Manipulating the Androgen Axis in mHSPC and CRPC

David F. Jarrard, MD
Vice Chair Urology, University of Wisconsin
Associate Director UW Carbone
Comprehensive Cancer Center

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DISCLOSURES

- Gregor Diagnostics
- NCCN Early Detection Guidelines
- PUER Health

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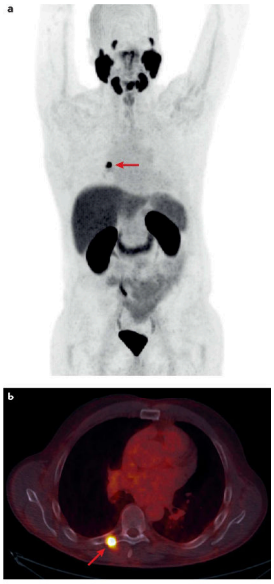
Case #1: 80yo with metastatic mCRPC low volume

- History of biochemical recurrence following radiation for locally advanced prostate cancer placed on ADT.
- Two years later, he develops a rising PSA while on LHRH therapy from 8 to 26ng/ml over 12 months.
- Testosterone is 19ng/dl.
- 2 bony metastases noted on imaging with enlarged pelvic and a retroperitoneal lymph nodes.
- No symptoms

Options for low volume M1 CRPC first line?



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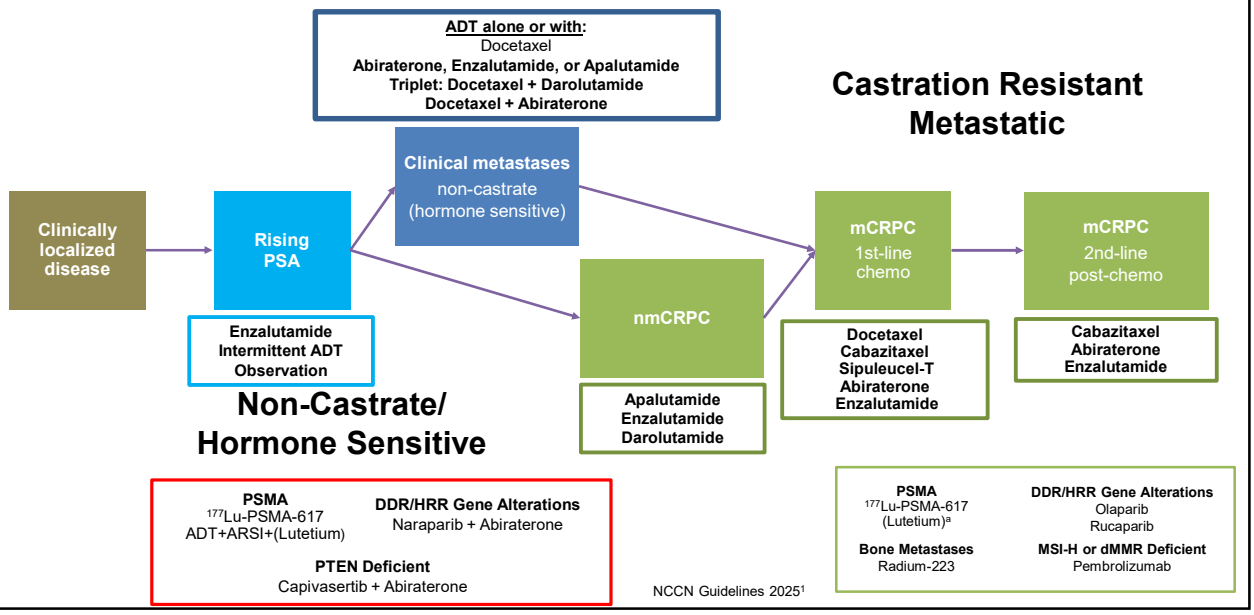
Current Prostate Cancer Therapeutic Landscape[1]



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Overview

- Mechanisms for CRPC development
  - AR enhancement and altered steroidogenesis
- Understand mechanisms and side effects of abiraterone, enzalutamide and other ARSIs
- Understand existing and new applications for oral androgen axis agents
- New insights into androgen deprivation therapy and its side effects

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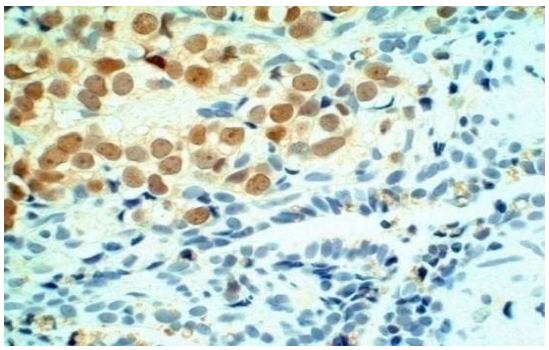
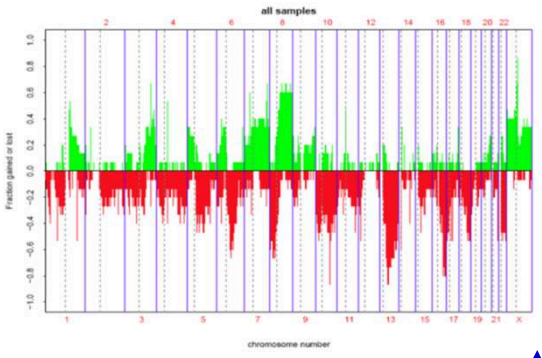
Amplified Androgen Receptor Levels in Castration Resistant Prostate Cancer



CRPC samples have robust AR expression
Mohler et al 2006



At autopsy – 73% of 15 samples exhibit AR amplification.
Friedlander/Paris et al

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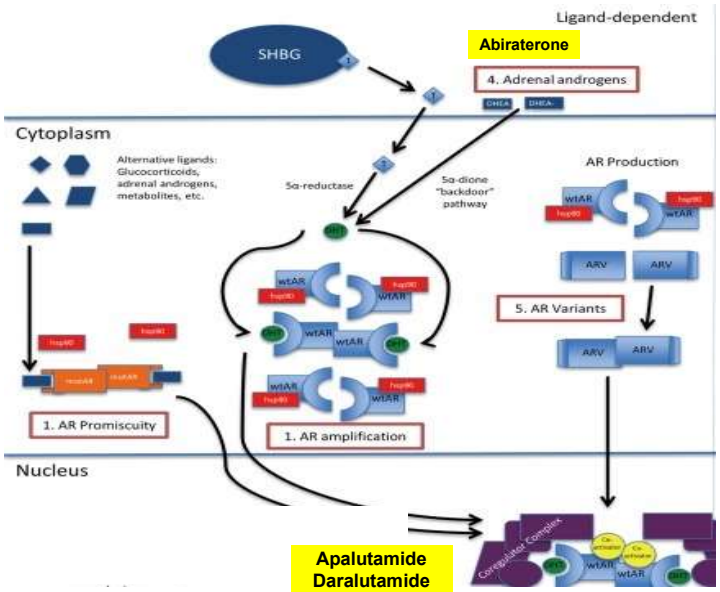
Ligand Dependent Mechanisms for Castration Resistance



Chandrasekar et al.

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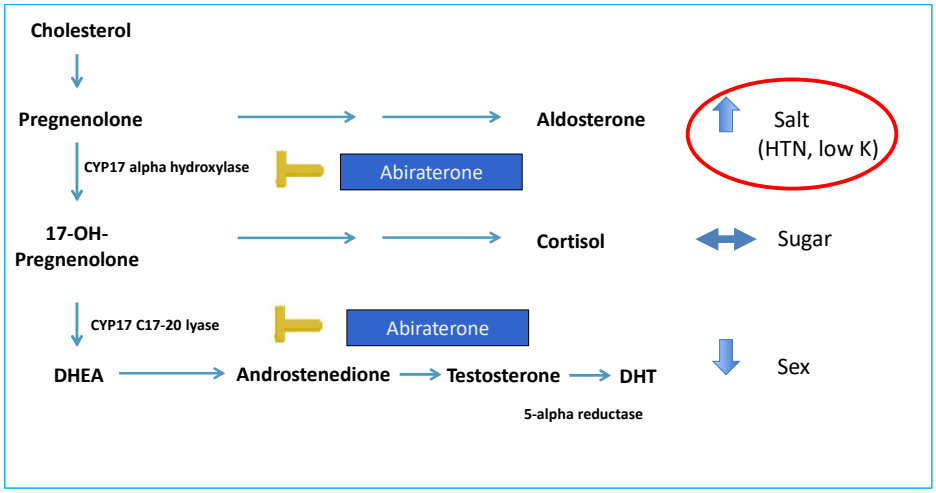
Abiraterone Mechanism Explains Side Effects



De Bono JS et al. *N Engl J Med*. 2011
Ryan et al. 2012 ASCO.

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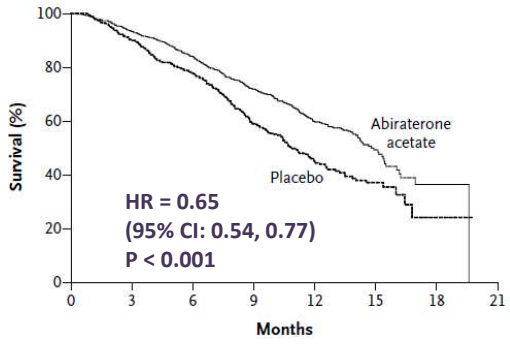
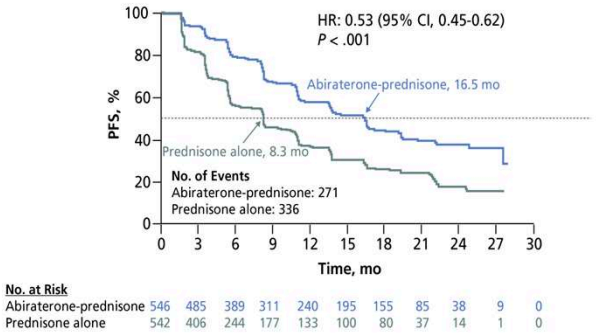
ABIRATERONE Improves Cancer-Specific Survival Post- and Pre-Chemotherapy in CRPC

Phase III trial (COU-AA-301): 1,195 patients, prior docetaxel



Phase III trial (COU-AA-302): 1088 patients no docetaxel



All secondary endpoints, including time to PSA progression, progression-free survival and PSA response rate favored the abiraterone-treated group.

de Bono et al. NEJM 2011, Ryan et al. Lancet Oncology, 2015

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Safety Data from Cou-AA-302

	AA + P (n = 542) %		Placebo + P (n = 540) %	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fatigue	39	2	34	2
Fluid retention	28	0.7	24	1.7
Hypokalemia	17	2	13	2
Hypertension	22	4	13	3
Cardiac disorders	19	6	16	3
Atrial fibrillation	4	1.3	5	0.9
ALT increased	12	5.4	5	0.8
AST increased	11	3.0	5	0.9

Most ALT and AST increases occurred during the first 3 months of treatment

Ryan CJ et al. *N Engl J Med.* 2013; 368:138-48.

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Minimizing the Side Effects of Abiraterone

- Taken on an empty stomach
- Give with Prednisone 5mg BID
- Liver function tests and electrolytes checked 2 wks after starting then routinely
  - For LFT elevation (AST, ALT or Bilirubin) hold until normalize
  - Restart at lower dose
- Routine assessments for hypertension and fluid retention
  - Treat hypertension and hypokalemia as needed
- Remember drug interactions (e.g. coumadin)

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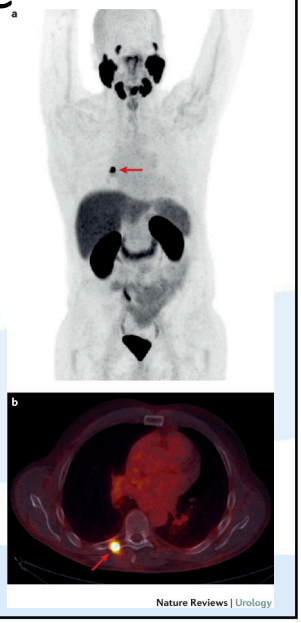
80yo with low volume mCRPC

29. In newly diagnosed mCRPC patients, who have not received prior androgen receptor pathway inhibitors, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (*Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]/Grade B [docetaxel]*)

30. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (*Conditional Recommendation; Evidence Level: Grade B*)



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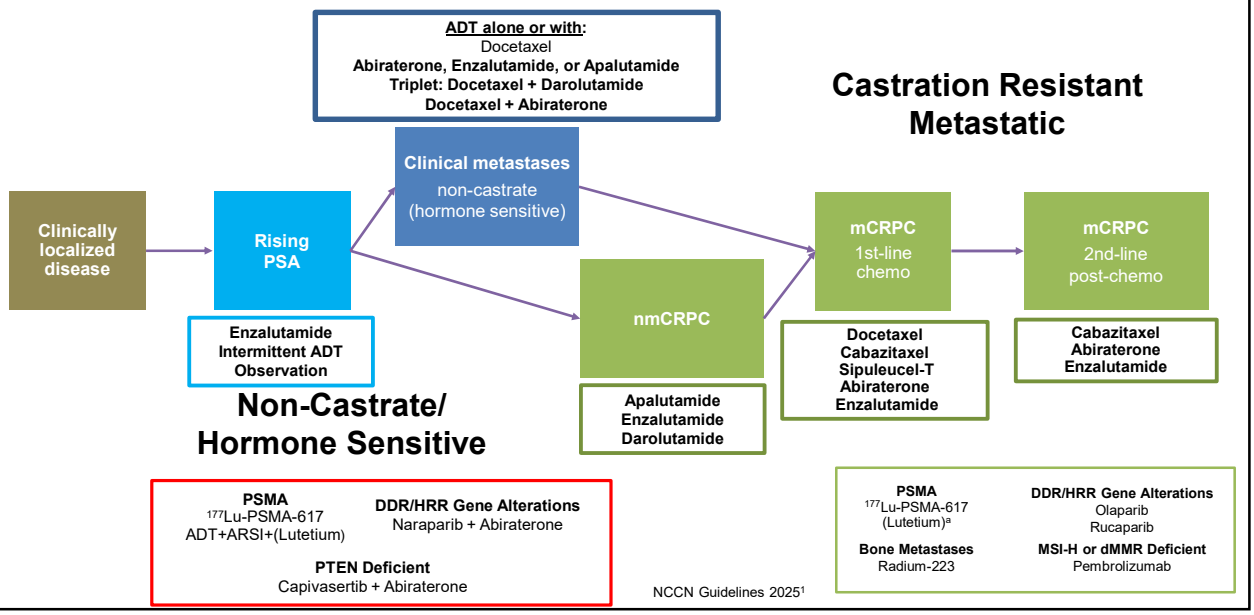
Current Prostate Cancer Therapeutic Landscape[1]



NCCN Guidelines 2025[1]

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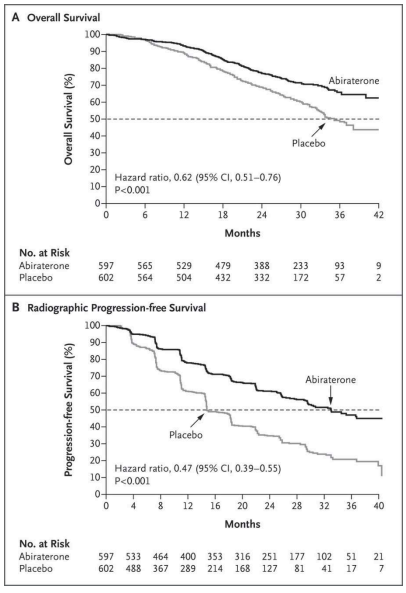
Abiraterone ± ADT for mHSPC: LATITUDE



- 1200 pt randomized "Hormone-naïve" men to Abiraterone (CYP17 inhibitor) + Lupron versus Lupron alone
- Reduced the risk of death by 38%, compared with Placebo
- Delayed cancer progression by 18 mo
- Side effects: HTN and liver enzyme elevations

NEJM June 2017

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Abiraterone Acetate

- Which patients?
  - FDA approved for men with metastatic CRPC *before* and *after* chemotherapy. (also *mHSPC with ADT; off label mOCRPC)*
- Side Effects
  - HTN, hypokalemia, edema, steroid induced hyperglycemia
- Which patients are poor candidates?
  - Cannot tolerate systemic steroids, i.e. brittle DM, gastric ulcer, rapidly progressive disease, infection
  - Cardiac disease (heart failure, edema)
  - Hepatic dysfunction, active viral hepatitis, ETOH abuse

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Randomized Trials: Oral AR Pathway Inhibitors

mHSPC*	m_0CRPC	mCRPC
Abiraterone (LATITUDE, STAMPEDE)	**Enzalutamide** (PROSPER)	**Abiraterone** (pre chemo COU-AA-301; post COU-AA-302)
Enzalutamide (ARCHES)	**Apalutamide** (SPARTAN)	**Enzalutamide** (pre chemo AFFIRM; post PREVAIL)
Apalutamide (TITAN)	**Daralutamide** (ARAMIS)	
Systemic treatment intensification (triplet)		
ADT + docetaxel ± abiraterone (± radiation) (PEACE-1)		
ADT + docetaxel ± Daralutamide (ARASENS)		

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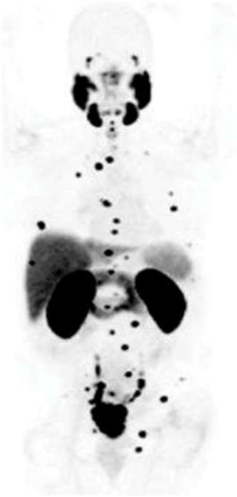
Case #2: 60yo with new diagnosis of metastatic HSPC - high volume

- Presents with bone pain and fatigue
- PSA 120 ng/ml
- GG5 prostate biopsy extensive
- Multiple pelvic bony metastases noted on imaging with enlarged pelvic and retroperitoneal lymph nodes.

Stage and Options?



F-18 DCFPyL PSMA PET

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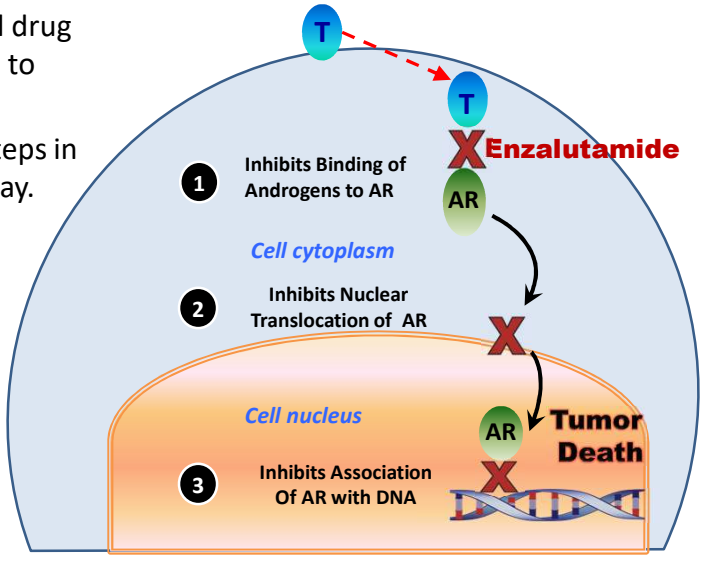
AR Signaling Inhibitors (ASIs)

- **Enzalutamide:** Oral drug rationally designed to target AR signaling
- Impacts multiple steps in AR signaling pathway.

- **Apalutamide** and **Daralutamide** have similar mechanisms of action



Tran et al. Science 2009;324:787–90.

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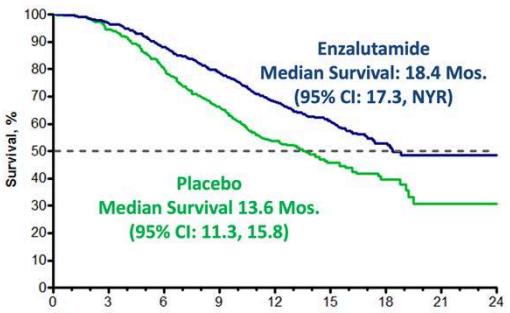
ENZALUTAMIDE Post- and Pre-Docetaxel Chemotherapy

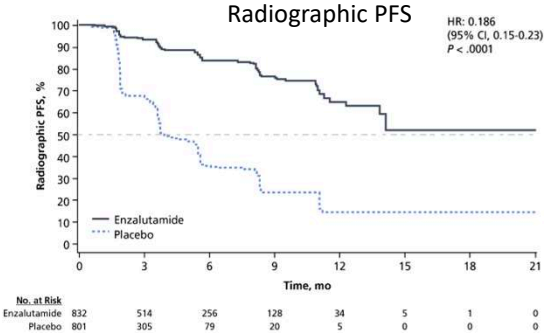
Phase III AFFIRM trial: 1,199 men
Overall survival HR = 0.63,(95% CI: 0.529, 0.752)P < 0.0001

Overall Survival



Phase III PREVAIL trial: 1,717 men
Overall survival HR 0.71, 95% CI [0.60-0.84] P<0.00

Radiographic PFS



	Estimated Median Radiographic PFS, mo (95% CI)
Enzalutamide	NYR (13.8-NYR)
Placebo	3.9 (3.7-5.4)

Beer TM et al. *NEJM* 371:424-33, 2014.

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PREVAIL: Enzalutamide Common Side Effects

	All Grades, %		Grade ≥ 3 Events, %	
	Enzalutamide (n = 871)	Placebo (n = 844)	Enzalutamide (n = 871)	Placebo (n = 844)
Fatigue	35.6%	25.8%	1.8%	1.9%
Back pain	27.0%	22.2%	2.5%	3.0%
Constipation	22.2%	17.2%	0.5%	0.4%
Arthralgia	20.3%	16.0%	1.4%	1.1%
Decreased appetite	18.1%	16.1%	0.2%	0.7%
Hot flush	18.0%	7.7%	0.1%	0%
Diarrhea	16.3%	14.1%	0.2%	0.4%
Hypertension	13.4%	4.1%	6.8%	2.3%
Asthenia	13.0%	7.9%	1.3%	0.9%
Fall	11.6%	5.3%	1.4%	0.7%
Weight loss	11.5%	8.4%	0.6%	0.2%
Edema peripheral	10.6%	8.2%	0.2%	0.4%
Headache	10.4%	7.0%	0.2%	0.4%

* *At least 10% on enzalutamide and ≥ 2% more than placeb*

	All Grades, %		Grade ≥ 3 Events, %	
	Enzalutamide (n = 871)	Placebo (n = 844)	Enzalutamide (n = 871)	Placebo (n = 844)
Hypertension	13.4%	4.1%	6.8%	2.3%
Any cardiac adverse event	10.1%	7.8%	2.8%	2.1%
ALT increased	0.9%	0.6%	0.2%	0.1%
Seizure	0.1%*	0.1%#	0.1%*	0

Beer TM, et al. *N Engl J Med.* 2014 Jul 31;371(5):424-33.

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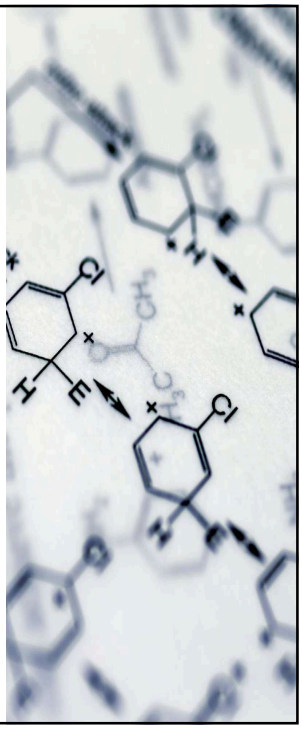
Minimizing and Managing Side Effects of Enzalutamide

- Dose reduce enzalutamide from 160 to 80mg when using with CYP2C8 inhibitor (statin : gemfibrozil)
  - Enzalutamide may affect serum levels of other CYP inducing agents. (i.e., warfarin)
- Consider dose reduction if profound fatigue
- Careful with meds that lower seizure threshold (e.g. buproprion)
- Dose holds can help prior to restarting with a reduced dose
  - half-life of enzalutamide ~8-9 days



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Enzalutamide and Androgen Receptor Signaling Inhibitors

- Which patients?
  - FDA approved for men with metastatic CRPC *before* and *after* chemotherapy. *M0 CRPC and mHSPC*
- Side Effects
  - Profound fatigue, HTN, constipation/diarrhea, rare seizure, Posterior Reversible Encephalopathy Syndrome (PRES)
- Which patients are poor candidates?
  - History of seizure, strokes, falls
  - Pts who already have significant fatigue
  - Advanced age (e.g. >70)?

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Other Androgen Signaling Inhibitors (ASIs)

- **Apalutamide** has similar mechanism of action
  - Trials: SPARTAN M_0 CRPC, TITAN mHSPC
  - Similar SE in moCRPC in addition to hypothyroidism (grade 1-2), Rash > placebo in mHSPC
- **Darolutamide** similar mechanism of action
  - Trials: ARAMIS M_0 CRPC, ARASENS mHSPC
  - Less penetration blood-brain barrier decrease fatigue, seizures, and HTN

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Which ASI Should Go First in Advanced Disease?

- Limited randomized data to guide in choosing first agent
  - Financial issues and clinical situation should dictate
- Avoid following ASI with another of similar mechanism
- Unique situations with rapid disease progression, significant symptoms and/or visceral disease consider:
  - Triplet therapy
  - Etoposide/cisplatin for neuroendocrine/small cell

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STOPCAP: Meta-Analysis of ARSIs in mHSPC

- 'Real world data'
- 7778 patients treated with ARSIs: ARSI + ADT improved survival compared to ADT
- No differences between 'amides' in responses (e.g. enzalutamide vs apalutamide)
- Note: Decreased overall survival with abiraterone in oldest age groups

Trial ID	Synchronous	High volume	Median age (IQR)	Docetaxel as part of SOC	cT4*
STAMPEDE (abi)	94%	56%*	67 (62-71)	0%	28%
LATITUDE (abi)	100%	94%	65 (60-70)	0%	27%
PEACE-1 (abi)	100%	57%	67 (60-72)	61%†	19%
ENZAMET (enz)	68%*	54%	69 (64-75)	45%†	14%
TITAN (apa)	86%*	63%	65 (60-70)	11%‡	19%
STAMPEDE (abi+enz)	93%	53%*	69 (63-74)	9%§	26%
SWOG 1216 (ort)	Unknown	Unknown	68 (62-74)	0%	Unknown

* Some data unavailable
† Stratified by planned use of docetaxel
§ Stratified by use of docetaxel
‡ Stratified by prior use of docetaxel

5-year absolute effects of ARPIs, by age group

		PFS	OS	PCSS*
Younger age groups (<75)	Abiraterone trial data	~25%	~16%	~17%
	Amide (± abi) trial data	~27%	~18%	?
Oldest age group (75+)	Abiraterone trial data	~8%	~0%	~9%
	Amide (± abi) trial data	~27%	~19%	?

GU ASCO 2025, Fisher et al.

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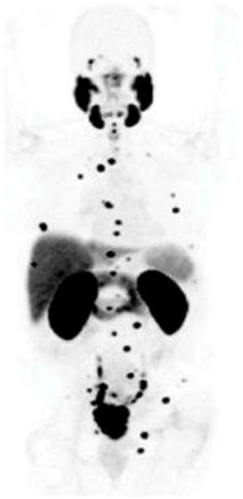
Case: 60yo with new diagnosis (de novo) of metastatic HSPC - high volume

- Options Include ADT plus:
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - Apalutamide
  - Docetaxel + Darolutamide (triplet)
  - Docetaxel + Abiraterone



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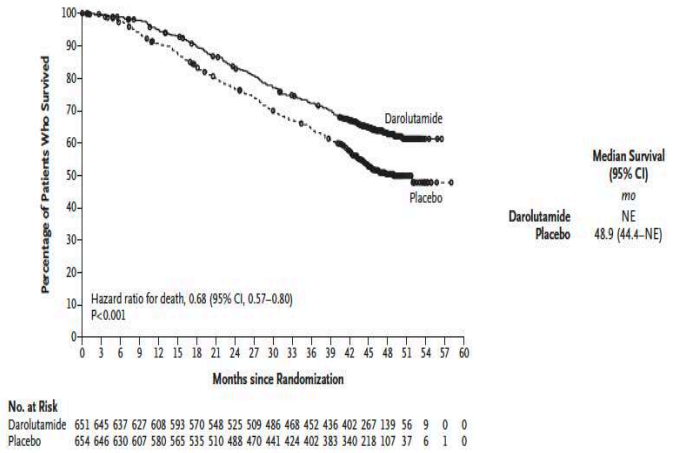
Triplet Therapy for mHSPC: ADT/Docetaxel ± Darolutamide (ARASENS)

- Improved median OS
  - 48.9 months vs NR
- Curves separate early at 9 months.
- Triplet therapy not meaningfully more toxic than ADT/Docetaxel
- Patients with aggressive features do very poorly on ADT alone



Smith et al NEJM 2023.

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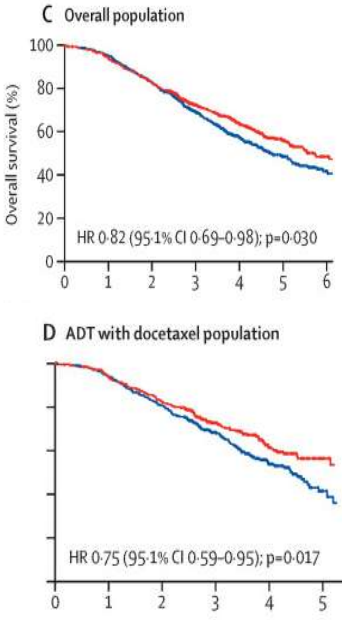
'Triplet' Therapy for mHSPC

- **ARASENS trial** for men with metastatic HSPC improves overall survival
- **PEACE-1 Trial**
  - 2x2 factorial design ADT and docetaxel ± abiraterone
  - Abi improves overall survival (0·75, 95·1% CI 0·59–0·95; p=0·017).
  - Increased Gr ≥3 events with abi arm (63% vs 52%; p=0.02)
- **Conclusion: Adding androgen signaling inhibitor to docetaxel + ADT improves OS**
  - Overtreatment for some patients
  - Increased cost
  - Must be chemofit



PEACE Trial : Fizazi. Lancet 2022.

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Choosing Between Docetaxel, an AR Pathway inhibitor or triplet therapy in mHSPC

- **ALL** patients should be offered treatment intensification
  - Triplet in *de novo* high volume disease or high volume
- Approach varies based on cost/SE/patient comorbidities
- Docetaxel: least expensive, done after 6 cycles, must be chemo-fit
- ARPI
  - Abiraterone: generic, requires K+/LFT/BP monitoring, long-term prednisone
  - Enzalutamide/Apalutamide/Daralutamide: expensive, less monitoring, long-term treatment, neurocognitive issues

Department of Urology
UNIVERSITY OF WISCONSIN
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ADT alone

ADT plus:

Abiraterone, Apalutamide, or Enzalutamide

Docetaxel

ADT plus:

Docetaxel + Darolutamide

Docetaxel + Abiraterone

ADT plus EBRT to primary tumor (for low-volume disease)

NCCN. Clinical practice guidelines in oncology: prostate cancer. 2025.

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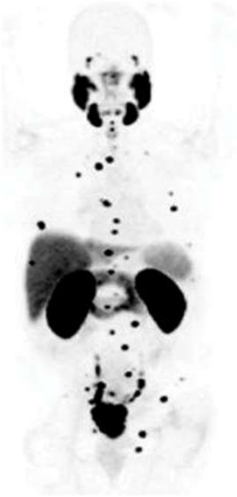
Case #2: 60yo with new diagnosis of metastatic HSPC - high volume

- Options Include ADT plus:
  - Docetaxel -chemo
  - Abiraterone
  - Enzalutamide
  - Apalutamide
  - Docetaxel + Darolutamide (triplet) *
  - Docetaxel + Abiraterone *

*Radiation to prostate in selected situations



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Understanding Adverse Events with ADT

Symptom	Notes
Hot flashes	Very common; can be mitigated using medications such as venlafaxine or gabapentin
Osteoporosis	Very common; estimated annual fracture risk of 1%-3%; calcium/vitamin D supplements
Fatigue	Very common; regular exercise may be beneficial; occurs independent of anemia or depression
Metabolic syndrome	Common; weight gain seen within 1 yr of ADT initiation; insulin resistance, dyslipidemia, and sarcopenic obesity reported
Erectile dysfunction	Common; both erectile dysfunction and reduced libido can have significant QoL effects; sexual health counseling referral may be beneficial
Cardiovascular disease	Unresolved; conflicting data from meta-analyses and observational studies; include primary and secondary CVD prevention measures
Thromboembolic disease	Unresolved; meta-analyses show association between VTE and ongoing ADT use, but tobacco use and acute hospitalization may be confounding factors

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Patil. Oncology (Williston Park). 2018; 32:470.

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Long Term: Increased Cardiovascular Risk with Androgen Deprivation Therapy

- ADT adversely affects cardiovascular disease risk factors including serum lipoproteins, insulin sensitivity, and obesity[1]
  - Meta-analyses report associations between ADT and risk of CV events and death[2]
- In patients receiving ADT/ASIs:
  - Recommend regular assessment of CV risk factors (eg, BP, lipids, blood glucose)
- In PRONOUNCE a randomized trial comparing cardiovascular safety of GnRH agonists (leuprolide) to antagonists (degarelix) showed no difference in major cardiac events[4]
- Concerns over prolonged AR/ASI treatment

1. Pinthus. J Urol. 2022 2. Levine. Circulation. 2010
3. AUA/SUO Guidelines. Prostate cancer.2022
4. Lopes. Circulation. 2021;144:1295 .

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Improving Hot Flashes the PATCH Trial: Transdermal Estradiol for Androgen Suppression

Event in Both Randomization Cohorts	LHRHa (n = 730)		tE2 patches (n = 807)		*P* Value
	Any Grade	Grade 3	Any Grade	Grade 3	
Gynecomastia	279 (38%)	6 (1%)	690 (86%)	34 (4%)	<.0001
Hot flushes	628 (86%)	23 (3%)	280 (35%)	1 (0.1%)	<.0001
Skin or subcutaneous toxicity	474 (65%)	11 (2%)	548 (68%)	2 (0.2%)	.20
Sexual or reproductive toxicity	671 (92%)	48 (7%)	732 (91%)	56 (7%)	.58

LHRHa and tE2 with comparable castration rate (94 vs 95%) and risk of CV event or sudden death (7.2(5.4-9.6) and 8.0 (6.2-10.4) at 36mo

Conclusion: Transdermal estrogen similar to LHRHa in CV mortality and efficacy

Langley. Lancet. 2021;397:581

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Take Home Points

- Combination of ADT and ASI are now standard of care in mHSPC with ADT
- Enzalutamide/Apalutamide/Daralutamide are direct androgen receptor inhibitors
  - *Preferred in pts who cannot tolerate systemic steroids (brittle DM, gastric ulcer disease)*
- Abiraterone is an androgen synthesis inhibitor (CYP17)
  - *Preferred in pts with seizure history, severe baseline fatigue, or on coumadin*
- 'Triplet therapy' for *de novo* high-volume/high-risk prostate cancer
- Monitoring and treating side effects must be considered for patients receiving ADT

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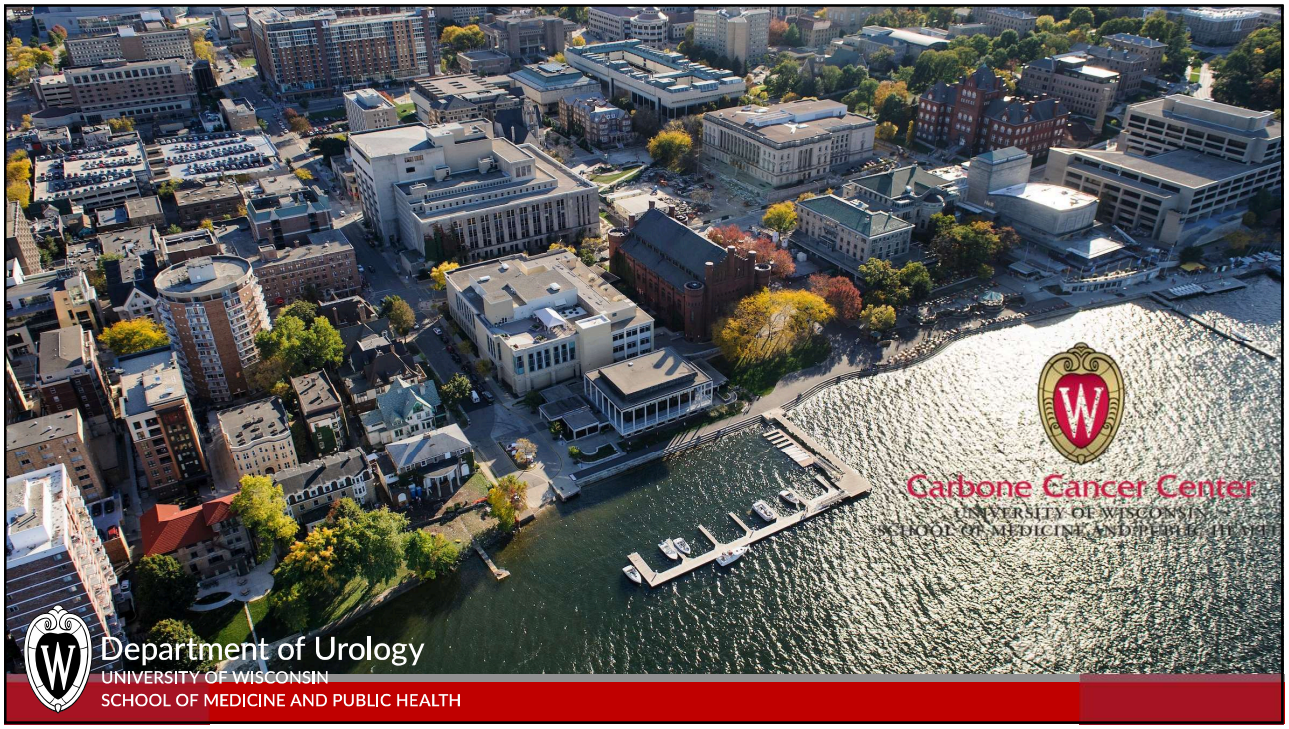

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