription of phosphodiesterase type 5 inhibitors (eg, sildenafil, vardenafil, tadalafil).• Refer men with persistent sexual dysfunction to a urologist, sexual health specialist, or psychotherapist to review treatment and counseling options.	0
<p>Sexual intimacy</p> <ul style="list-style-type: none">• Encourage couples to discuss their sexual intimacy and refer to counseling or support services as appropriate.• Prescribe medication as described above to address erectile dysfunction.• Instruct couples on use of sexual aids to improve erectile dysfunction for men/male partners as well as postmenopausal symptoms for women. Refer to mental health professional with expertise in sex therapy.	0

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JOURNAL OF CLINICAL ONCOLOGY

Cardiovascular Disease With Androgen Deprivation: The (forgotten) Role of Testosterone

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- Conflicting associations between cardiovascular risks and mortality
- Non-statistically significant risk of cardiovascular mortality in men with localized prostate cancer undergoing ADT in (RTOG) 92-02, RTOG 86-10, and RTOG 85-31
- Statistically significant increased risk in others

The New York Times

Hormone Therapy for Prostate Cancer Tied to Dementia

Androgen deprivation therapy for prostate cancer is associated with an increased risk of Alzheimer's disease and other forms of dementia.



By **Nicholas Bakalar**

July 3, 2019



Original Investigation | Oncology

July 3, 2019

Association Between Androgen Deprivation Therapy Use and Diagnosis of Dementia in Men With Prostate Cancer

Ravishankar Jayadevappa, PhD^{1,2,3}; Sumedha Chhatre, PhD⁴; S. Bruce Malkowicz, MD²; [et al](#)

» [Author Affiliations](#) | [Article Information](#)

JAMA Netw Open. 2019;2(7):e196562. doi:10.1001/jamanetworkopen.2019.6562

FROM THE JOURNALS

No ADT-dementia link in large VA prostate cancer cohort study

Publish date: October 15, 2018

Author(s): [Andrew D. Bowser](#)

FROM JAMA ONCOLOGY

In contrast to other recent studies, androgen deprivation therapy (ADT) had no link to dementia in a observational cohort study of more than 45,000 men with prostate cancer who received definitive radiotherapy, investigators have reported.

VOLUME 35 · NUMBER 30 · OCTOBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk of Alzheimer's Disease Among Senior Medicare Beneficiaries Treated With Androgen Deprivation Therapy for Prostate Cancer

Seo Hyon Baik, Fabricio Sampaio Peres Kury, and Clement Joseph McDonald

Conclusion

These data suggest that ADT treatment has no hazard for AD and no meaningful hazard for dementia among men age 67 years or older who are enrolled in Medicare.

Denosumab decreases bone loss in men on ADT (non-metastatic)

	Denosumab	Placebo
Dose	60 mg SQ q 6 mos	60 mg SQ q 6 mos
Change in lumbar spine BMD from baseline to end of study period*	5.60%	-1.00%
Treatment difference (95% CI)	6.7% (6.2, 7.1)	
p-value	< 0.0001	

- Similar to breast cancer treatment
- Conservative (desk fan, black cohosh tea)
- SSRIs (selective serotonin uptake inhibitors) – venlafaxine, citalopram or bupropion (NDRI)
- Gabapentin
- Oxybutinin – anticholinergic drug treatment for overactive bladder
 - 86% reduction in hot flushes in 5 mg bid ($P < 0.1$)¹

- ADT is an important part of treatment in prostate cancer
- It may be associated with side-effects
- Ongoing issues as to the duration of treatment and ways to mitigate side-effects are ongoing

THANK YOU!

Questions?