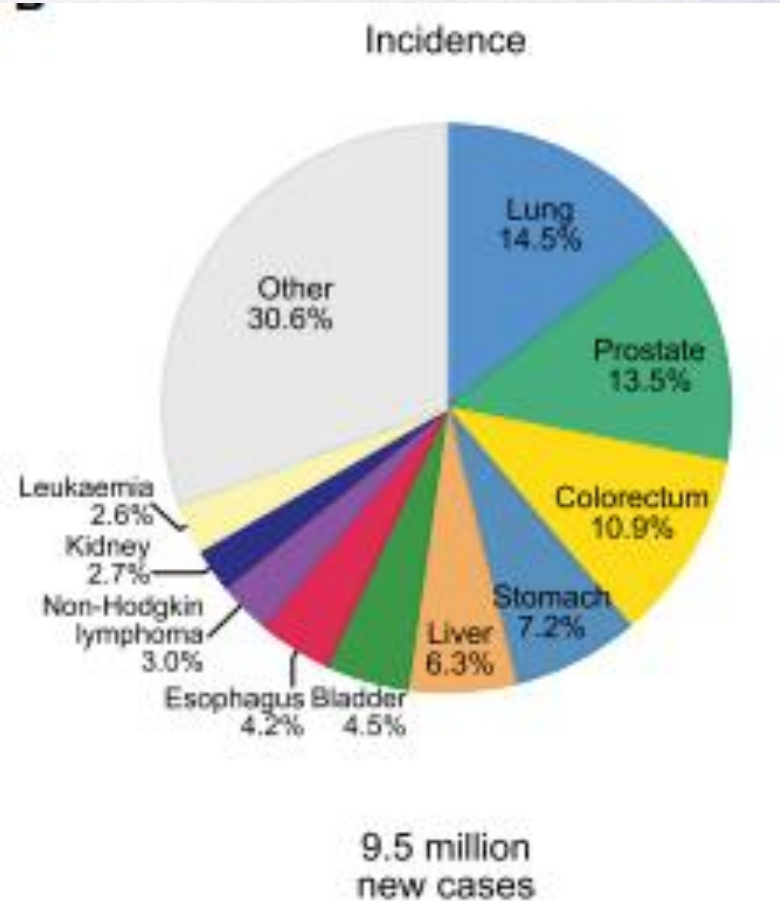
Hormonal therapy in Carcinoma Prostate

Prostate Cancer-Burden

- 2nd most frequent cancer and 5th leading cause of cancer death in men.
- 2nd leading site of cancer among males in Indian cities like Delhi, Kolkata, Pune.[2]
- Hormonal therapy is the mainstay of treatment for men with prostate Ca



Global cancer statistics 2018
Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.

[2]Jain et al. Epidemiology of prostate cancer in India. Meta Gene. 2014

Hormonal therapy- how is it effective?

LHRH

Anterior Pituitary

LH

Testis

Androgen Production and Action

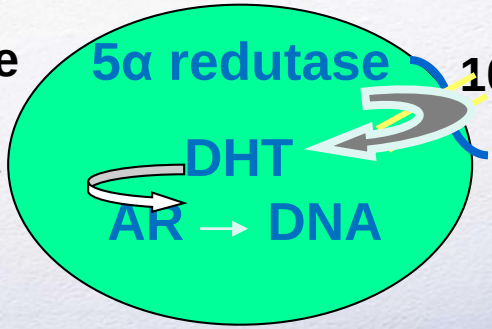
Adrenal gland

steroids

conversion

90% Testosterone

10% Testosterone



Prostate cancer cell

Hormonal therapy- how is it effective in Ca Prostate?

LHRH

Anterior Pituitary

LH

Testis

Androgen Deprivation

steroids

conversion

90% Testosterone

10% Testosterone

Prostate cancer cell

Androgen Deprivation in Ca Prostate -the discovery!

- In 1940-50s Dr Charles Huggins discovered orchiectomy leads to significant reduction in Prostate Ca. Nobel Prize in 1966

- Schally discovered structure of LHRH, developed LHRH agonists, demonstrated decreased testosterone levels with daily doses; Nobel Prize in 1977

Strategies of Androgen Deprivation

SURGICAL CASTRATION

- Orchiectomy

MEDICAL CASTRATION

- Inhibition of LHRH / LH release
- Ablation of androgen sources
- Inhibition of androgen synthesis
- Antiandrogens

Strategies for Androgen Deprivation

estrogens

LHRH

LHRH Agonists

LHRH Antagonists

Anterior Pituitary

LH

Surgical Castration

Testis

90% T

Nonsteroidal antiandrogen

Adrenal gland

steroids

conversion

10% T

5α redutase

DHT

Finasteride

AR → DNA

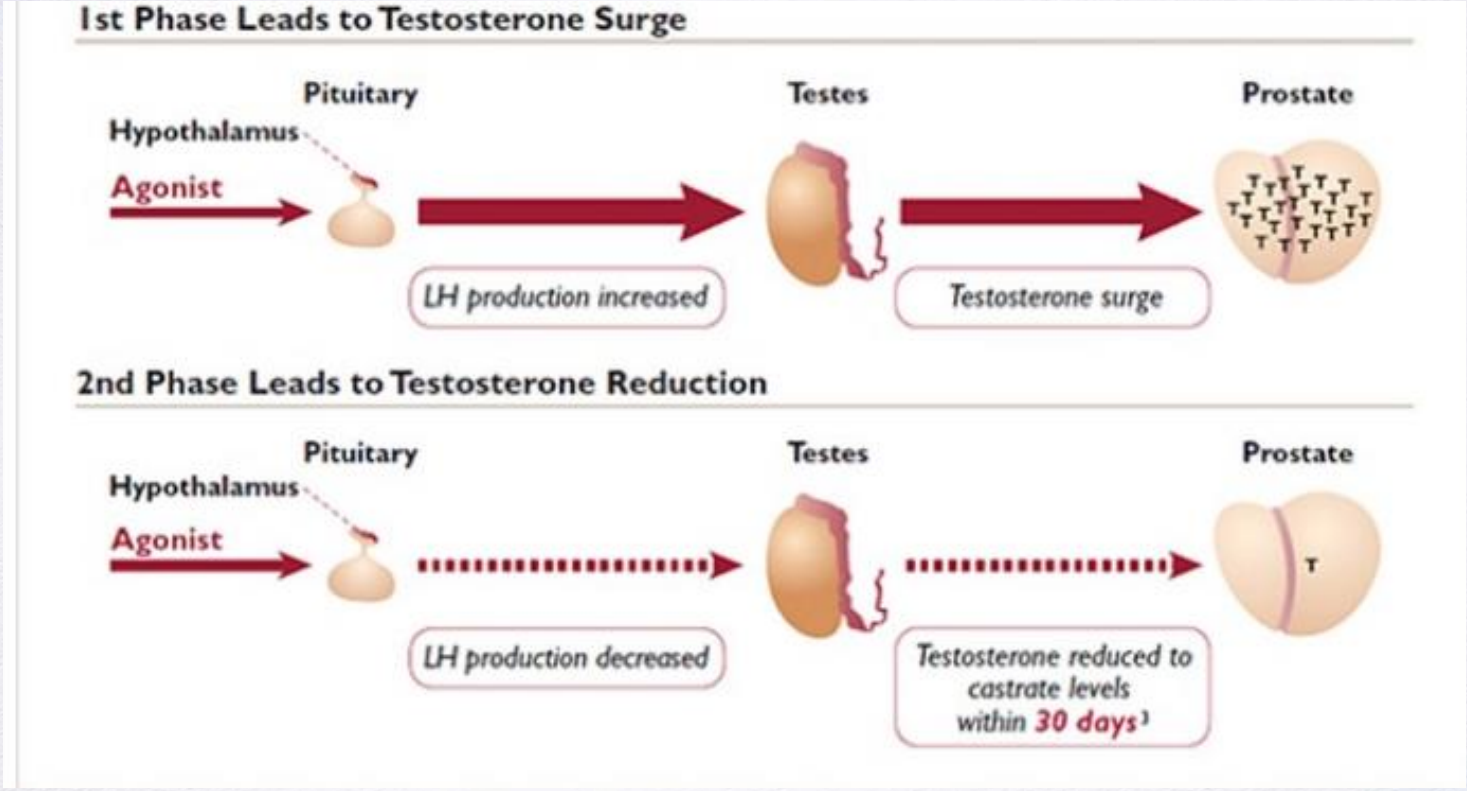
Orchiectomy (Surgical Castration)

- **Bilateral orchiectomy quickly reduces circulating testosterone levels to castration level (less than 50 ng/dL)**

  - **Simple procedure**
  - **Compliance not a problem**
  - **No flare**
  - **Nonreversible**
  - **Carries significant psychological burden**

Inhibition of LHRH / LH release

- **LH-RH agonists**
  - **Leuprolide, Goserelin, Triptorelin, Histrelin**

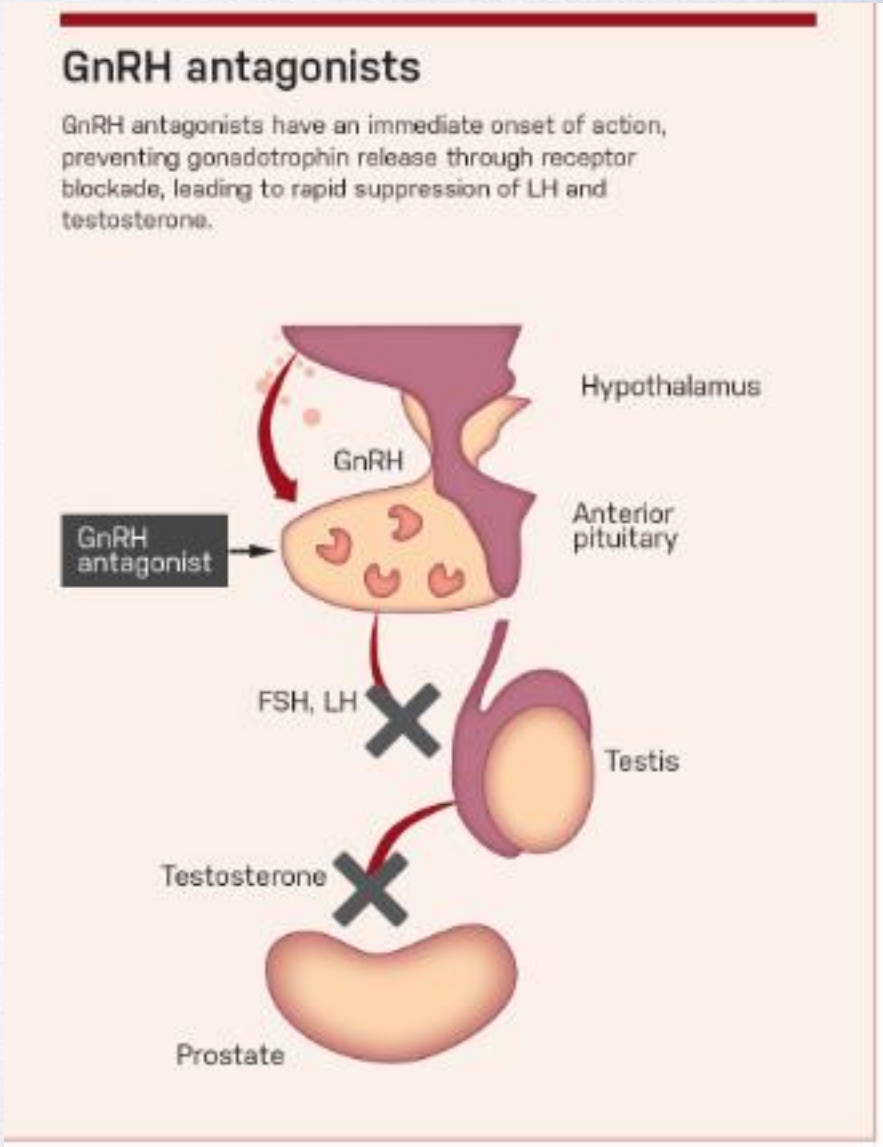


Desensitization of LH-RH receptor in Anterior Pituitary after chronic exposure to LHRH

Testosterone flare-Coadministered with antiandrogens for 2-3 weeks

LH-RH Antagonists

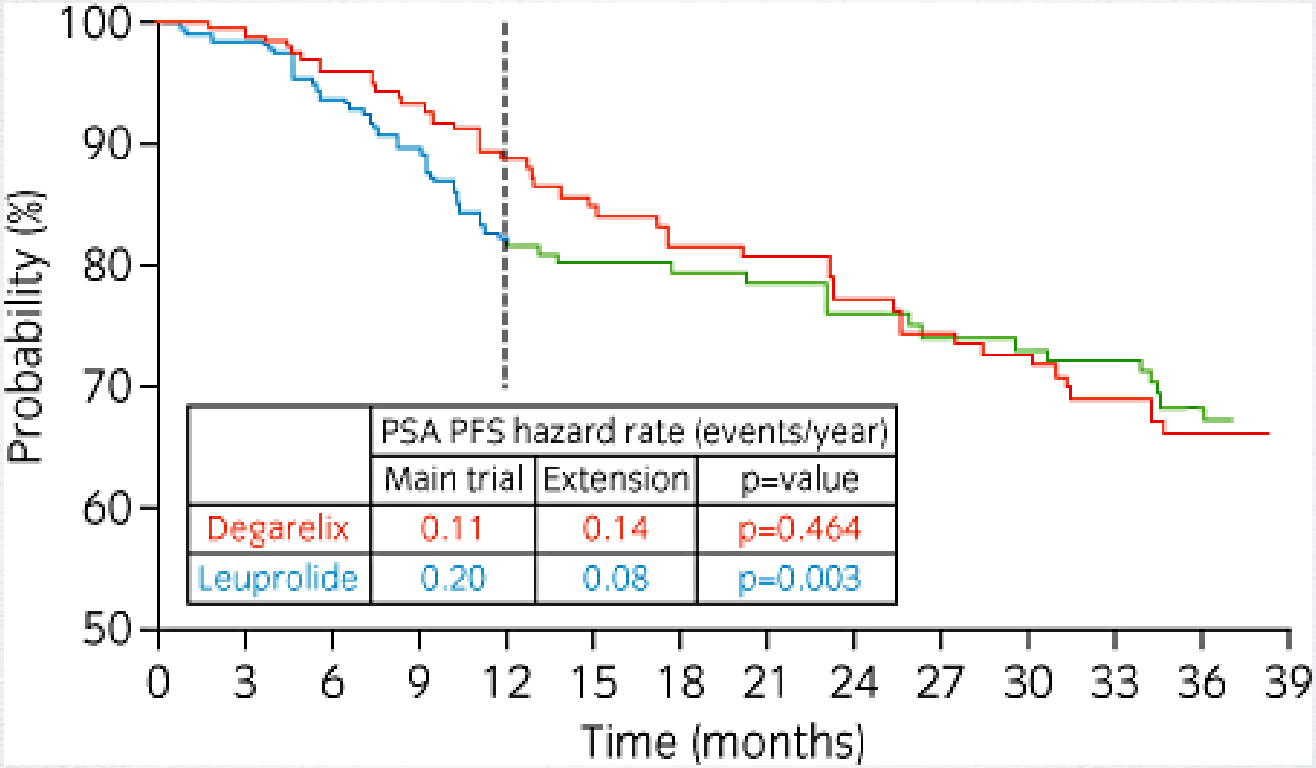
- **Competitive inhibitors of LHRH**
  - No testosterone flare (no need for antiandrogen coadministration)
  - Rapid Onset
  - Persistent suppression.
  - When rapid fall in testosterone is desired like bladder outlet obstruction, spinal cord compression, then LHRH antagonist preferred



https://www.urotoday.com/

Generic	Brand	Route	Dosing
Goserelin acetate implant	**Zoladex**	S/C	3.6mg every month 10.8mg every 3 months
Leuprolide acetate depot	**Lupron Depot**	IM	7.5mg every month 22.5mg every 3 months 30mg every 4 months
Leuprolide acetate injectable	**Eligard**	S/C	7.5mg every month 22.5mg every 3 months 30mg every 4 months 45mg every 6 months
Histrelin implant	**Vantas**	S/C	50mg yearly
Leuprolide acetate implant	**Viadur**	S/C	65mg yearly
Triptorelin pamoate injectable	**Trelstar Depot**	IM	3.75mg every month 11.25mg every 3 months
Abarelix	**Plenaxis**	IM	100mg on Day 1,15, 29 followed by 100mg 4 weekly
Degarelix	**Firmagon**	S/C	240 mg once f/b 80 mg per month

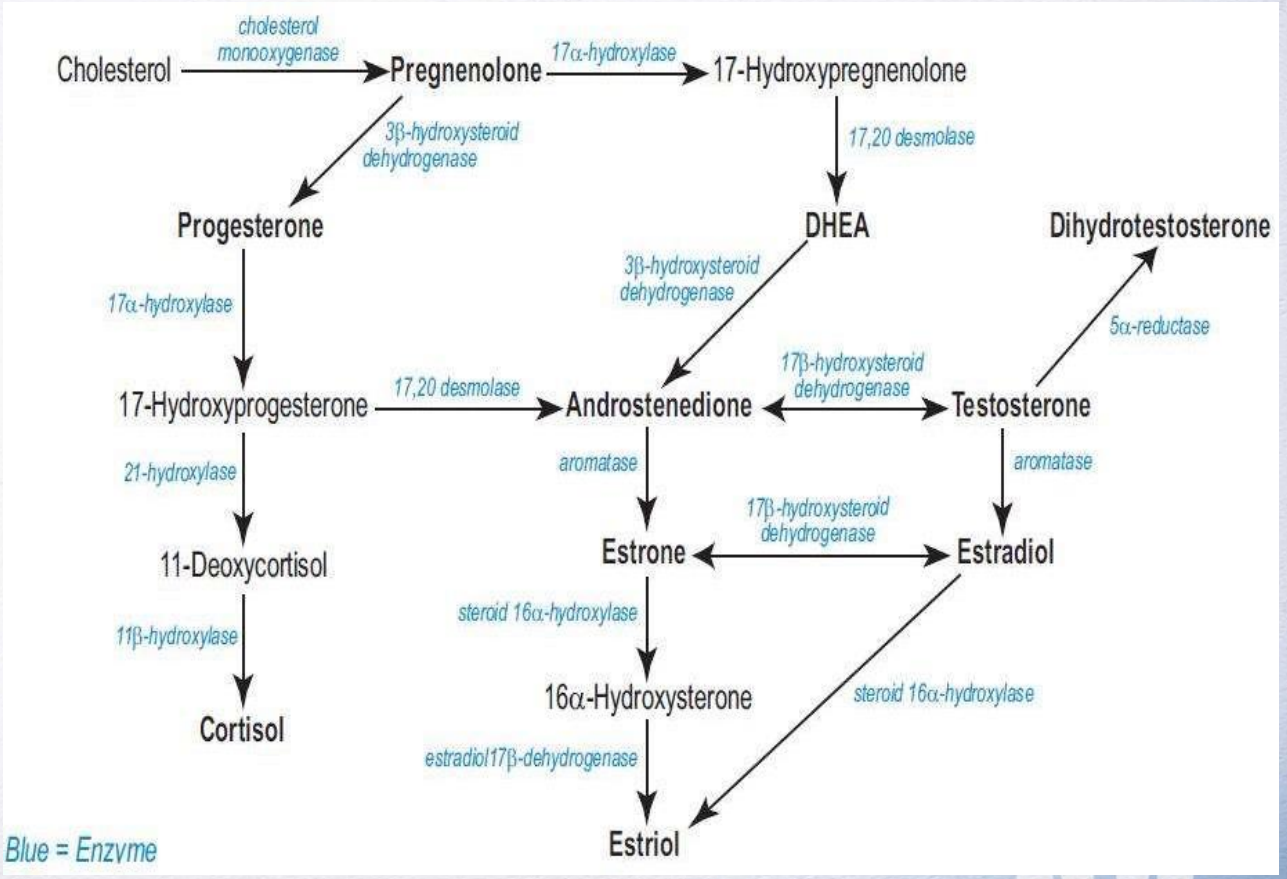
- GnRH agonists vs. antagonists



(Crawford, J Urol, 2011)

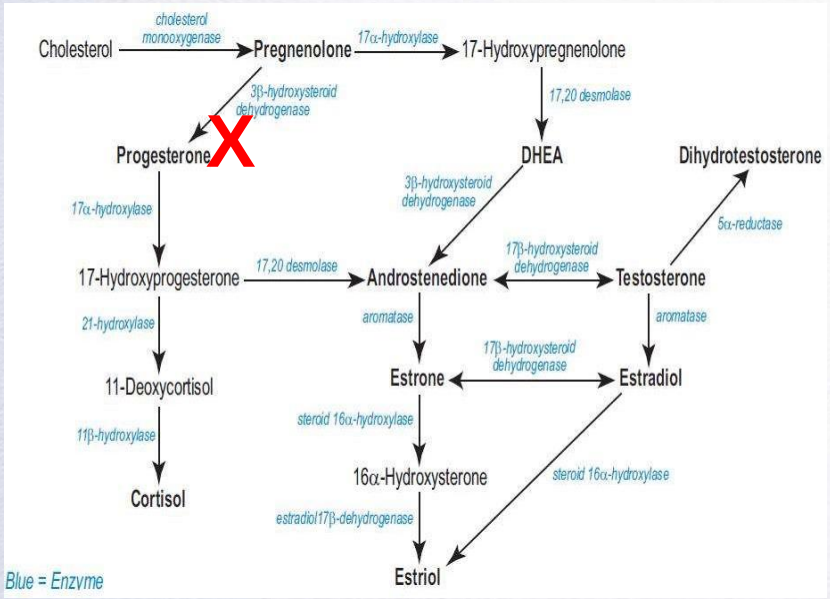
Inhibition of androgen synthesis

- Aminoglutethimide
- Ketoconazole
- Abiratirone



Inhibition of androgen synthesis

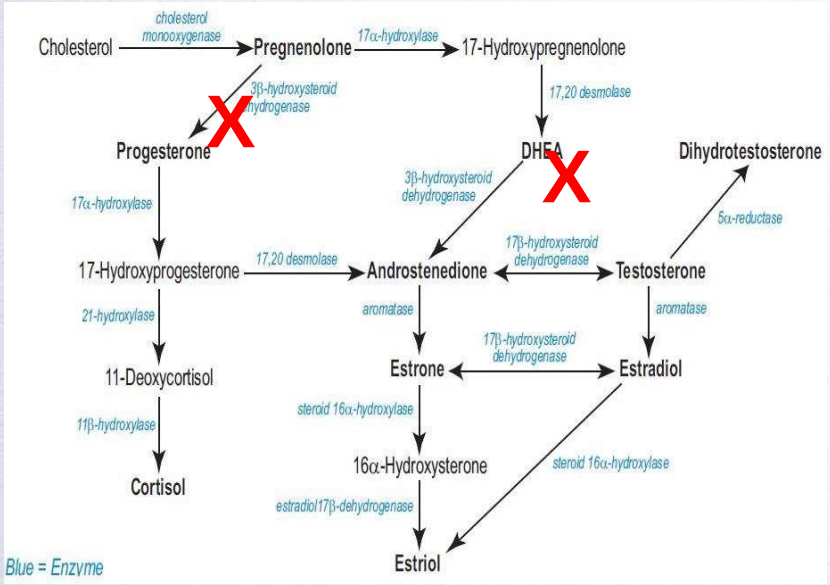
- **Aminoglutethimide**
- Ketoconazole
- Abiratirone



- ***Aromatase* inhibitor**
  - Cholesterol → Pregnenolone
- "Medical adrenalectomy"
- Required glucocorticoid + mineralocorticoid Rx with high side effect profile

Inhibition of androgen synthesis

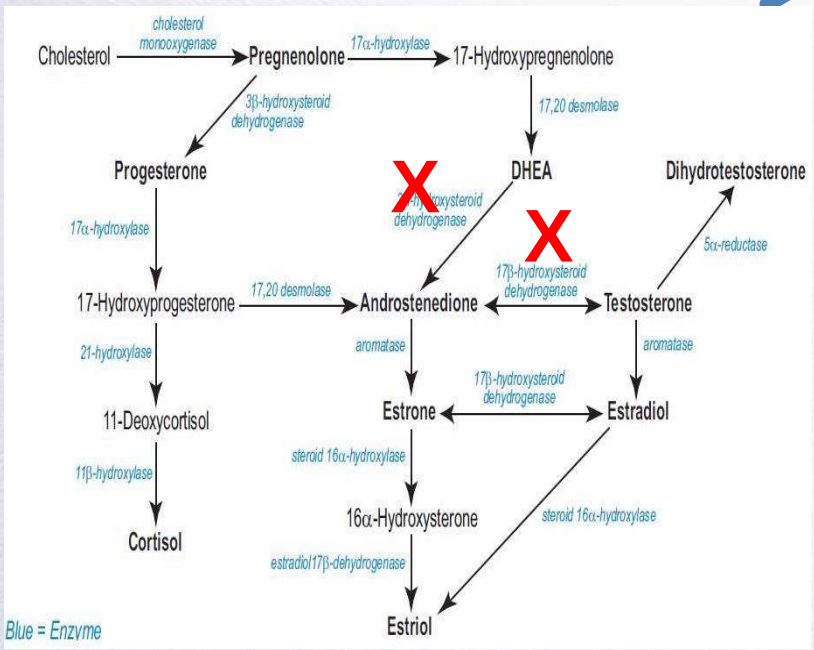
- Aminoglutethimide
- **Ketoconazole**
- Abiratirone



- **Antifungal and *Cytochrome P-450* inhibitor**
  - Blocks cholesterol side chain cleavage
  - Blocks *17,20 desmolase* in DHEA synthesis
- Requires hydrocortisone Rx
- AEs: GI distress, hepato-toxicity, and medication interactions
- CRPC

Inhibition of androgen synthesis

- Aminoglutethimide
- Ketoconazole
- **Abiratirone**



- **Potent, selective inhibitor of *Cytochrome P-17A***
  - Inhibits *17-alpha-hydrolase* and *17,20-lyase*
  - Causes increased ACTH and increase in mineralocorticoids → Requires prednisone Rx
- Very effective androgen suppression (T<1ng/mL)
- AEs: Hypertension, hypokalemia, fluid retention

Antiandrogens

- **Cyproterone acetate**
- Flutamide
- Nilutamide
- Bicalutamide
- Enzalutamide
- Apalutamide

- **Steroidal competitive AR-antagonist**
- Lowers testosterone through central inhibition of GnRH via activation of progesterone receptor
- Severe cardiovascular complications (up to 10%)

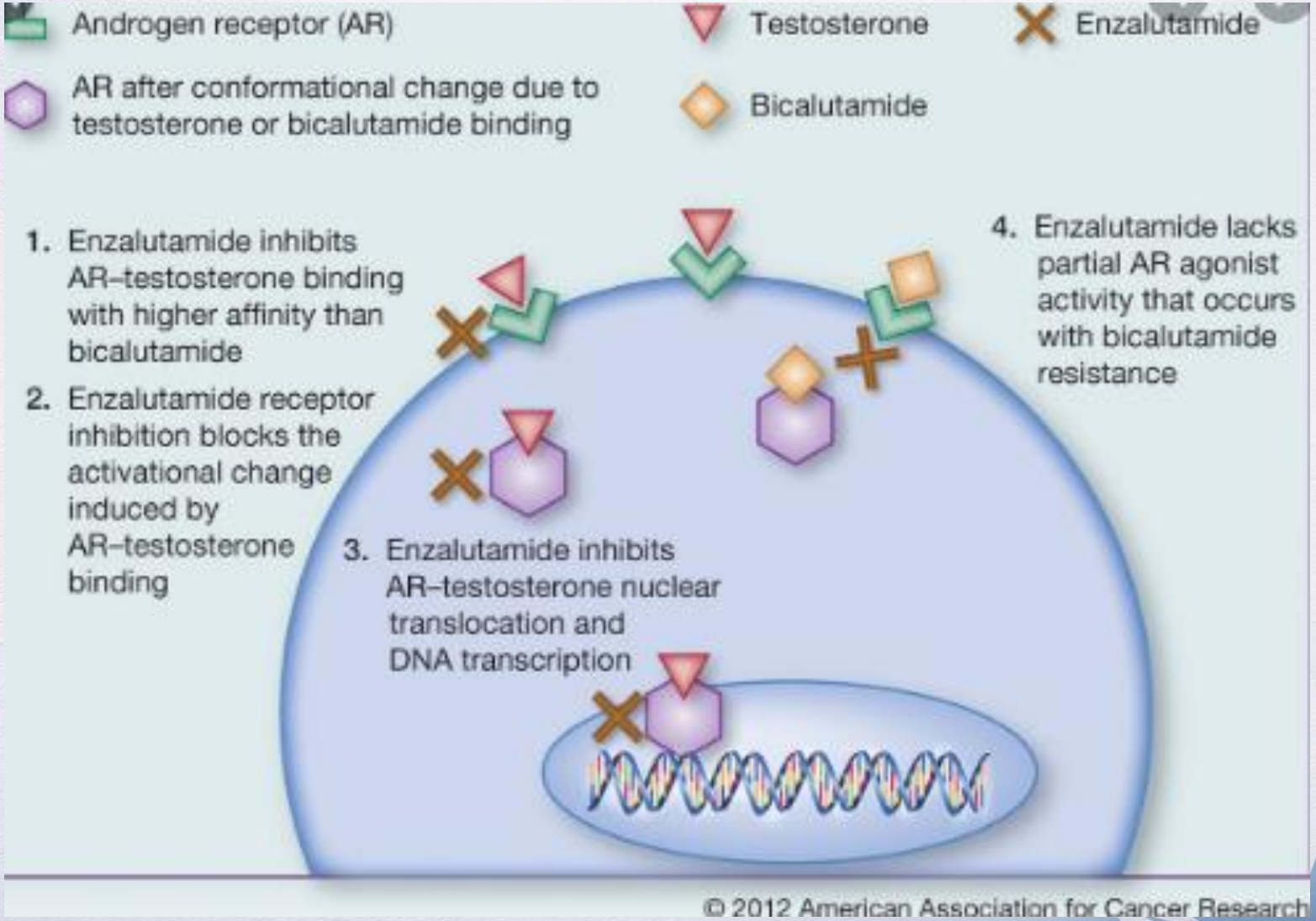
Antiandrogens

- Cyproterone acetate
- **Flutamide**
- **Nilutamide**
- **Bicalutamide**
- Enzalutamide
- Apalutamide

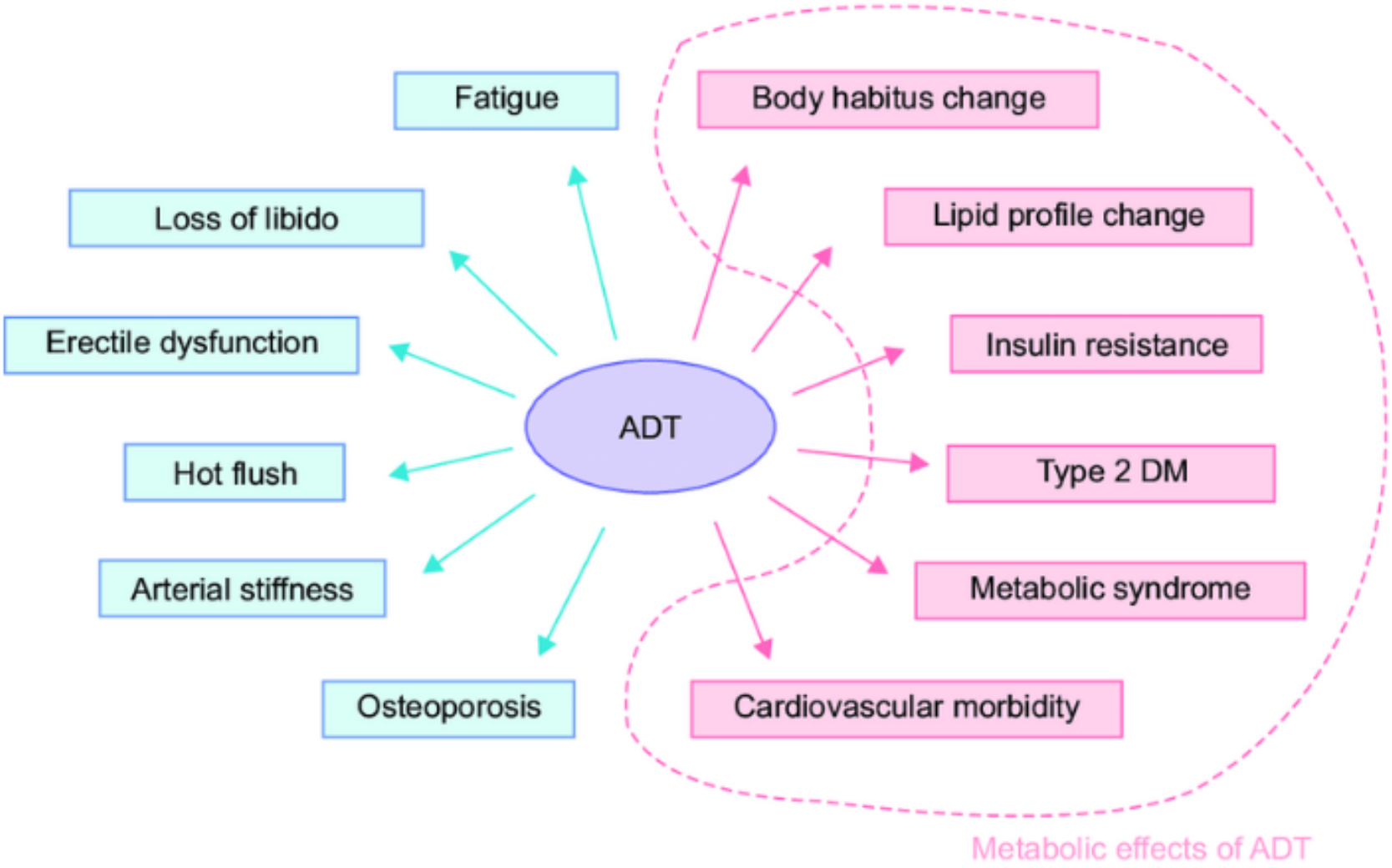
- **Non-steroidal competitive AR antagonists**
- Raise T levels by 1.5x
  - T→estradiol = gynecomastia and breast pain (up to 70%)
- Partial agnonist activity
- Generally inferior as monotherapy to other forms of surgical or pharmaceutical castration

Antiandrogens

- **Enzalutamide/Apalutamide- Non-competitive AR antagonist**



Adverse effect of ADT



Adverse effects of androgen deprivation therapy (ADT). Inside the dotted line represents metabolic effects of ADT. DM, diabetes mellitus.

https://www.researchgate.net/

Adverse Effects: Osteoporosis

- Bone loss on ADT
  - Baseline ~50% osteopenic/osteoporotic
  - ADT causes increased bone turnover, decreased mineral density, increased risk of fractures
- +21-54% RR of fracture
- Screening
  - Baseline DEXA scan
- Treatment
  - Exercise
  - Calcium + Vit D3 Supplementation
  - Bisphosphinates or denosumab (RANK-L inhibitor) if high fracture risk

Indication/Timing of ADT? Whom to give

Low Risk – No role

Intermediate risk – NAHT + Conc + Adjuvant (short course 4-6 months)

High risk -NAHT + Conc + Adjuvant (long course 2-3 years)

N1M0 disease- EBRT +long term ADT + Abiraterone

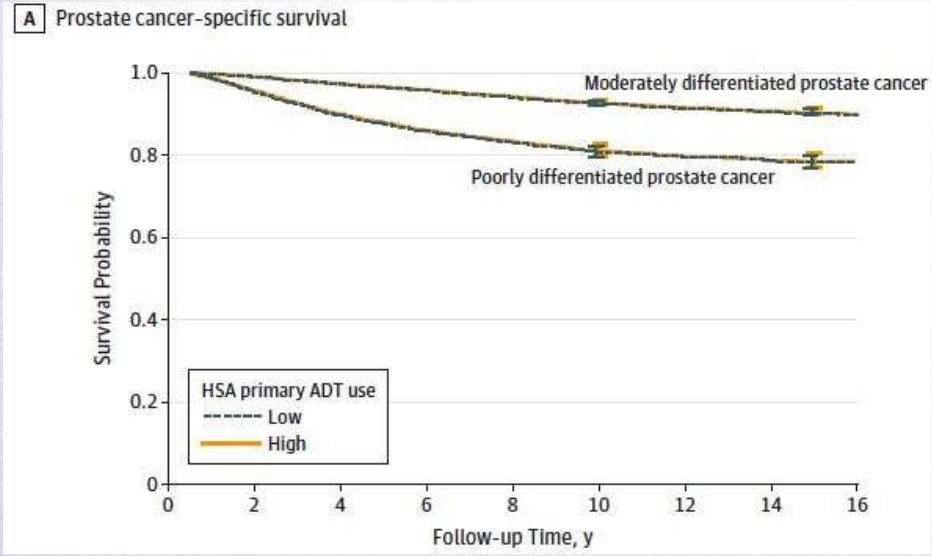
Recurrence after RT or Surgery

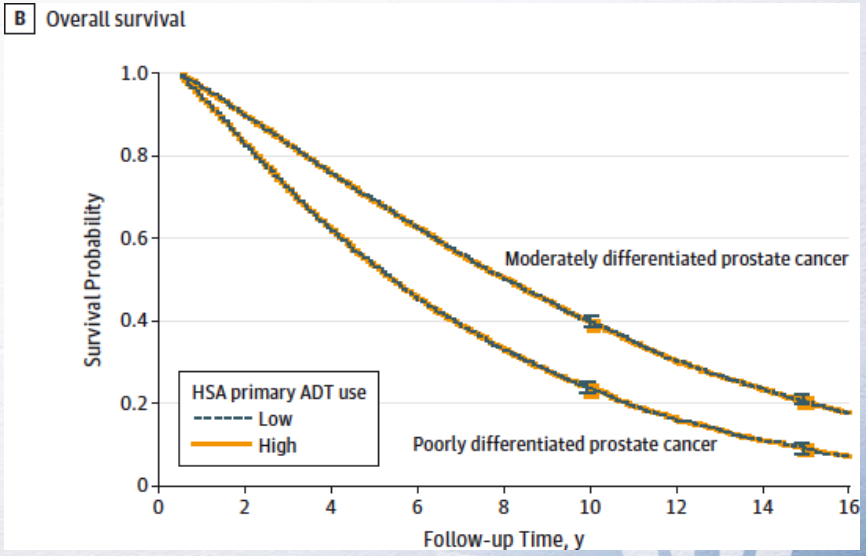
Metastatic – Long term ADT
+Abiraterone/Doce/Enzalutamide/Apalutamide

ADT for low risk localized Ca prostate

NCCN: No

- Lu-Yao, JAMA Internal Med, 2014
  - SEER-Medicare analysis of 66,717 men
  - Diagnosed with T1-T2 CaP and started on primaryADT
  - No improved 15 years DSS or OS





ADT for intermediate risk localized Ca Prostate

- **Short term ADT with RT improves OS**

Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991

Michel Bolla ✉, Philippe Maingon, Christian Carrie, Salvador Villa, Petros Kitsios, Philip M.P. Poortmans...

- 75% of the study population was intermediate risk
- Six months of concomitant and adjuvant AS improves biochemical and clinical DFS of intermediate- and high-risk cT1b-c to cT2a

EAU guidelines

Disease State	Recommendation	Strength rating	Clinical trial	Drug used
Intermediate risk disease	For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy, in combination with short-term neoadjuvant plus concomitant androgen deprivation therapy (ADT) (four to six months).	Strong	Jones et al 2011* Krauss et al 2010**	Goserelin & Leuprolide Investigator choice
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak		

EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1 * . *Jones*, C.U., et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med, 2011. 365: 107. ***Krauss*, D., et al. Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys, 2011. 80: 1064.

ADT for high risk localized Ca Prostate

In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).

Trials : RTOG 9202
EORTC 22863
RTOG 8531

RTOG 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

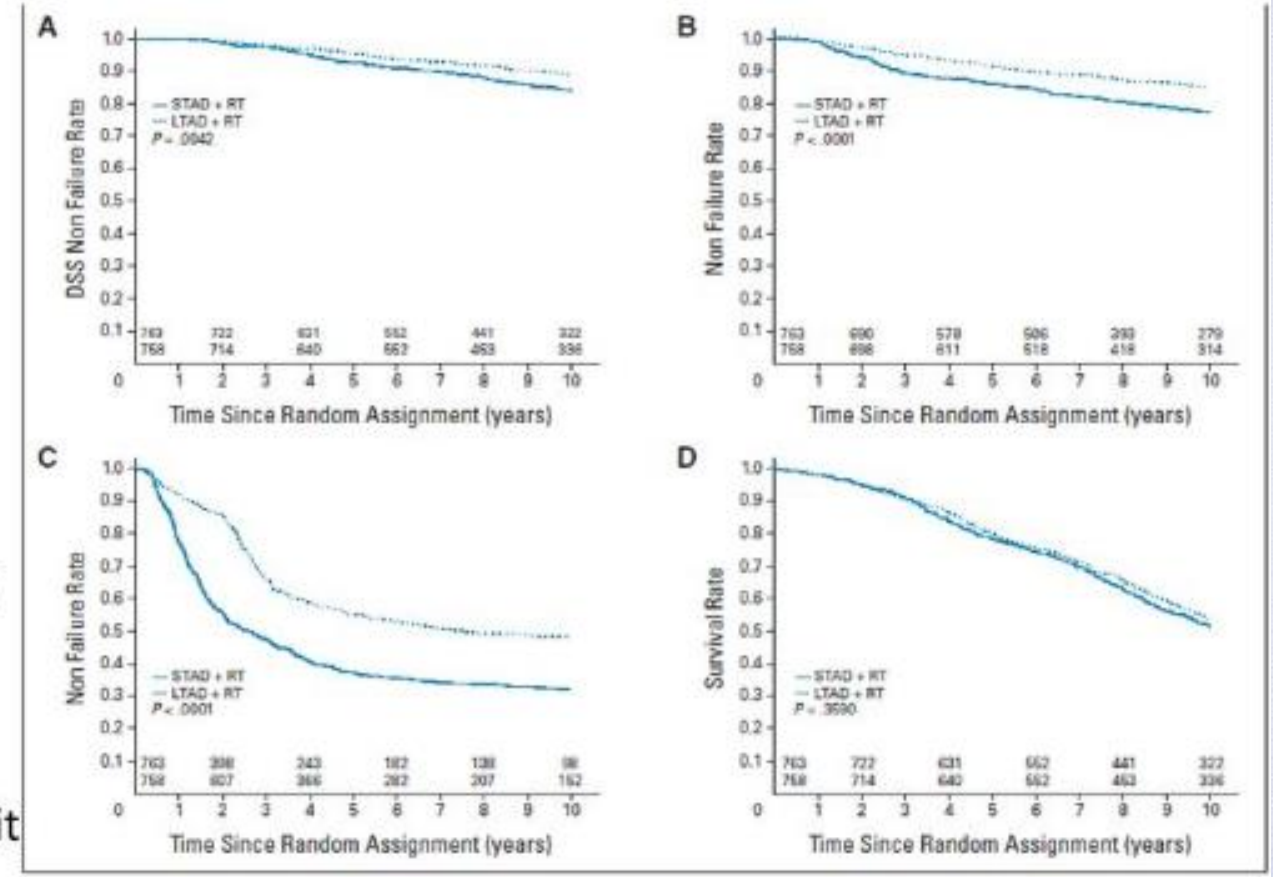


Fig 1. (A) Disease-specific survival, (B) distant metastasis failure, (C) biochemical failure, and (D) overall survival for all eligible patients. STAD, short-term androgen-deprivation therapy; LTAD, long-term androgen-deprivation therapy; RT, radiotherapy.

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

Disease State	Recommendation	Strength rating
Rx after RP	Only discuss adjuvant treatment in men with a post-operative prostate-specific antigen (PSA) < 0.1 ng/mL	Strong
	Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients	Strong
	Discuss three management options with patients with pN+ disease after an extended lymph node dissection, based on nodal involvement characteristics:	Weak
	1. Offer adjuvant ADT for node-positive (pN+).	
	2. Offer adjuvant ADT with additional radiotherapy.	
	3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	

EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1 Rx: Treatment; RP: Radical Prostectomy.

ADT for M0 biochemical recurrence (BCR)

- Early vs. Delayed ADT
  - Long natural history *(Pound, JAMA, 1999)*
    - BCR –*(8 years)*→ Metastasis –*(5 years)*→ Death
  - Unclear effect on survival
    - Delays PSA progression but ?OS effects *(Loblaw 2007; Messing 2006)*

- Timing of ADT depends on patient and prognostic factors
  - Younger patients with **rapid PSA velocity** → ADT
  - Older patients with slow PSA velocity → observe

Timing of ADT Summary

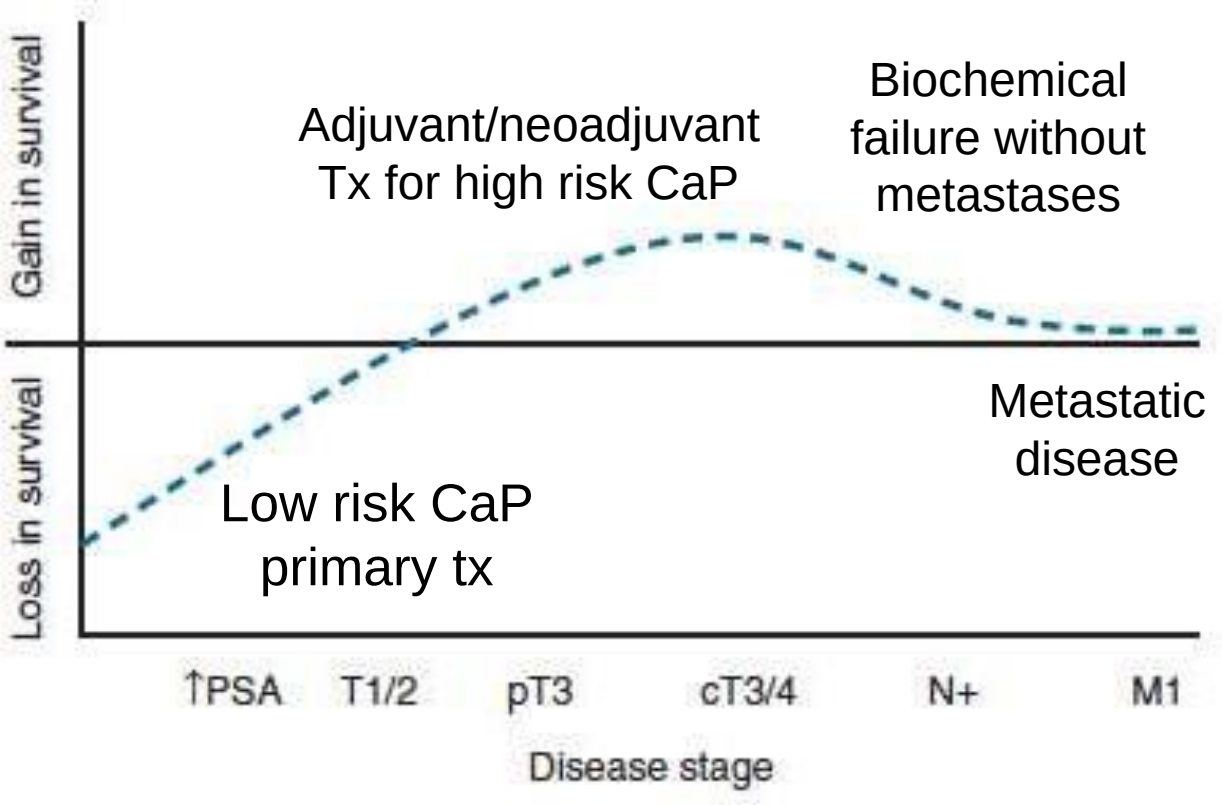
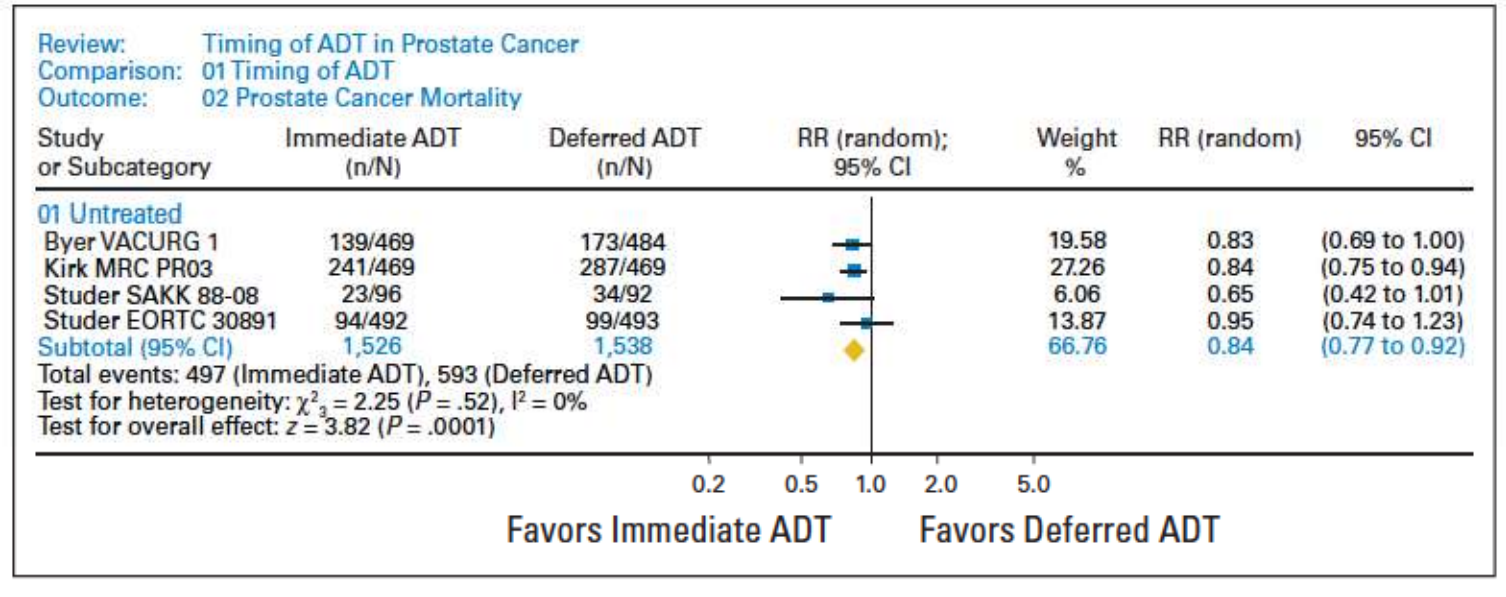


Figure 109–10. Based on available clinical trial data, the hypothetical gain or loss in overall survival based on the time in the natural history of the disease that ADT is instituted, as demonstrated by the *dotted line*. (Concept and figure courtesy of P. Iversen.)

ADT for M1 castration naïve prostate CA

- Gold standard for patients with metastatic disease at presentation
  - Immediate ADT seems to improve DSS, but not OS
  - Decreases symptoms and potential complications



(Loblaw, 2007 ASCO Practice Guideline Meta-Analysis, JCO)

TREATMENT OPTIONS IN mHSPC

DOCETAXEL

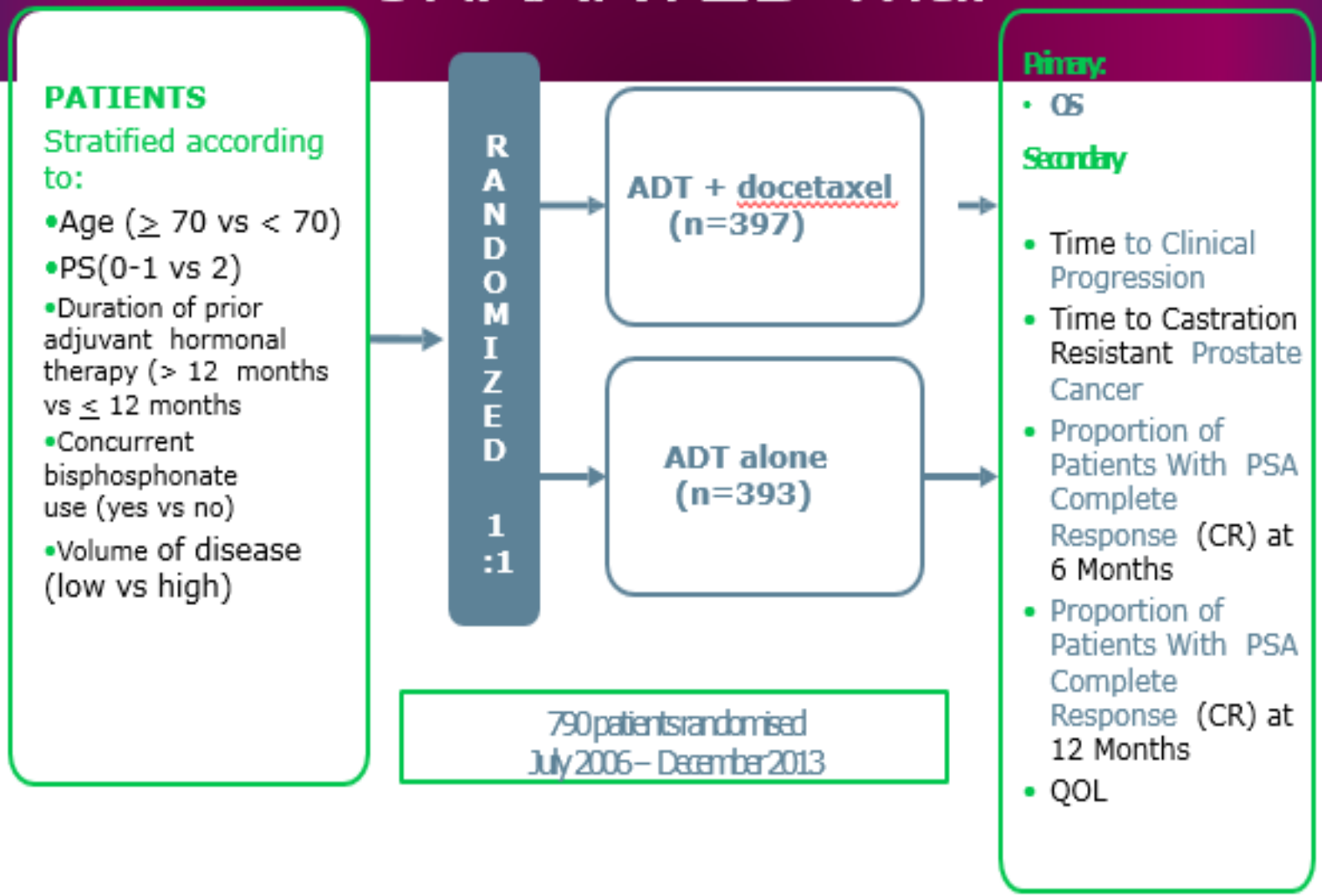
ABIRATERONE

ENZALUTAMIDE

APALUTAMIDE

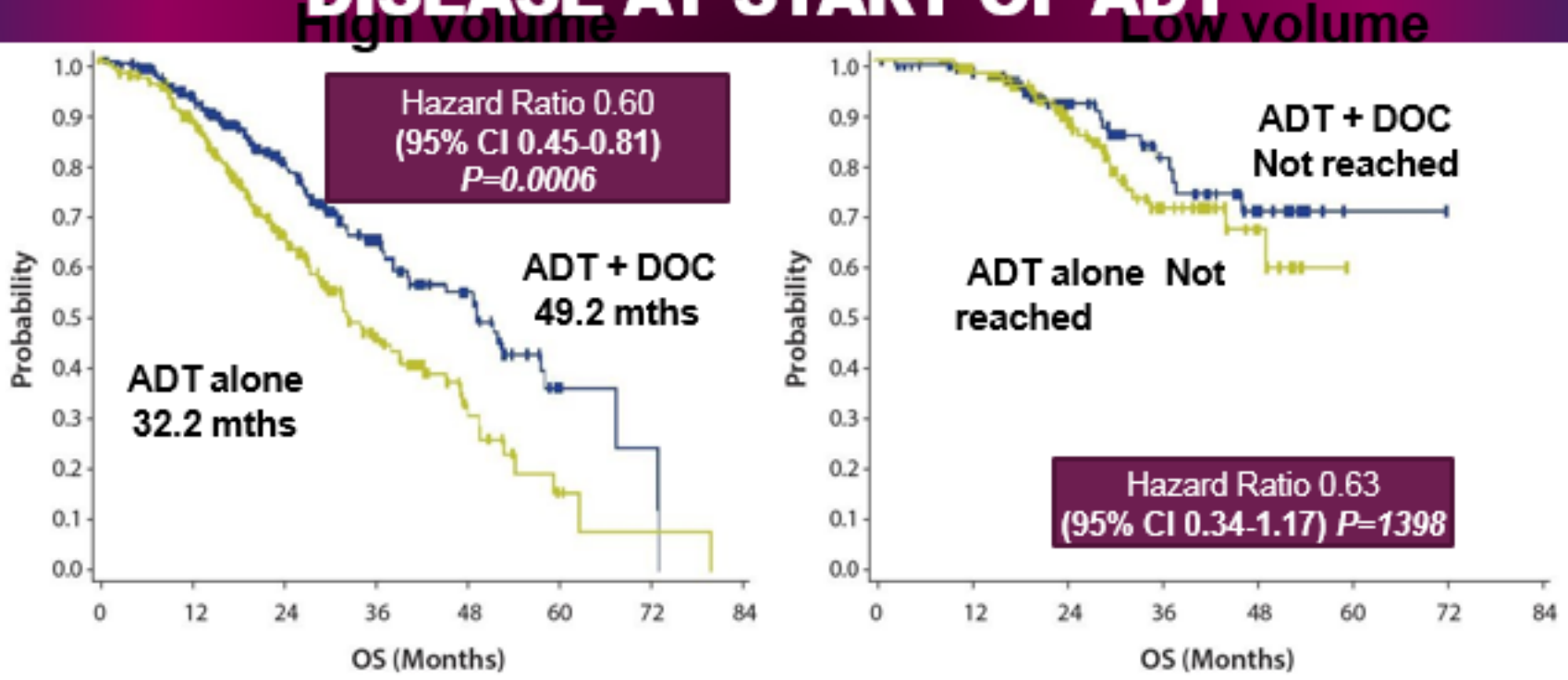
2015 → 2017 → 2019

CHAARTED Trial



Sweeney CJ, et al. N Engl J Med. 2015;373:737-746

OVERALL SURVIVAL BY EXTENT OF METASTATIC DISEASE AT START OF ADT



- **17-month benefit in median OS (from 32.2 to 49.2 months)** for high volume
- We projected 33 months in ADT arm with collaboration of SWOG9346 team

ADT: androgen deprivation therapy; DOC: Docetaxel 75 mg/m²

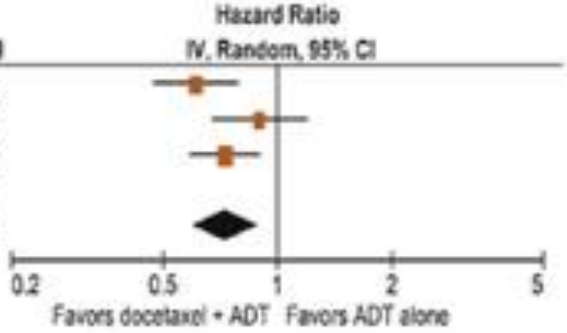
From N Engl J Med, Sweeney C, *et al.*, Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer, 373, 737-46

A

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.133	397	393	32.1%	0.61 [0.47, 0.79]
GETUG-AFU 15	-0.1054	0.1468	192	193	28.8%	0.90 [0.67, 1.20]
STAMPEDE Docetaxel	-0.3147	0.1086	362	725	39.1%	0.73 [0.59, 0.90]
Total (95% CI)			951	1311	100.0%	0.73 [0.60, 0.90]

Heterogeneity: Tau² = 0.02; Chi² = 3.66, df = 2 (P = 0.15); I² = 48%

Test for overall effect: Z = 3.03 (P = 0.002)



RECOMMENDATION #1

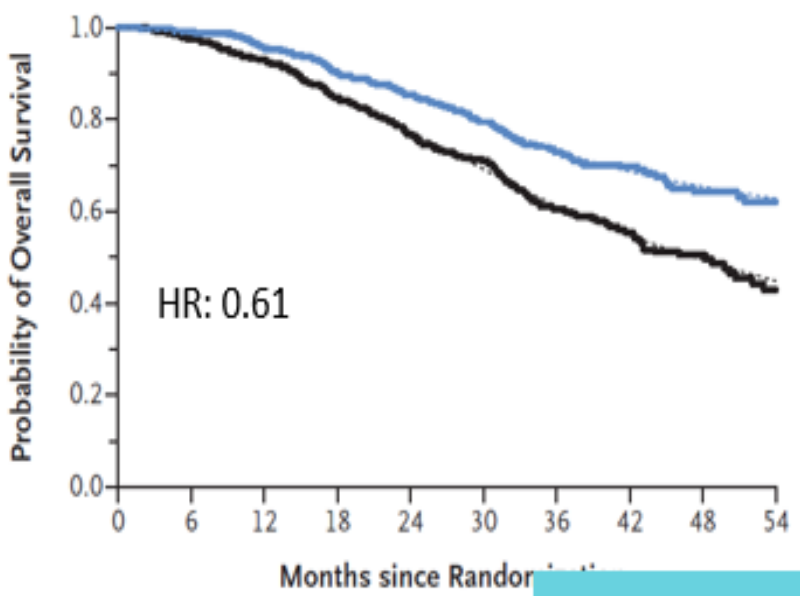
Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

Reprinted from Eur Urol 69. 4. Tucci M. et al., Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. 563–73.

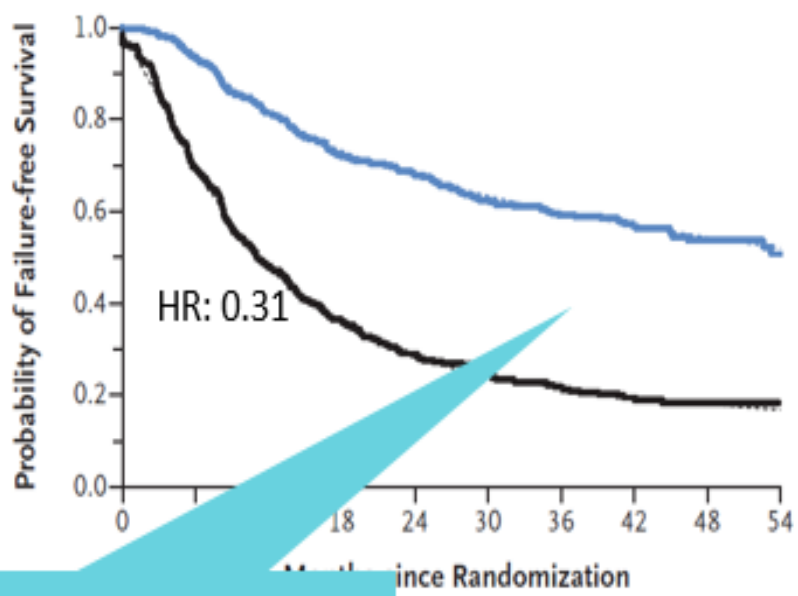
STAMPEDE: ADT + Abiraterone + Prednisolone vs ADT Alone

Randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)

OS in Patients With Metastatic Disease



Failure-Free Survival in Patients With Metastatic Disease

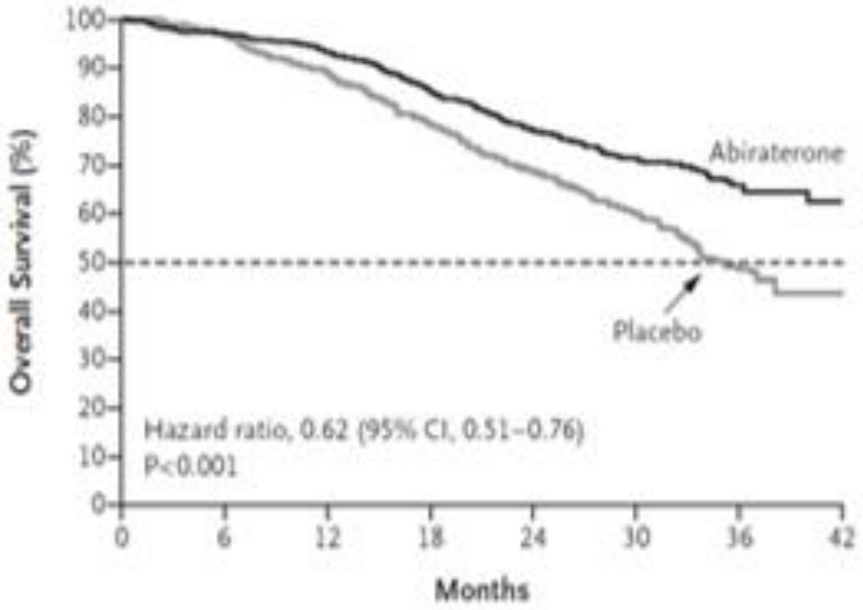


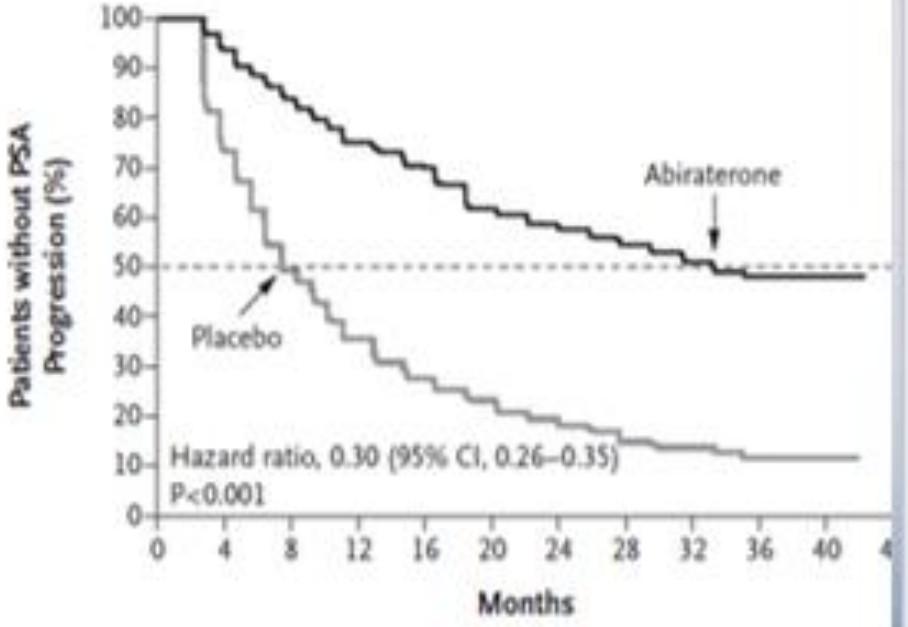
James ND, et al. N Engl J Med. 2017;377:338-351. Cli

Similar OS and better FFS implies better salvage RX

LATITUDE: ADT + Abiraterone + Prednisone vs ADT + Dual Placebo in Metastatic Castrate-Sensitive PC

Randomized, double-blind phase III trial in patients with newly diagnosed disease (N = 1199)





Fizazi K, et al. N Engl J Med. 2017;377:352-360.

ENZAMET – Study Design

- Phase III, randomized, open-label, multicenter clinical trial

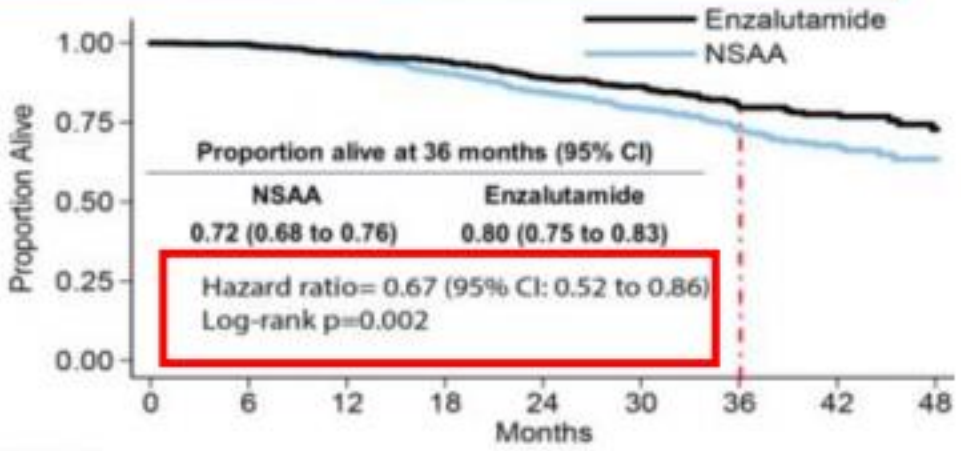
Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)

- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Results

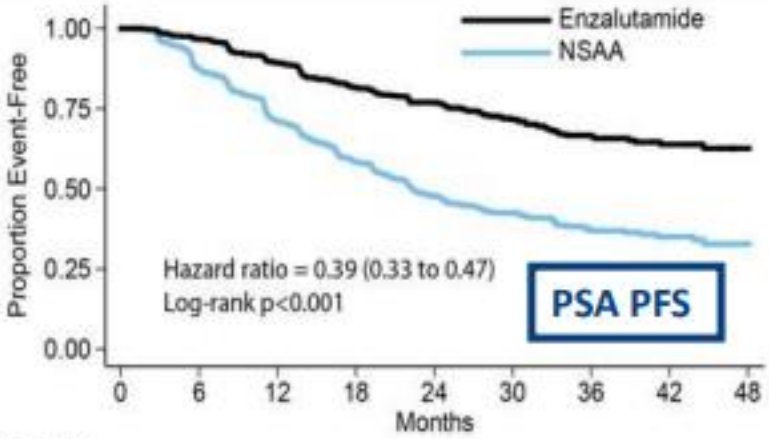
Primary endpoint: OS



Number at risk

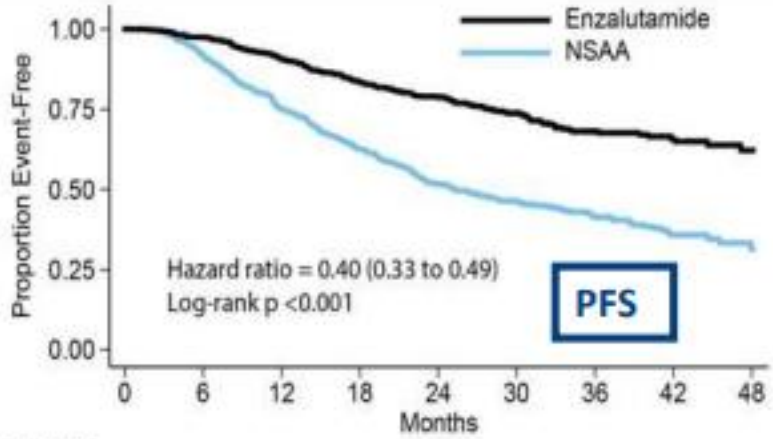
NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Secondary endpoint: PFS (PCWG2)



Number at risk

NSAA	562	486	395	322	249	161	78	44	17
Enzalutamide	563	543	500	455	411	269	146	77	34



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Modified By Christopher Sweeney at 2019 ASCO Annual Meeting

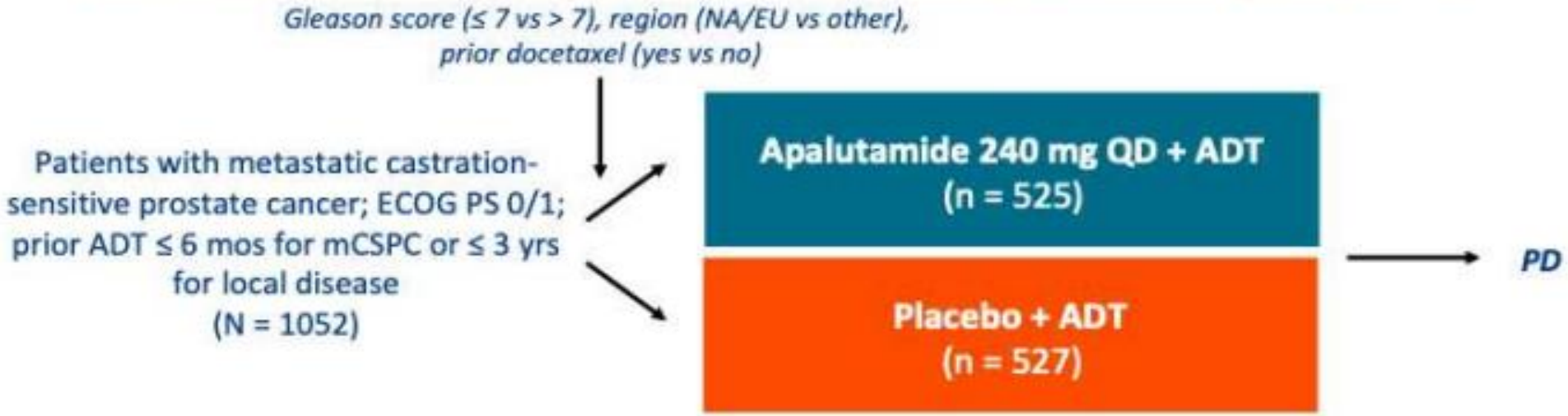
ENZAMET – Conclusions

- Enzalutamide demonstrated improved survival compared with standard NSAA in patients with mHSPC
  - 36-mo OS: 80% for enzalutamide vs 72% for NSAA (HR: 0.67; *P* = .002)
  - Similar OS benefit in patients with low and high volume of metastases
- Increased toxicity was shown with the addition of enzalutamide, as expected
  - Patients who were also treated with docetaxel experienced more chemotherapy-related toxicity
- The study investigators concluded that enzalutamide is an appropriate option for men with mHSPC starting on ADT

Davis et al NEJM 2019

TITAN – Study Design

- International, randomized, double-blind, placebo-controlled phase III trial



Primary endpoints: OS, radiographic PFS

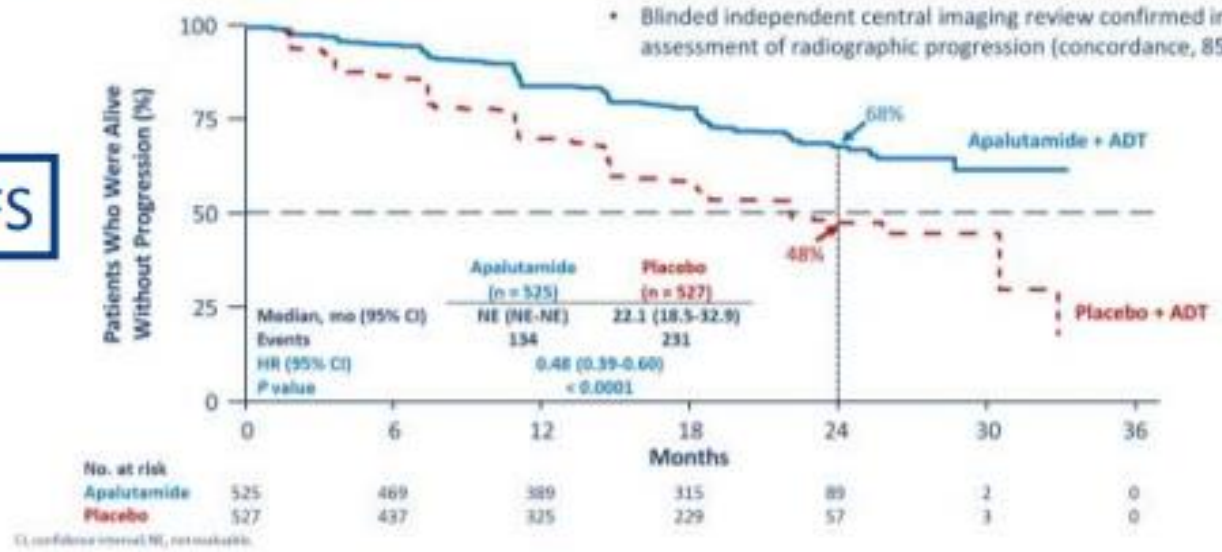
Secondary endpoints: time to pain progression, time to SRE, time to chronic opioid use, time to cytotoxic chemotherapy

Exploratory endpoints including: time to PSA progression, PFS2

Presented By Kim Chi at 2019 ASCO Annual Meeting

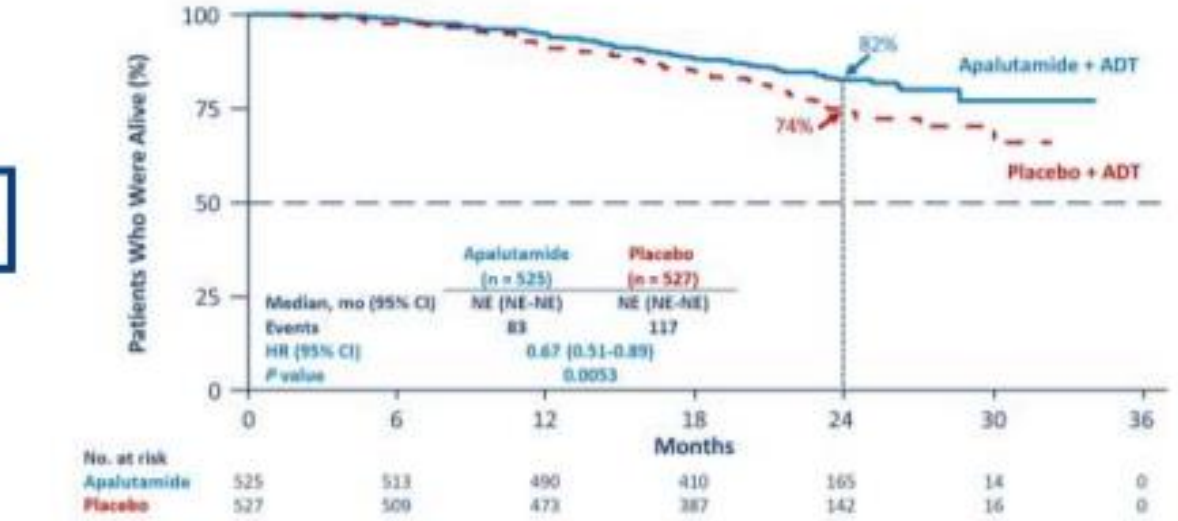
TITAN – Results

rPFS



Apalutamide significaIntly reduced risk of rPFS or death by 52%

OS



Apalutamide significaIntly reduced risk of death by 33%

Modified By Kim Chi at 2019 ASCO Annual Meeting

HOW TO CHOOSE BETWEEN UP-FRONT TREATMENTS IN mHSPC

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE APALUTAMIDE
Duration of treatment	➢ Short term treatment	➢ Long term treatment	➢ Long term treatment
Toxicities	➢ Peripheral neuropathy, hair loss	➢ Liver enzymes, electrolytes	➢ CNS (seizure), falls
Corticosteroids	➢ Use of corticosteroids	➢ Use of corticosteroids	➢ No use of corticosteroids
Setting	➢ High volume	➢ Any	➢ Any

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, MD • Prof Nicholas D James, PhD • Christopher D Brawley, MSc • Prof Noel W Clarke, ChM • Alex P Hoyle, MRCS • Adnan Ali, MBBS • et al. Show all authors • Show footnotes

Open Access • Published: October 21, 2018 • DOI: https://doi.org/10.1016/S0140-6736(18)32486-3 •

- RT to the prostate no improvement in OS in unselected patients.
- RT did improve overall survival & FFS in those with a low metastatic burden without compromising on side effect profile.
- Can be a standard treatment in this subgroup.
- Extrapolating results from these findings-

1. RT may improve survival in pelvic node-positive disease
2. for prevention of symptomatic local events

EAU Guidelines for the first-line treatment of metastatic disease

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Do not offer AR antagonists monotherapy to patients with M1 disease.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong

https://uroweb.org/guideline/prostate-cancer/#6

ADT use in COVID era: NCCN Recommendation

What is to be avoided

1. First level

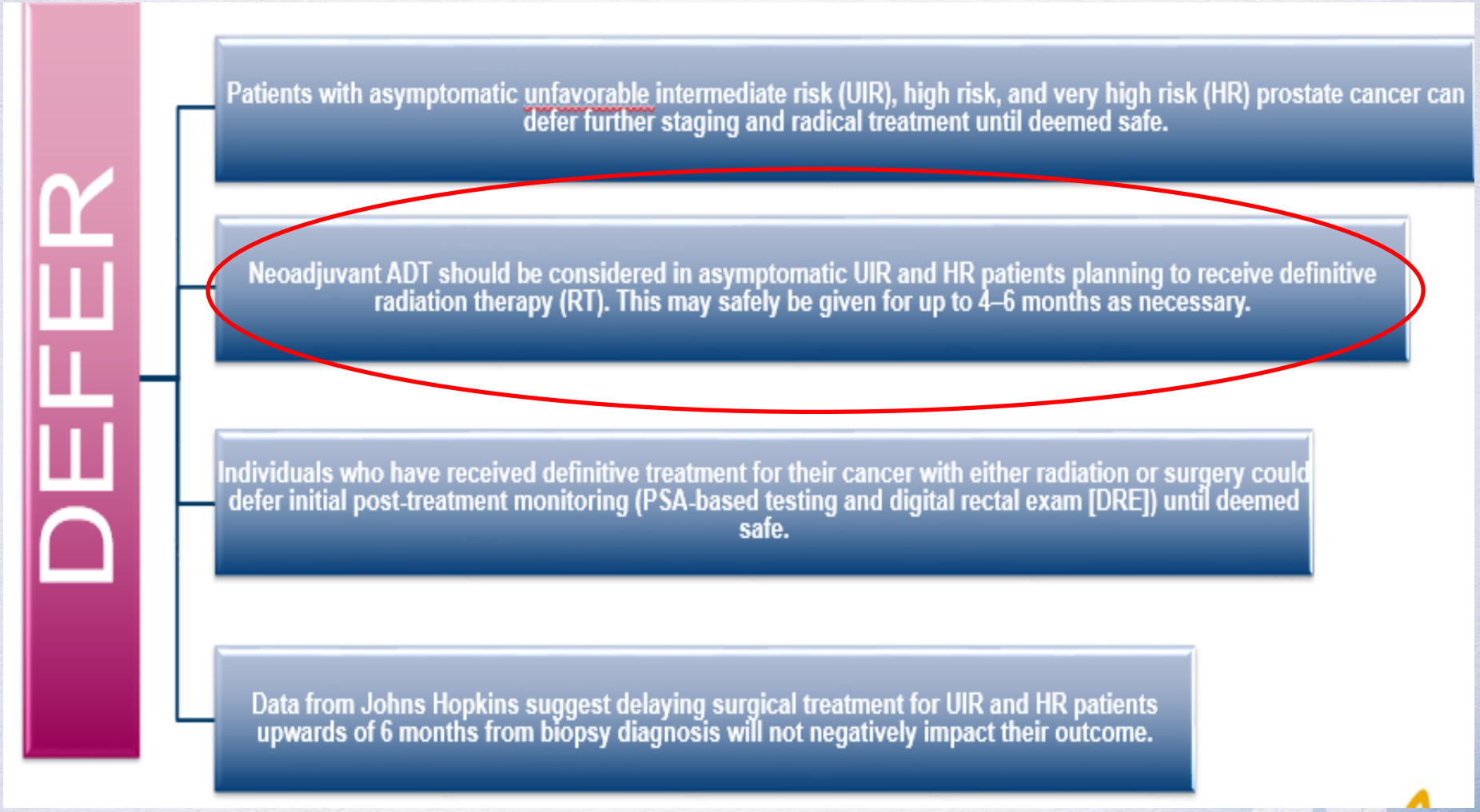
Prophylactic whole pelvic radiation therapy (WPRT) should be avoided during this time due to the increased risk of grade IV lymphopenia.

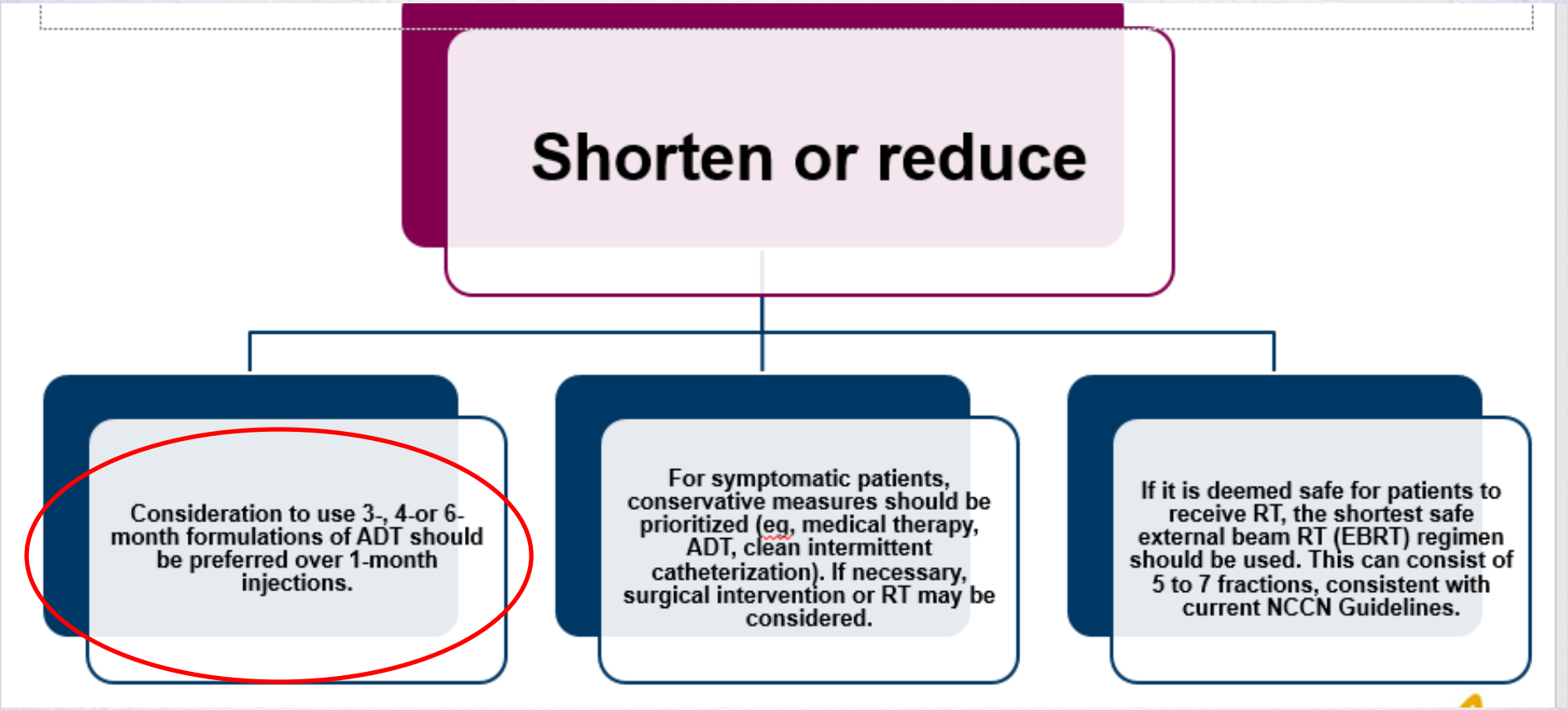
Patients with very low, low, and favorable intermediate risk (IR) disease should not undergo further staging, active surveillance, confirmatory testing/monitoring, and treatment until deemed safe.

For patients with non-metastatic disease, avoid initiating androgen deprivation therapy (ADT) for patients with a prostate-specific antigen (PSA) doubling time of >9 months.

Once ADT is initiated or intermittent ADT is started, consider remote telehealth visits and PSA/testosterone and other laboratory monitoring to avoid clinic exposures.

Care of Prostate Cancer Patients During the COVID-19 Pandemic: Recommendations of the NCCN


DEFER
Patients with asymptomatic unfavorable intermediate risk (UIR), high risk, and very high risk (HR) prostate cancer can defer further staging and radical treatment until deemed safe.
Neoadjuvant ADT should be considered in asymptomatic UIR and HR patients planning to receive definitive radiation therapy (RT). This may safely be given for up to 4–6 months as necessary.
Individuals who have received definitive treatment for their cancer with either radiation or surgery could defer initial post-treatment monitoring (PSA-based testing and digital rectal exam [DRE]) until deemed safe.
Data from Johns Hopkins suggest delaying surgical treatment for UIR and HR patients upwards of 6 months from biopsy diagnosis will not negatively impact their outcome.


Shorten or reduce
Consideration to use 3-, 4-or 6-month formulations of ADT should be preferred over 1-month injections.
For symptomatic patients, conservative measures should be prioritized (eg, medical therapy, ADT, clean intermittent catheterization). If necessary, surgical intervention or RT may be considered.
If it is deemed safe for patients to receive RT, the shortest safe external beam RT (EBRT) regimen should be used. This can consist of 5 to 7 fractions, consistent with current NCCN Guidelines.

Conclusion

- Hormonal therapy is a highly effective initial systemic therapy for Prostate cancer
- It is a low toxicity treatment but there are impacts on QOL
- ADT shows benefit in all 3 stages of prostate cancer (localized, locally advanced, metastatic) with an extensive safety and efficacy data
- Choice of drug depends on treatment cost, dosing, speed of onset, safety and tolerability, clinician experience and patient's wish

THANK YOU

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