ANDROGEN TARGETED THERAPY ACROSS THE CONTINUUM OF PROSTATE CANCER

A Review of Evolving Best Practices

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Presentation Outline

- Role of testosterone (T), androgen receptor (AR) and androgen signaling pathways in Prostate Cancer
- ADT
  - Therapeutic options
  - Defining a strong foundation of Prostate Cancer treatment
  - Efficacy and safety including CV health
  - Monitoring
  - Personalization
- Progression to CRPC
- Building on ADT, the role, efficacy and safety of androgen pathway inhibitors
  - Androgen biosynthesis inhibition
  - 3rd generation antiandrogens
- Key Messages

Historical Developments in Prostate Cancer

1780
Castration
John Hunter

1867
First perineal prostatectomy

1904
First radical prostatectomy

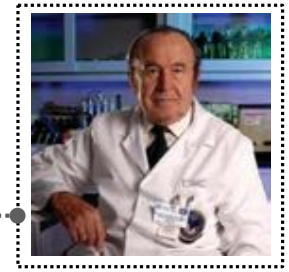
1940
Huggins -endocrine control, use of orchiectomy, and estrogen treatment (Awarded Nobel Prize)

1900 1940 1970 1980 1990 2000 2010 2020

1970s
Discovery and characterization of androgen receptor

1970s
Steroidal and non-steroidal antiandrogens available

1970s
Schally and Guillemin-LHRH discovery (Awarded Nobel Prize)



1980s
Long-acting synthetic LHRH agonists

1995
Bicalutamide available

2003
First GnRH antagonist (abarelix)

2008
Degarelix approved

2011
Abiraterone approved

2012
Second-generation antiandrogen approved (enzalutamide)

2018
Apalutamide approved in nmCRPC

The future…
New androgen receptor-targeted drugs, vaccines, biomarkers, genetic research

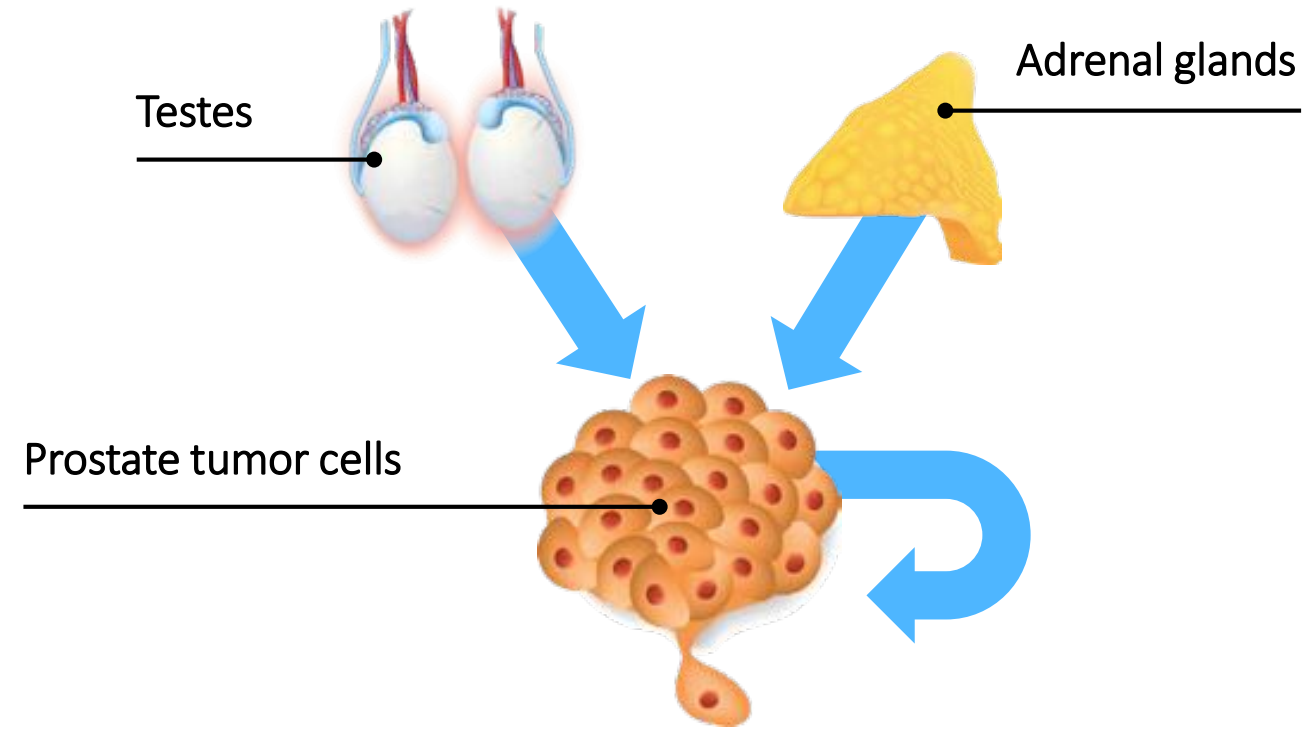
SOURCE: Dr. ED Crawford

Sources of Androgen Production

Activation of the AR signaling pathway by androgen is **critical** for prostate cancer tumor growth and disease progression

Reducing availability of androgen (T) to bind and activate the AR (lowering androgen levels or blocking receptor) **decreases** tumor cell proliferation

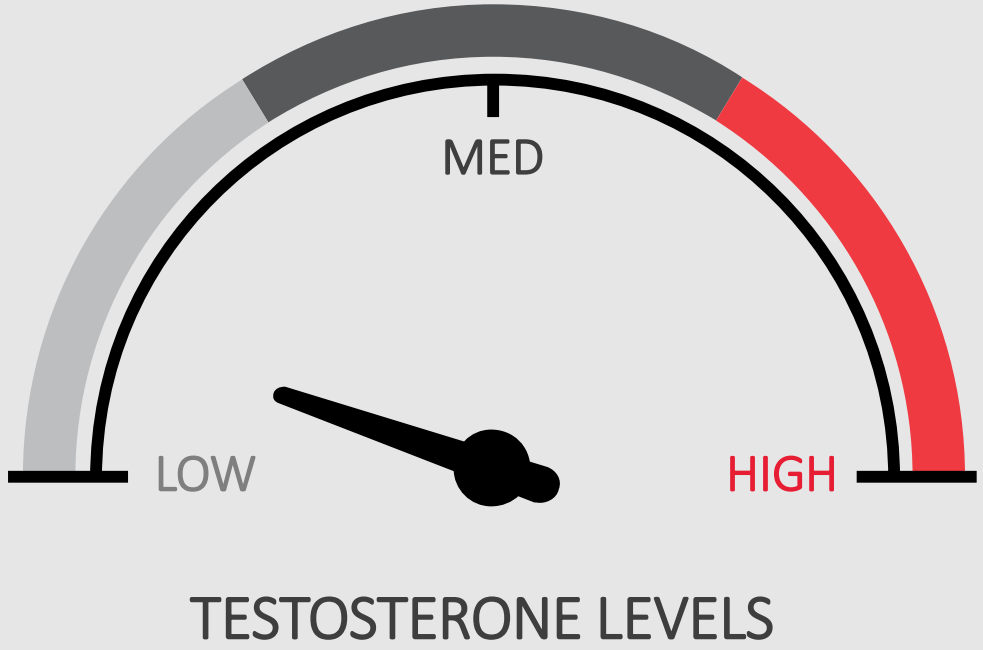
Therefore, targeting the AR by reducing serum T to castrate levels via **ADT** has become standard of care for patients with advanced prostate cancer



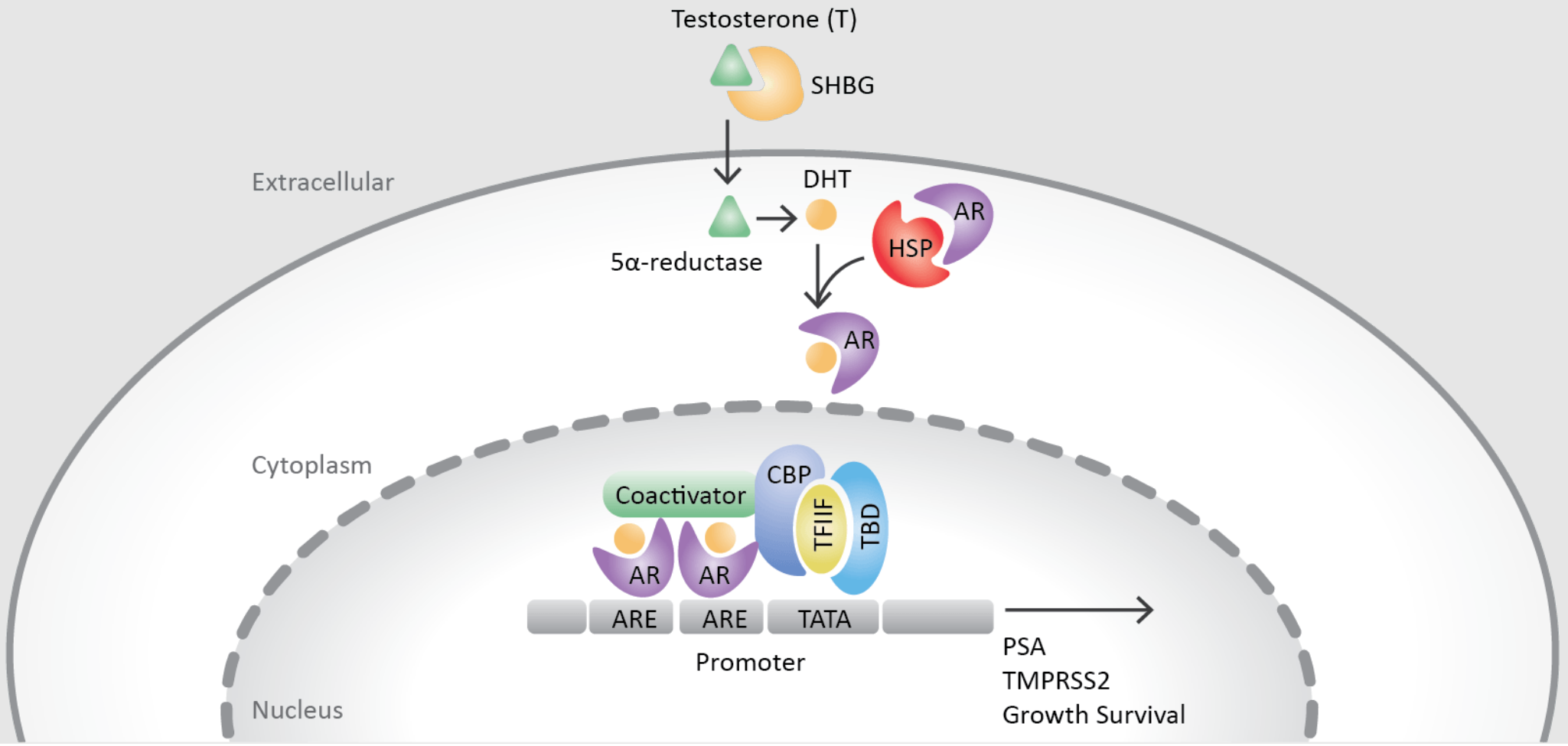
Androgens are produced at 3 sites

ADT is Foundational in Treatment of Advanced Prostate Cancer

- Prostate Cancer is androgen dependent
- Primary ligand is T
- Goal is to lower and maintain T to castrate levels and/or block activity at AR
- Maximally deprive tumor environment of T
- There is a range of therapeutic options for effective ADT
- Potential for maximal androgen targeted therapy



Androgen and AR Action



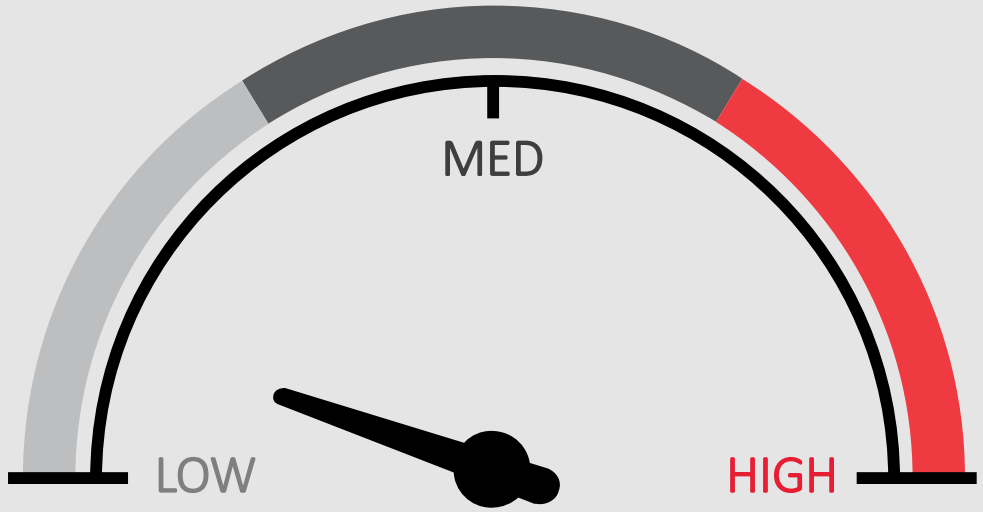
ADT: Goals of Therapy

- Achieve and maintain an environment of low T activity
  - Suppress T to castrate levels
    and/or
  - Effectively block AR
- Rapid onset of suppression
- Block effect of surge if appropriate
- Reduce T to < 20ng/dL
- Consistent T suppression
  - No escapes or microsurges

- Achieve low nadir T
- Personalization
  - Tailor to patients' lifestyles and schedules
- Minimize side effects
- Consider cost
- Improve patient outcomes
  - Reduce morbidity
  - Extend survival

Maximal Suppression of T is Clinically Meaningful

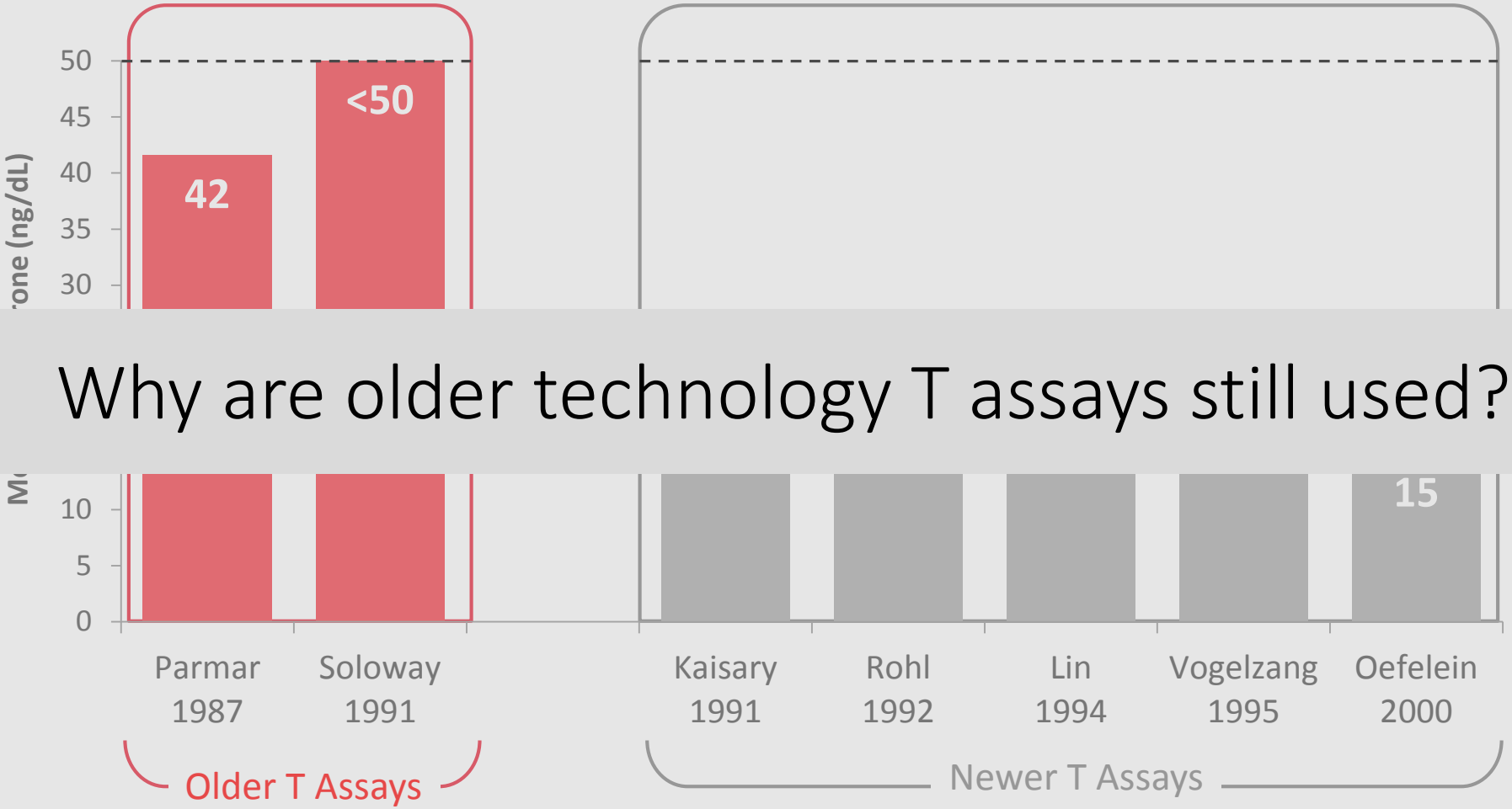
- **ADT** (androgen deprivation therapy) is really androgen deprivation of the tumor (**ADTumor**)
- Block T stimulation of tumor
  - lower T to castrate levels
  - add antiandrogen to block AR
- Newer targeting agents lower T activity at the AR by
  - inhibition of T synthesis
  - inhibition of receptor binding



Androgen deprivation of the tumor requires a strong foundation of ADT

SOURCE: Dr. ED Crawford

What is the Definition of Castrate Levels of T?



Why are older technology T assays still used?

Retrospective Analyses Show T Levels <20 Clinical Benefit

Primary Author	Year	# of Patients	Retrospective (R) Prospective (P)	Delay To CRPC	Improve Survival	Castration Threshold (ng/dL)	Hazard Ratio for Death*
Morote	2001	73	R	✓	✓	<20	2.8
Perachino	2008	162	R		✓	<20	1.92
Perachino	2010	129	R		✓	n/a	1.33
Bertaglia	2013	153	P	✓	✓	<30	0.45**
Dason	2013	32	P	✓		<32	n/a
Klotz (PR-7)	2015	626	P		✓	<20	2.8

				T Level Breakthrough (ng/dL)	Adverse Effect on PSA
Pickles	2012	2196	Database Review	30 – 50 >50	✓ (P=0.008) ✓ (P=0.003)

* HR for death in patients above castration threshold
**HR for death in patients below castration threshold

Regulatory Requirements for Drug Approval

FDA and European Union Regulatory Authorities require drugs to demonstrate suppression of T to <50 ng/dL for approval

Guidelines: Testosterone Targets During ADT

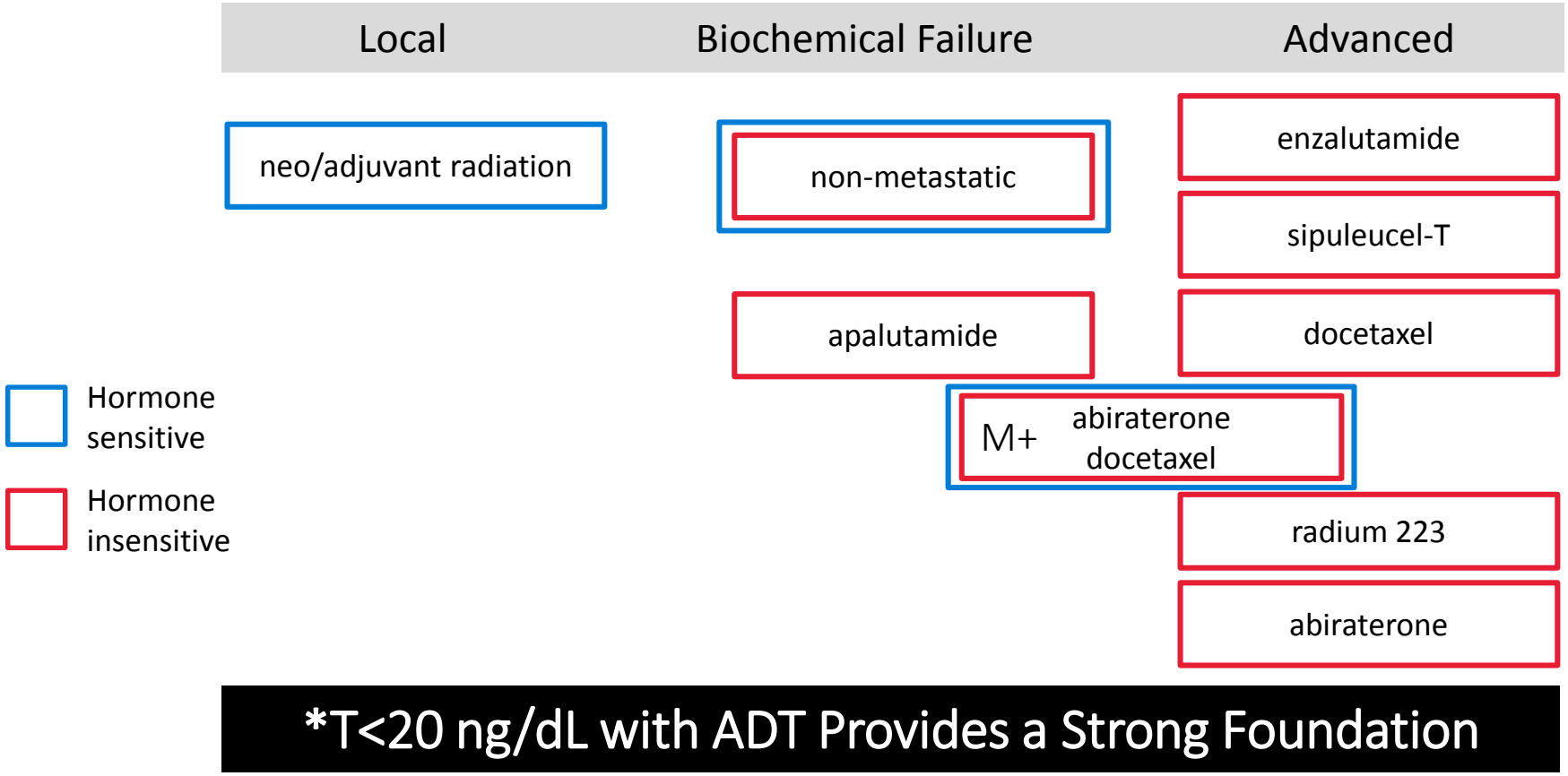
- **2012 Bethesda (US) Consensus** recommended 20 ng/dL for serum T during ADT in patients with advanced PCa as levels between 20-50 ng/dL have poor clinical outcomes
- **2016 EAU Guidelines** define target for T during ADT as <20 ng/dL
- **2018 Canadian Urologic Association Consensus** encourages adoption of ≤20 ng/dL as castrate level, recommends regular monitoring of T and PSA (3–6m) as clinically appropriate during ADT. Reassess strategy if T not suppressed or PSA rises regardless of adequate T suppression
- **NCCN Guidelines** recommend T target level of <50 ng/dL for ADT
- **AUA Guidelines** make no recommendation on T target level for ADT

Initiation of ADT

— VS —

- Goal is to reach and maintain castrate level of T
  - high risk local disease (neoadjuvant and adjuvant)
  - biochemical failure
  - metastatic disease
  - continue ADT during CRPC
- Options for castration
  - orchiectomy
  - medical
    - antiandrogens
    - LHRH agonists
    - LHRH antagonists

ADT Strong Foundation for Prostate Cancer



***T<20 ng/dL with ADT Provides a Strong Foundation**

* FDA and European Union Regulatory Authorities require drugs to demonstrate suppression of T to <50 ng/dL for approval

SOURCE: Dr. ED Crawford

Bilateral Orchiectomy: *"Gold Standard"*

ADVANTAGES

- Simple surgical procedure
- Rapid and pronounced control of T
- Lower cost

DISADVANTAGES

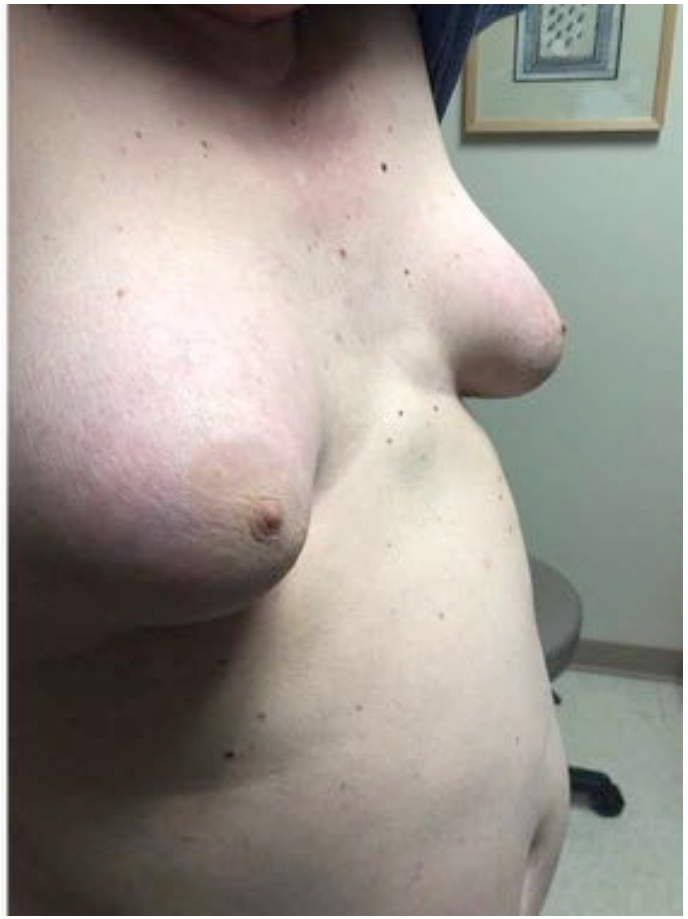
- Negative psychological effect
- Irreversible
- Broad spectrum of side effects
  - vasomotor, sexual, metabolic, CV, bone loss
- Elevated FSH

Antiandrogens

- 1st generation
  - Flutamide
  - Nilutamide
- 2nd generation
  - Bicalutamide
- Theoretically represent ideal ADT
- Monotherapy less effective than medical or surgical castration
- Effective in combination with LHRH therapies

Side Effects of Anti-Androgen Monotherapy

Gynecomastia

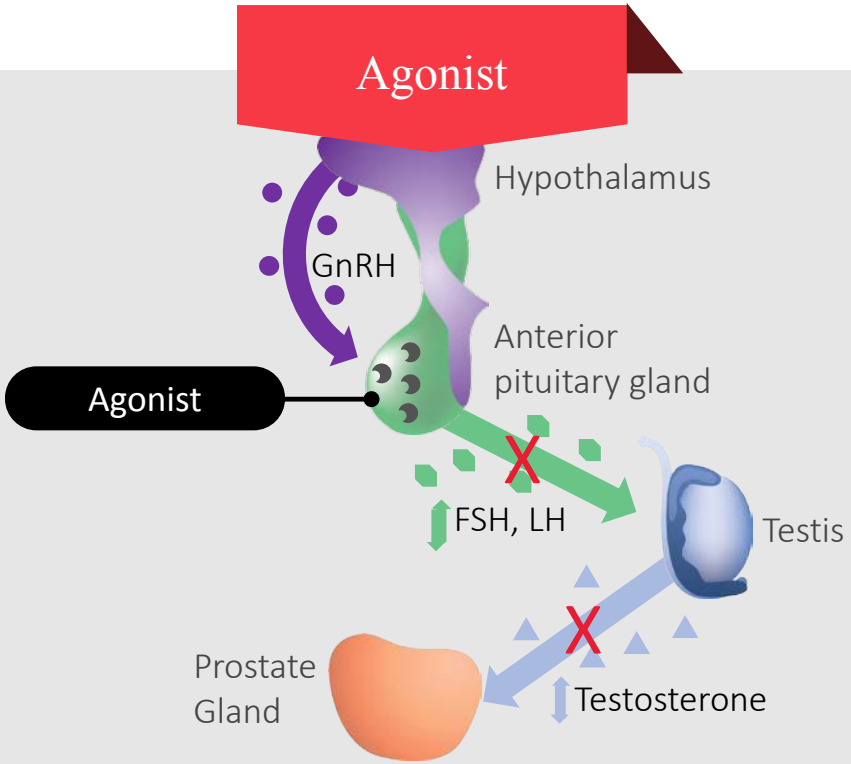


- **Flutamide**
  - Diarrhea, hepatotoxicity (some fatal)
- **Nilutamide**
  - Nausea, dark light accommodation, alcohol intolerance, hepatotoxicity
- **Bicalutamide**
  - Nausea, diarrhea, constipation, hepatotoxicity

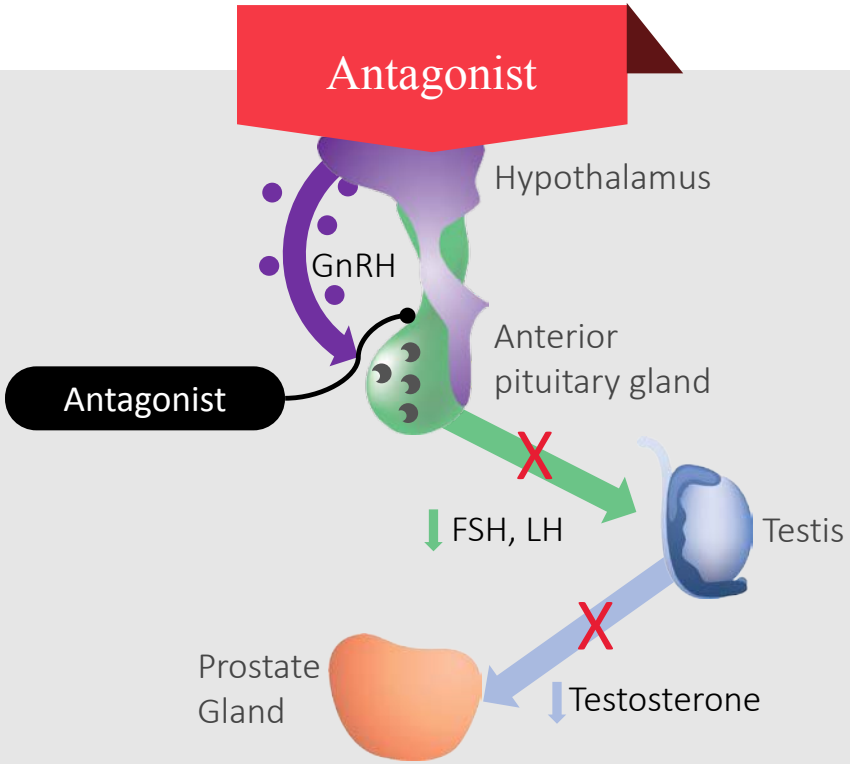
LHRH Agonists/Antagonists

- LHRH therapies developed to address some side effects of estrogens and bilateral orchiectomy
- Extended dosing available (1, 3, 4, 6, 12m)
- Formulations include SC and IM injections, implants

Mechanism of Action: LHRH Agonists and Antagonists



- Initial surge in FSH, LH and T
- Prolonged suppression of LH and T
- Potential microsurges in LH and T with repeat injection
- FSH suppression not maintained long term



- Rapid suppression of FSH, LH and T
- No microsurges
- Prolonged suppression of FSH, LH and T

FSH: follicle-stimulating hormone; LH: luteinizing hormone

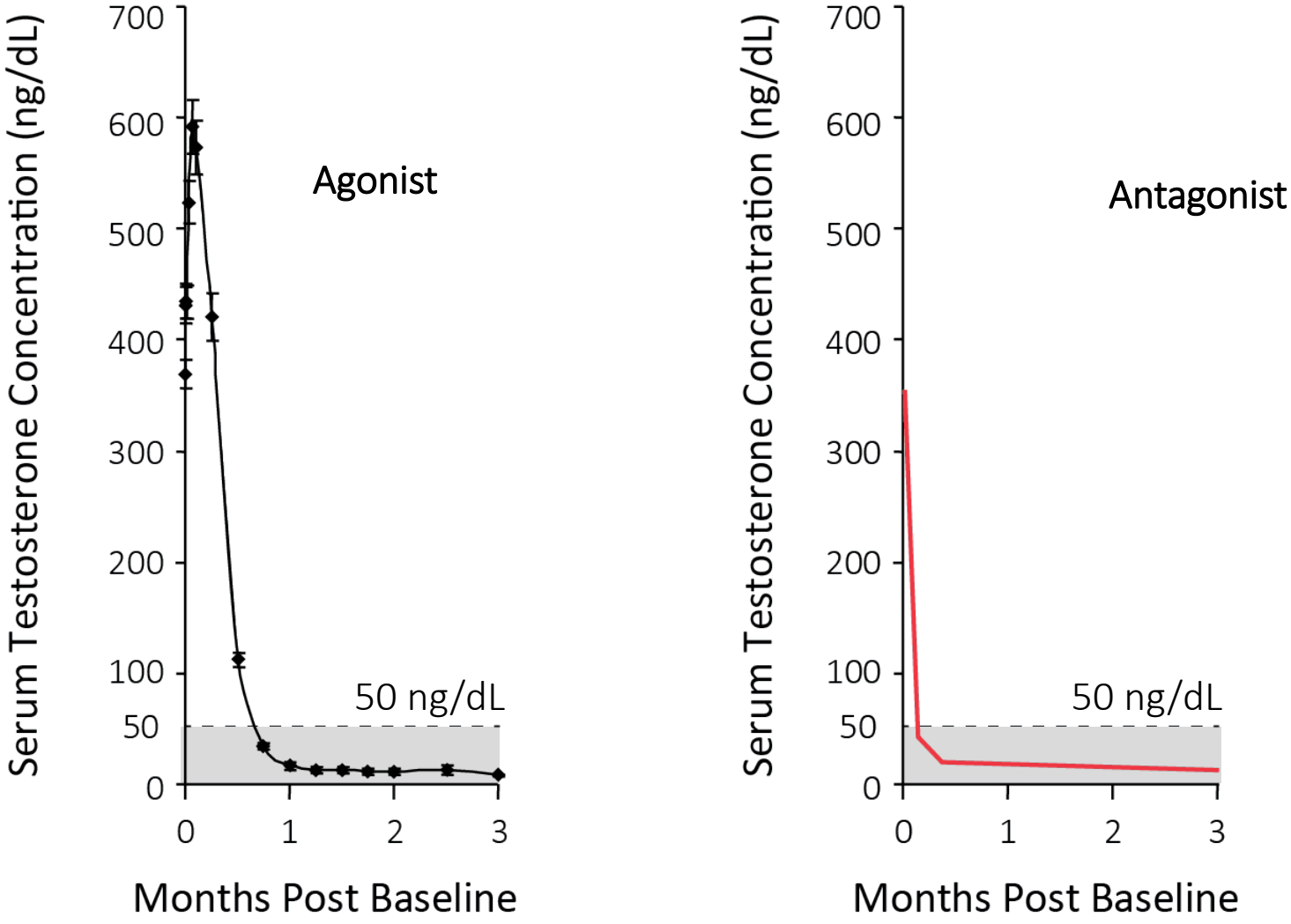
Summary Table of LHRH Therapy Options

Attributes	leuprolide SC	leuprolide IM	triptorelin	goserelin	degarelix†
Needle Gauges	**18** (45mg) **20** (7.5, 22.5, 30 mg)	**23** (all doses)	**21** (all doses)	**16** (3.6mg) **14** (10.8mg)	**27**
Route of Administration	subcutaneous	intramuscular	intramuscular	subcutaneous	subcutaneous
Dosing Intervals (months)	1 ✓ 3 ✓ 4 ✓ 6 ✓	1 ✓ 3 ✓ 4 ✓ 6 ✓	1 ✓ 3 ✓ 4 6 ✓	1 ✓ 3 ✓ 4 6	1 ✓ 3 4 6
Injection Volume per Dose (mL)	0.25 0.375 0.50 0.375	1.0 1.5 1.5 1.5	2.0 2.0 2.0	2.0 2.0	2x3.0* 4.0*

† – LHRH antagonist

* – Initial dose of 240mg (2 x 3 mL), followed by monthly maintenance doses of 80mg (4 mL)

Representative LHRH Analogs T Suppression Profiles

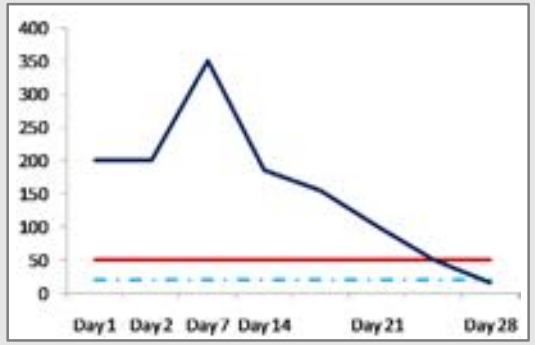


LHRH Therapies: Attributes of ADT

Testosterone surge/flare

Surges are T increases >15% for 2 days during first 2 weeks of therapy. Flares are clinical manifestations of surges

Detrimental-YES



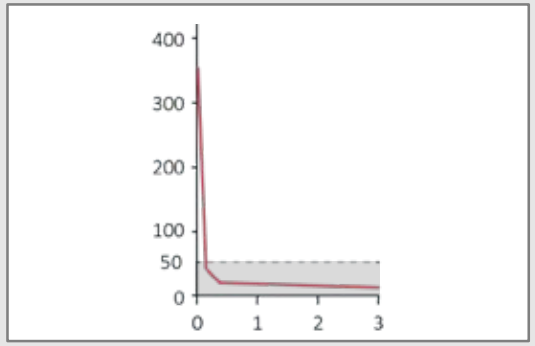
Onset of T suppression

How quickly castrate T level achieved.

Antagonist 2-3 days

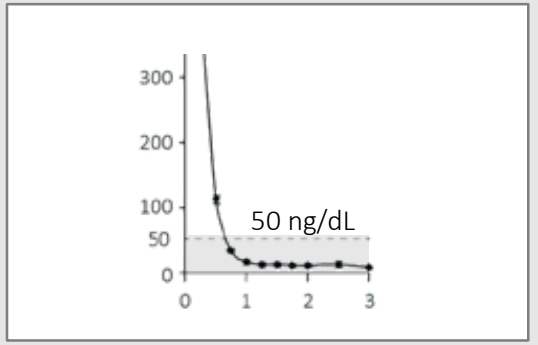
Agonist ~3 weeks

Detrimental-YES



T suppression level

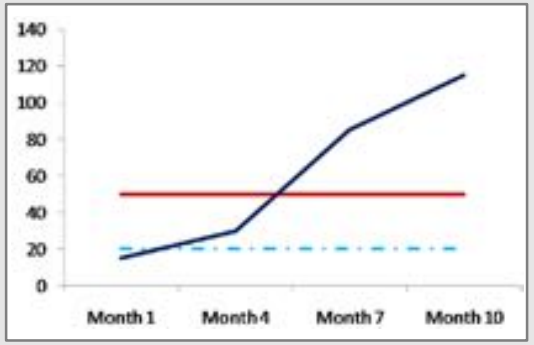
Target level of T



T failures

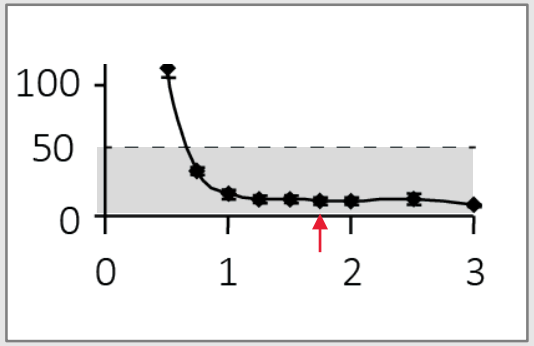
Single T value >100 ng/dL or 2 consecutive values >50 ng/dL

Detrimental-YES

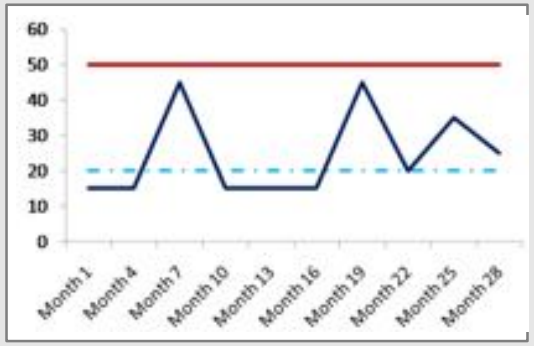


LHRH Therapies: Attributes of Therapy to Consider

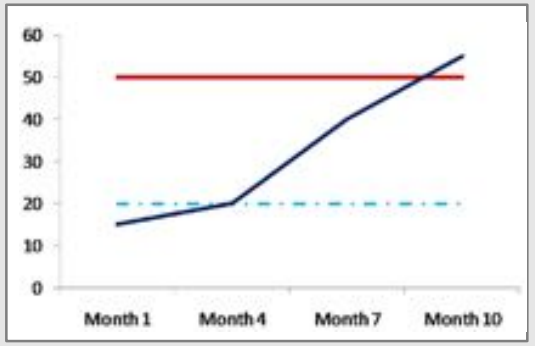
Nadir T
lowest level of T measured during therapy



T microsurges: T increase ≥25 ng/dL within 4 weeks following a subsequent injection of agonist
Detrimental-LIKELY



T escapes
at least 1 T value >50 ng/dL
Detrimental-LIKELY



Potential Adverse Events Associated with ADT

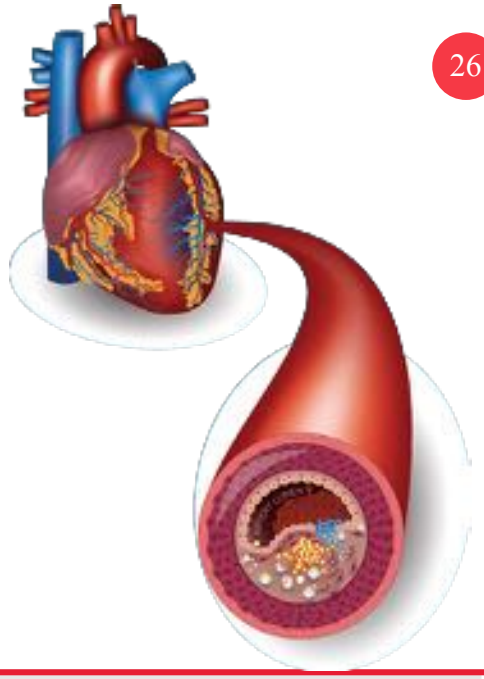
AFFECTS QOL

- Hot flashes
- Loss of libido
- Erectile dysfunction
- Fatigue

MEDICAL ISSUES

- Osteoporosis/ skeletal events
- Diabetes
- Neurocognitive disease
- Anemia
- Gynecomastia
- Thinning of body hair
- Testicular atrophy
- Cardiovascular disease

ADT and Cardiovascular Disease



Risk of MI, stroke, or CV death in PCa patients

>2% per year

Risk of MI, stroke, or CV death in PCa patients on ADT

>4% per year

CVD risk considered high if global risk estimate for hard CVD events of

≥2% per year

Prolonged ADT exposure for > 2 years associated with increased odds of CVD, but only in

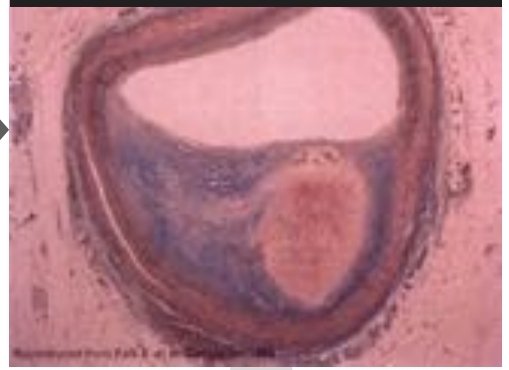
men over 74

Hypothesis for Increased CVD Risk with ADT

CVS
(atherosclerosis) risk factors

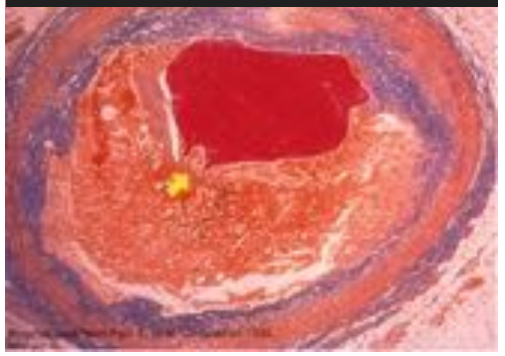
- Hyperglycemia
- Central adiposity
- Dyslipidemia
- Changes in lifestyle

The vulnerable plaque



Cardiovascular Event

Disrupted plaque with occlusive thrombus



Testosterone
FSH

Plaque vulnerability

SOURCE: Dr. J Pinthus

CVD & ADT: Patient Management Recommendations

Monitor

- Serum glucose
- Lipids
- Blood pressure
- Weight

Lifestyle changes

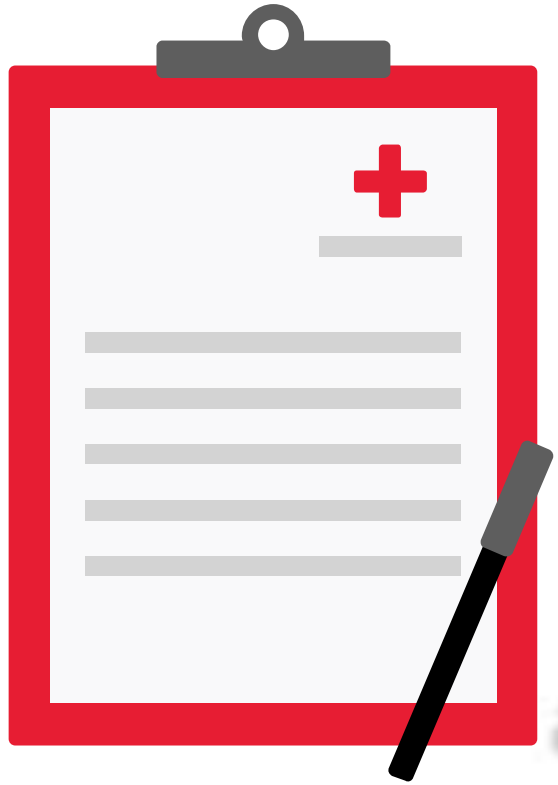
- Personalized aerobic exercise program (meta-analysis showed 30% reduction in CV mortality)
- Smoking cessation, dietary changes, moderation of alcohol consumption

Medical interventions, co-care with cardiologist

- Statins reduce CV mortality and reduce progression of coronary atherosclerosis
- Consider therapies for diabetes, hypertension and risk of thrombosis

Monitoring During ADT

- Confirm efficacy
  - Routinely measure PSA **and** T
- Monitor for Adverse Events
  - BM density
  - CVD (eg. cholesterol, BP, weight, smoking)
  - Glucose
- Ensure therapy compliance
  - Injection timing
- Shared care/caregiver feedback
- Team approach for patient management



Review and switch therapies if necessary

Personalizing ADT: Considerations for Selection of Therapy

- T suppression profile
- Adverse events
- Injection features
  - site location
  - SC v IM
  - local injection reactions
  - dosing intervals
- Comorbidities
- Concomitant therapies e.g. anti-coagulants
- Muscle mass
- Wheelchair-bound
- Intermittent Therapy?
  - patients with nmCRPC, moderate risk of progression with good initial response to ADT
  - patients with low burden of metastases and complete response to ADT
- Cost
- Lifestyle
- Compliance

SOURCE: Dr. ED Crawford

Overall Conclusions ADT

- PCa is hormone-sensitive
- ADT is the critical foundational therapy for advanced disease
- Understanding efficacy and AE profile of ADT facilitates selection of initial drug and optimization/ improvement of patients' health outcomes
- Efficacy goals
  - Rapid onset of T suppression
  - Maintain T <20 ng/dL
  - Low nadir T
  - Minimize microsurge/escapes
- Other goals of ADT
  - Minimize side effects
  - Maximize QOL
- Personalize therapy for each patient
  - Block T surge with antiandrogen?
  - Monitor efficacy and safety
    - T, PSA, CV markers, BMD, BP, glucose,
  - Recommend lifestyle changes
    - smoking, diet, weight, exercise
- Review and switch therapy if necessary
- Encourage primary care and cancer care providers to work together and optimize care

Androgen Receptor-Based Disease Progression to CRPC

Mechanisms of Escape

Potential AR Escape Mechanisms from Therapeutic Pressure:

ABUNDANCE

Amplification and/or overexpression of the AR

Production of AR ligand by PCa cells

Overexpression of AR coactivators

These Mechanisms Characterize Progression on Initial ADT

ACTIVITY

Gain-of-function AR mutations conferring ligand promiscuity

Ligand-independent AR activation

Constitutively active AR splice variants

Goals of Therapy in CRPC

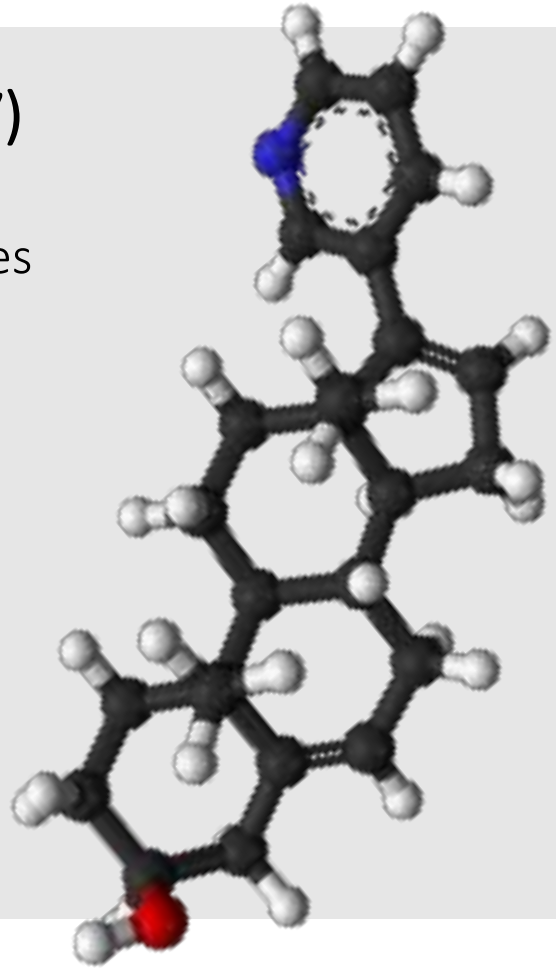
PROLONG	• Life
PREVENT	• Pain • Complications (e.g. skeletal events) • Decline in performance status
PRESERVE	• Quality of life • Performance status

Newer Therapies: Androgen Pathway Inhibitors

- 1st generation ADT drugs (antiandrogens) target the AR
- 2nd generation ADT drugs (LHRH agonists/antagonists) target LHRH receptors
- 3rd generation drugs have additional mechanisms and are described as androgen pathway inhibitors (APIs)
- APIs further reduce activation of AR beyond ADT:
  - Reduce T levels to almost zero (eg. abiraterone)
  - More effectively block AR signaling (eg. enzalutamide)
- All APIs require concomitant ADT
- APIs initially approved for mCRPC, now also approved in mCSPC and nmCRPC
- Efficacy of APIs demonstrates importance of androgen signaling pathway across disease continuum

Abiraterone Acetate

- Abiraterone **inhibits 17 α-hydroxylase/C17,20-lyase (CYP17)**
  - CYP17 involved in androgen biosynthesis
  - CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues
- **First approved in 2011 for mCRPC**
- **Now approved in 2018 for mCSPC**
- Concomitant use with prednisone to prevent excess mineralocorticoid effects
- Food effect requires dosing 1 hour before or 2 hours after a meal



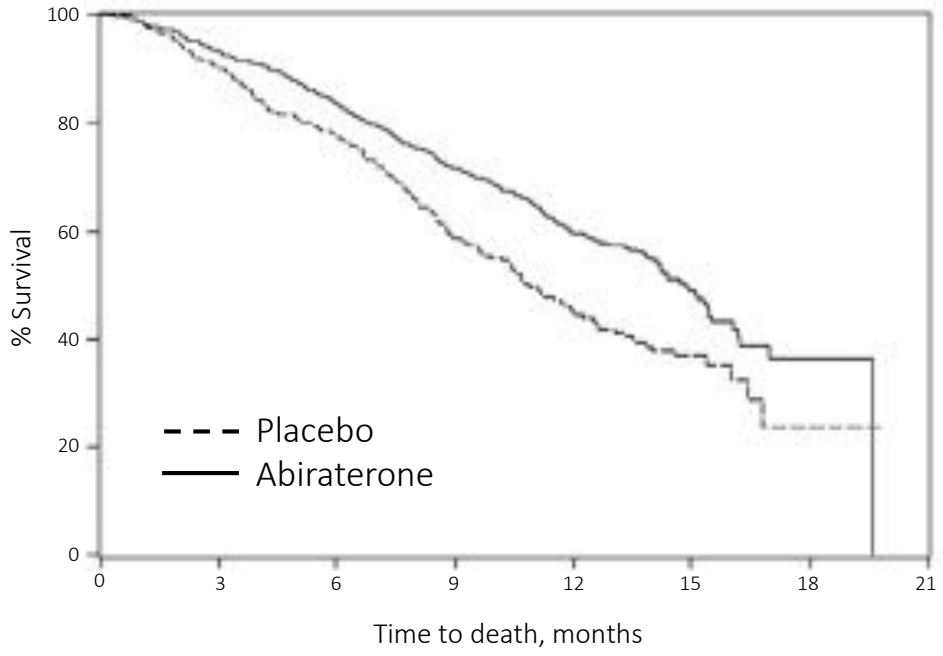
Abiraterone Efficacy mCRPC

COU-AA-301 Trial (post-chemotherapy)

Patients with metastatic CRPC
who had received prior chemotherapy

Median survival (months) 15.8 v 11.2 (placebo)
Hazard ratio 0.740

Kaplan-Meier Overall Survival Curves in COU-AA-301

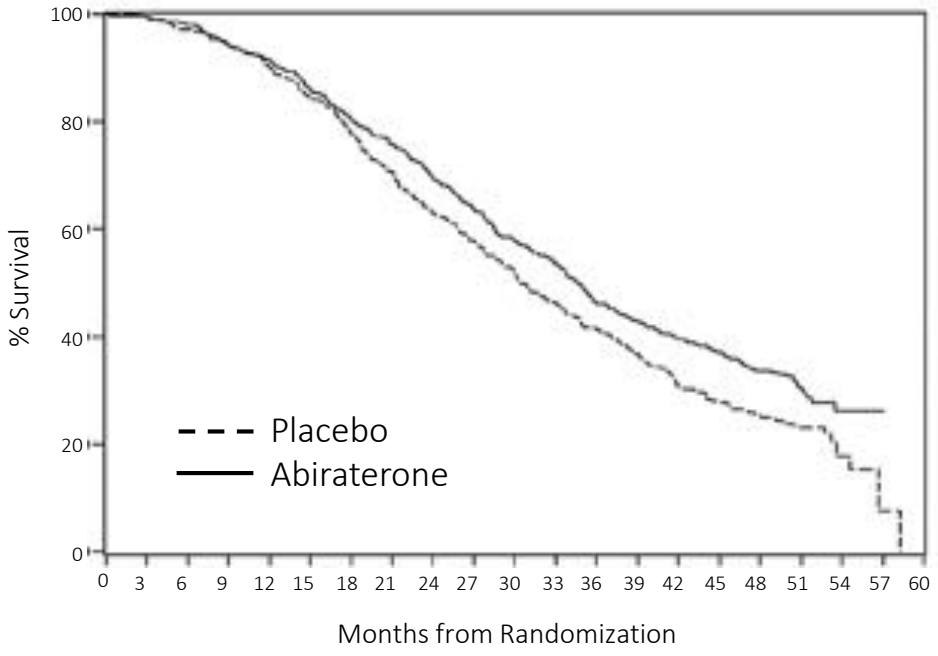


COU-AA-302 Trial (pre-chemotherapy)

Patients with metastatic CRPC
who had not received prior chemotherapy

Median survival (months) 34.7 v 30.3 (placebo)
Hazard ratio 0.81

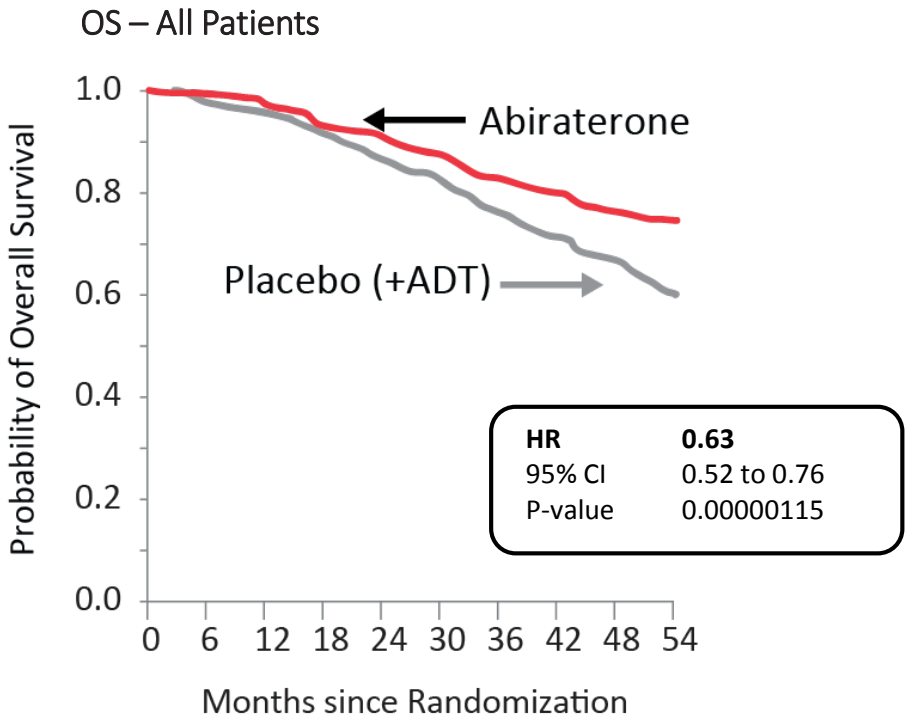
Kaplan Meier Overall Survival Curves in COU-AA-302



Abiraterone in mCSPC/Newly Diagnosed Metastatic Disease

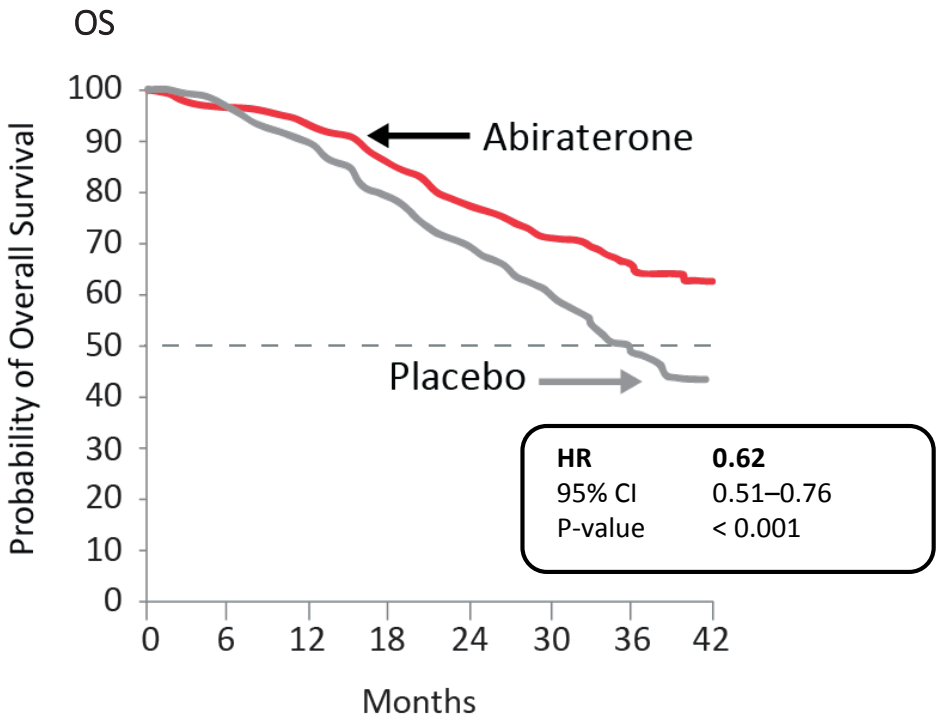
STAMPEDE Trial

- Improved overall survival by 37% (shown)
- Improved failure free survival by 71%
- Improved symptomatic skeletal events by 55%



LATITUDE Trial

- Improved overall survival by 38% (shown)
- Improved PFS by 53%
- Improved PSA progression by 70%
- Improved symptomatic skeletal events by 30%



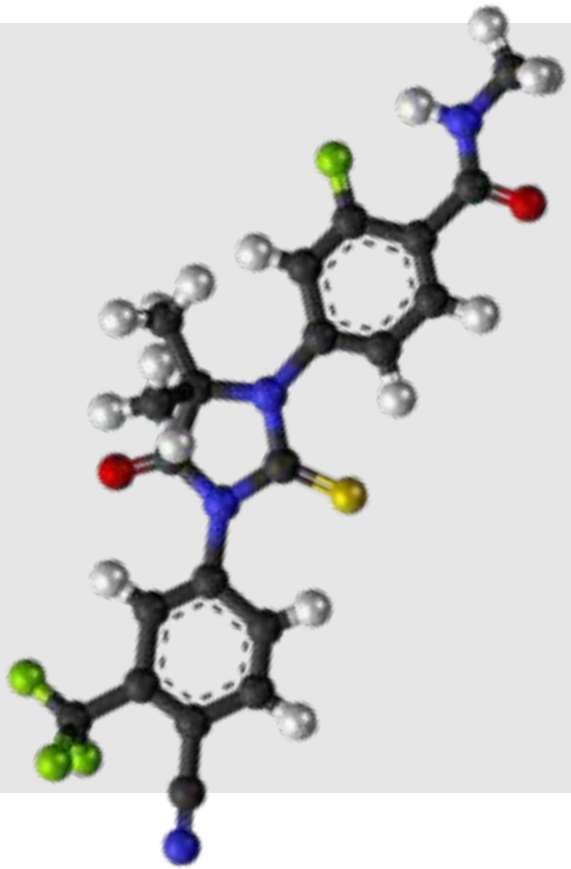
Potential Side Effects of Abiraterone

Fatigue	Diarrhea
Arthralgia	Vomiting
Hypertension	URTI
Nausea	Cough and Headache
Edema	Adrenocortical insufficiency
Hypokalemia	Hepatotoxicity
Fluid retention	
Hot flush	

Some events relate to concurrent use of prednisone

Enzalutamide

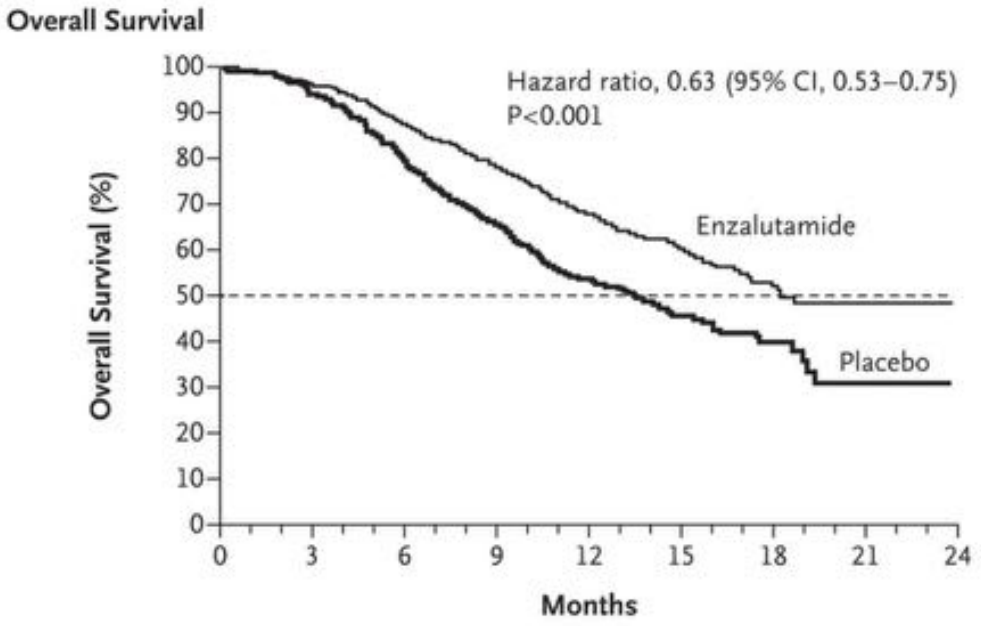
- Enzalutamide is a **3rd generation AR inhibitor**
- Has activity at 3 places
  - Blocks binding of androgen to AR
  - Prevents AR from entering cell nucleus
  - Inhibits AR binding to DNA
- **First approved in 2012 for mCRPC**
- **Now approved in 2018 for nmCRPC**



Enzalutamide Efficacy in mCRPC

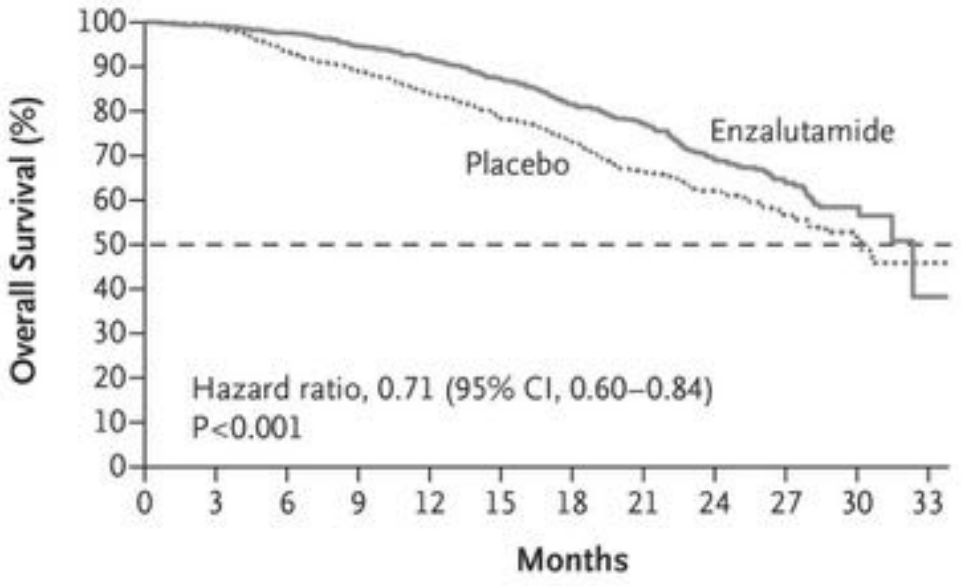
Affirm Trial (post-chemotherapy)

- OS 18.4m for enzalutamide group versus 13.6m placebo group
- HR for death in enzalutamide group, 0.63
- time to PSA progression: 8.3m enzalutamide v 3.0m placebo, HR 0.25; P<0.001



Prevail Trial (pre-chemotherapy)

- PFS at 12m: 65% for enzalutamide v 14% placebo (81% risk reduction; HR 0.19; P<0.001)
- 29% reduction in risk of death; HR 0.71; P<0.001

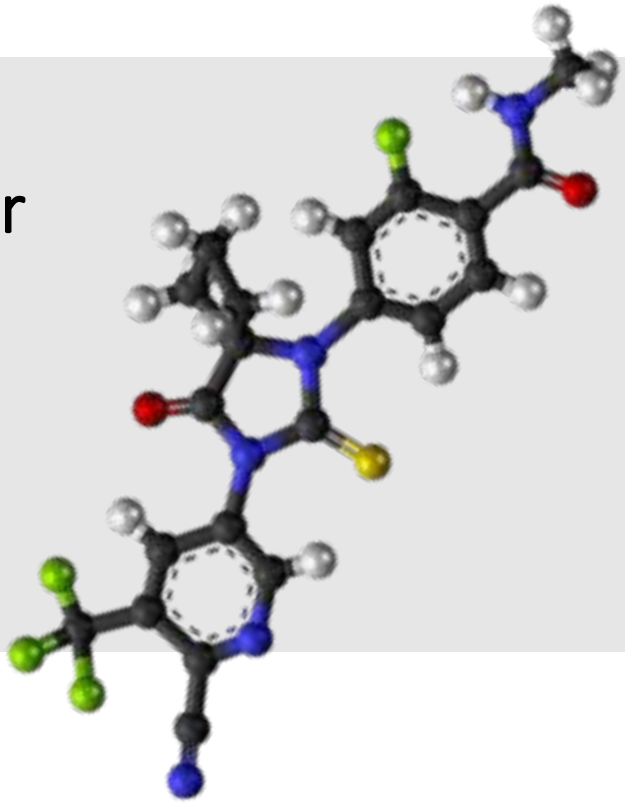


Potential Side Effects of Enzalutamide

- Seizures
- Fatigue
- Back pain
- Decreased appetite
- GI disorders, arthralgia
- Hot flashes
- URTI
- Edema
- Dyspnea
- Musculoskeletal pain
- Weight loss
- Headache
- Hypertension
- Dizziness
- Ischemic heart disease
- Falls
- Posterior reversible encephalopathy syndrome

Apalutamide

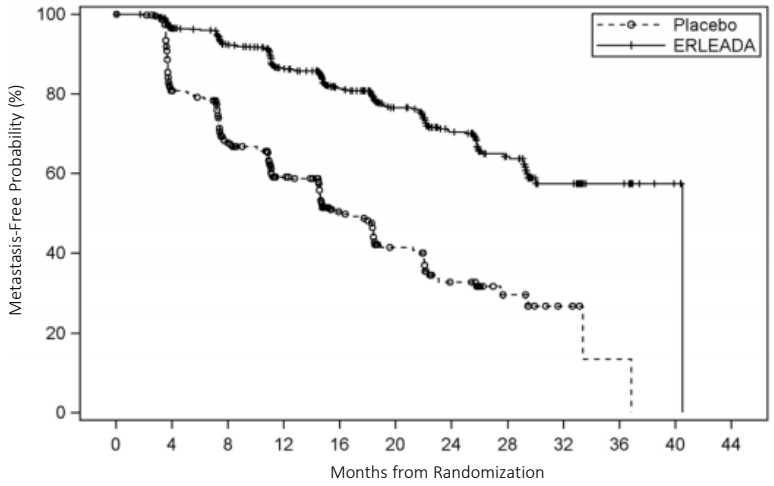
- Apalutamide is a **3rd generation AR inhibitor** that binds directly to the ligand-binding domain of the AR
- **First approved in 2018 for nmCRPC**



Apalutamide and Enzalutamide in nmCRPC

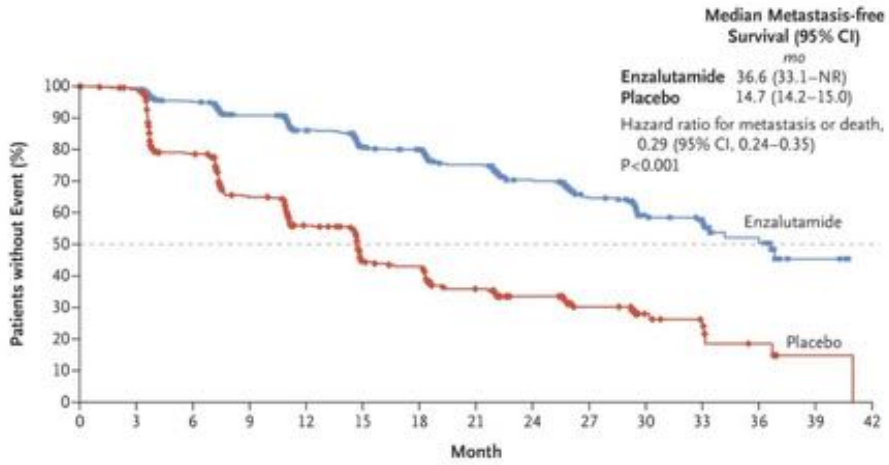
SPARTAN Trial (apalutamide)

- 40.5m v 16.2m for metastasis free survival
- 40.5m v 16.6m to metastasis
- 40.5m v 14.7m progression free survival
- HR 0.28



PROSPER Trial (enzalutamide)

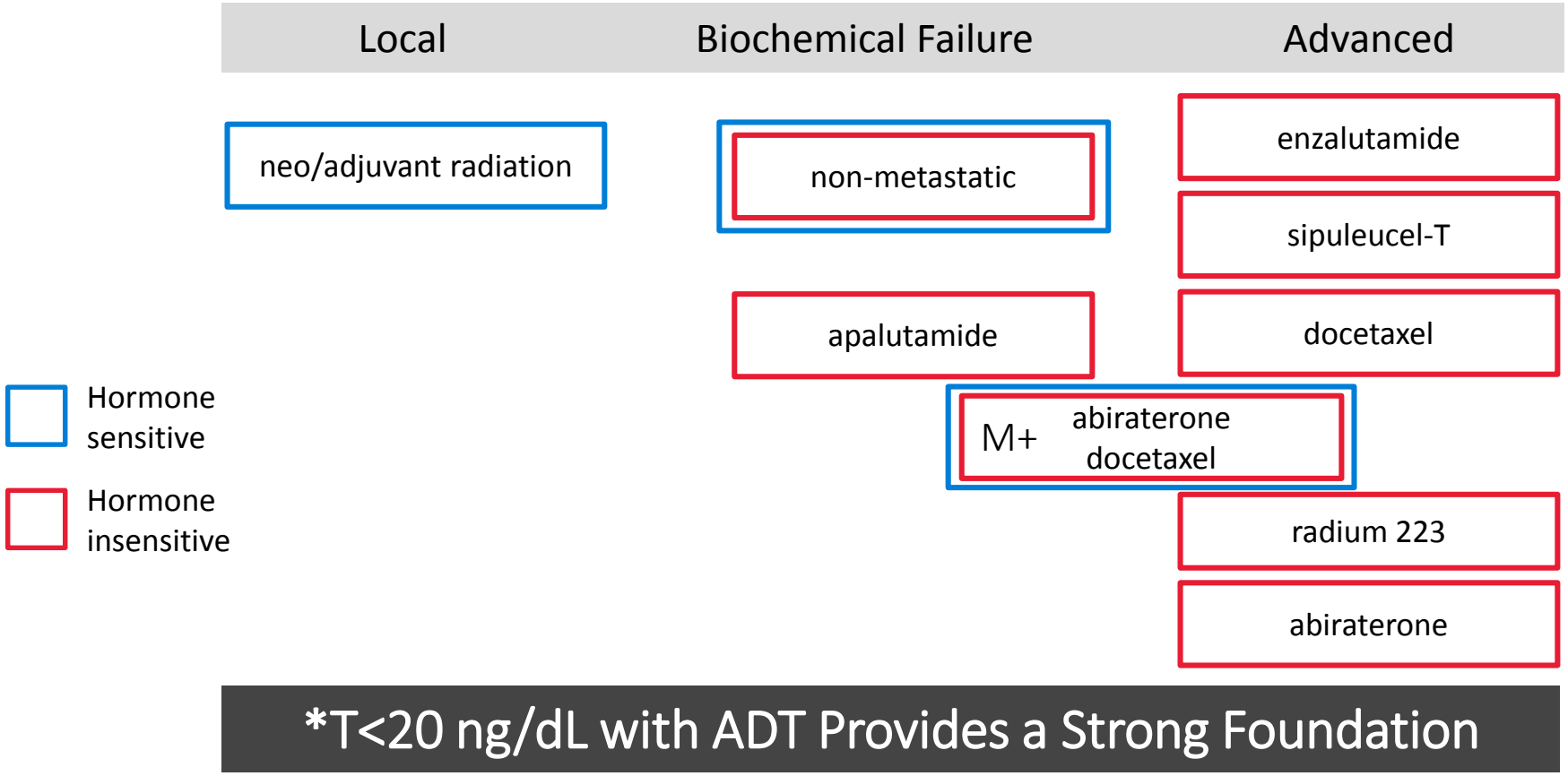
- median metastasis-free survival was 36.6m for enzalutamide v 14.7m for placebo group (HR for metastasis or death, 0.29; P<0.001
- time to PSA progression (37.2m for enzalutamide v 3.9m for placebo; hazard ratio, 0.07; P<0.001; progression occurred in 22% v 69% of patients)



Potential Side Effects of Apalutamide

Fatigue	Arthralgia
Hypertension	Falls and fractures
Rash	Hot flush
Hypothyroidism	Decreased appetite
Diarrhea	Peripheral edema
Nausea	Seizures
Weight loss	

ADT Strong Foundation for Prostate Cancer



* FDA and European Union Regulatory Authorities require drugs to demonstrate suppression of T to <50 ng/dL for approval

SOURCE: Dr. ED Crawford

API Conclusions

- Near complete inhibition of AR activation with APIs produces survival benefit in patients with CRPC and CSPC
- Reinforces importance of achieving lowest T by ADT alone
  - Lower nadir T in 1st year correlates with longer time to CRPC and longer CSS
  - Patients with higher baseline T derived more benefit
- Be observant of additional side effects
  - Hepatotoxicity
  - Falls/fractures
  - Seizures
- Identify drug resistance (ARV-7)
- Personalize therapy for each patient
  - Selection of initial API
  - Modify if necessary

Androgen Targeted Therapy Across the Continuum of Prostate Cancer: Key Messages

- ADT is foundational
- Lower and maintain T to castrate levels and/or block activity at AR
- Selection of ADT
  - orchiectomy, antiandrogen, LHRH therapy
  - onset, flare management
  - <20 target, nadir level, minimize escapes/microsurges
  - intermittent v continuous therapy
  - safety profile
  - patient experience/factors
  - cost
- Monitoring is critical
  - T, PSA, BMD, compliance, etc.
  - onset of CRPC
- Management of CVD patient
  - glucose, lipids, BP, weight
  - exercise, smoking cessation, dietary changes, alcohol consumption
  - selection of ADT
  - co-care with cardiologist
- When APIs initiated
  - continue effective ADT
  - select which API
  - identify and manage AE
  - monitor for drug resistance

Androgen Deprivation Therapy ⇄ Androgen Deprivation of the Tumor

THANK YOU

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