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Management of Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC)

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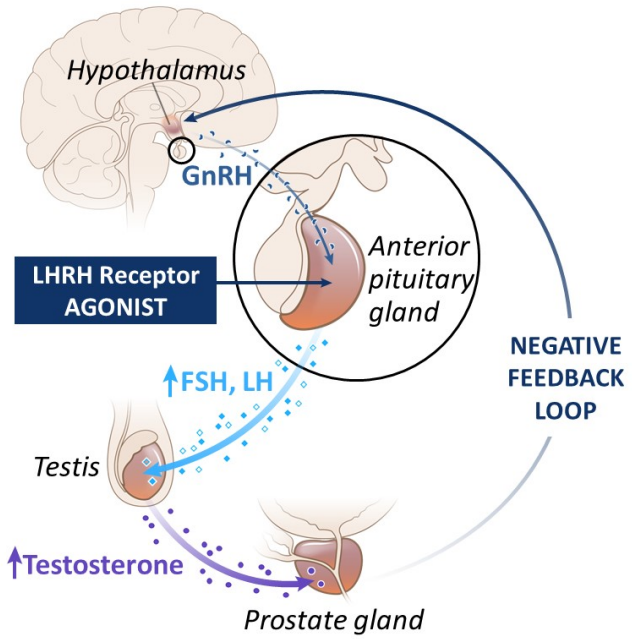
Chief, genitourinary cancer section

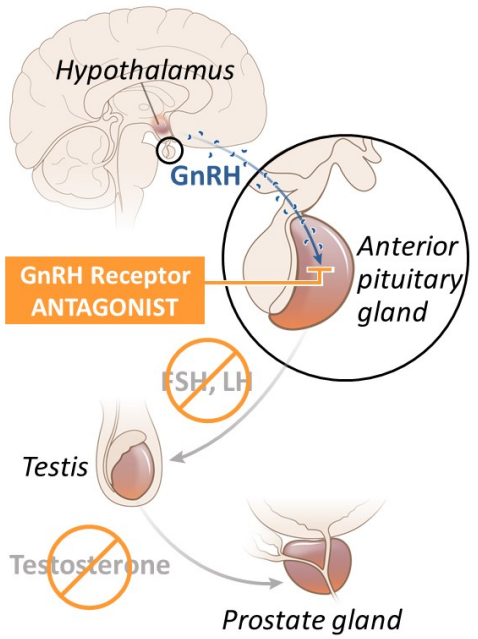
Overview

- Relugolix – oral testosterone suppressor
- Timing and selection factors for ADT in biochemical recurrence

Courtesy of Tanya B Dorff, MD

LHRH agonist vs antagonist MOA and side effect profile





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PRESENTED BY: Neal Shore, MD, FACS
Carolina Urologic Research Center, SC, USA

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	Relugolix (N = 622)	Leuprolide (N = 308)
Hot flush	54.3%	51.6%
Fatigue	21.5%	18.5%
Constipation	12.2%	9.7%
Diarrhea*	12.2%	6.8%
Arthralgia	12.1%	9.1%
Hypertension	7.9%	11.7%

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Relugolix vs Leuprolide HERO trial: population

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)
Median age (range) — yr	72 (48–91)	71 (47–97)	71 (47–97)
Age category — no. (%)			
≤75 yr	444 (71.4)	220 (71.4)	664 (71.4)
>75 yr	178 (28.6)	88 (28.6)	266 (28.6)
Presence of metastatic disease — no. (%)	198 (31.8)	97 (31.5)	295 (31.7)
Clinical disease presentation — no. (%)			
Evidence of biochemical or clinical relapse after local primary intervention with curative intent†	309 (49.7)	158 (51.3)	467 (50.2)
Newly diagnosed androgen-sensitive metastatic disease	141 (22.7)	70 (22.7)	211 (22.7)
Advanced localized disease not suitable for primary surgical intervention with curative intent	172 (27.7)	80 (26.0)	252 (27.1)

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HERO trial: relugolix vs leuprolide - Endpoints

	Relugolix	Leuprolide	
Sustained T <50 (1○ endpoint)	96.7%	88.8%	P <0.001
Confirmed PSA response d15	79.4%	19.8%	P < 0.001
Mean FSH level	1.72	5.95	P <0.001
T recovery >280 at d90 post d/c	54%	3%	P = 0.002

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Relugolix showed a better cardiovascular safety profile compared to leuprolide

Event	Relugolix (N=622)		Leuprolide (N=308)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event — no. (%)	578 (92.9)	112 (18.0)	288 (93.5)	63 (20.5)
Serious adverse event — no. (%)	76 (12.2)	61 (9.8)	47 (15.3)	35 (11.4)
Fatal adverse event — no. (%)	7 (1.1)	—	9 (2.9)	—
MACE — no. (%)†	18 (2.9)	8 (1.3)	19 (6.2)	4 (1.3)
Without a history of MACE — no./total no. (%)	15/538 (2.8)	—	11/263 (4.2)	—
With a history of MACE — no./total no. (%)	3/84 (3.6)	—	8/45 (17.8)	—

2/3 of patients had cardiovascular risk factors;
<15% had prior MACE

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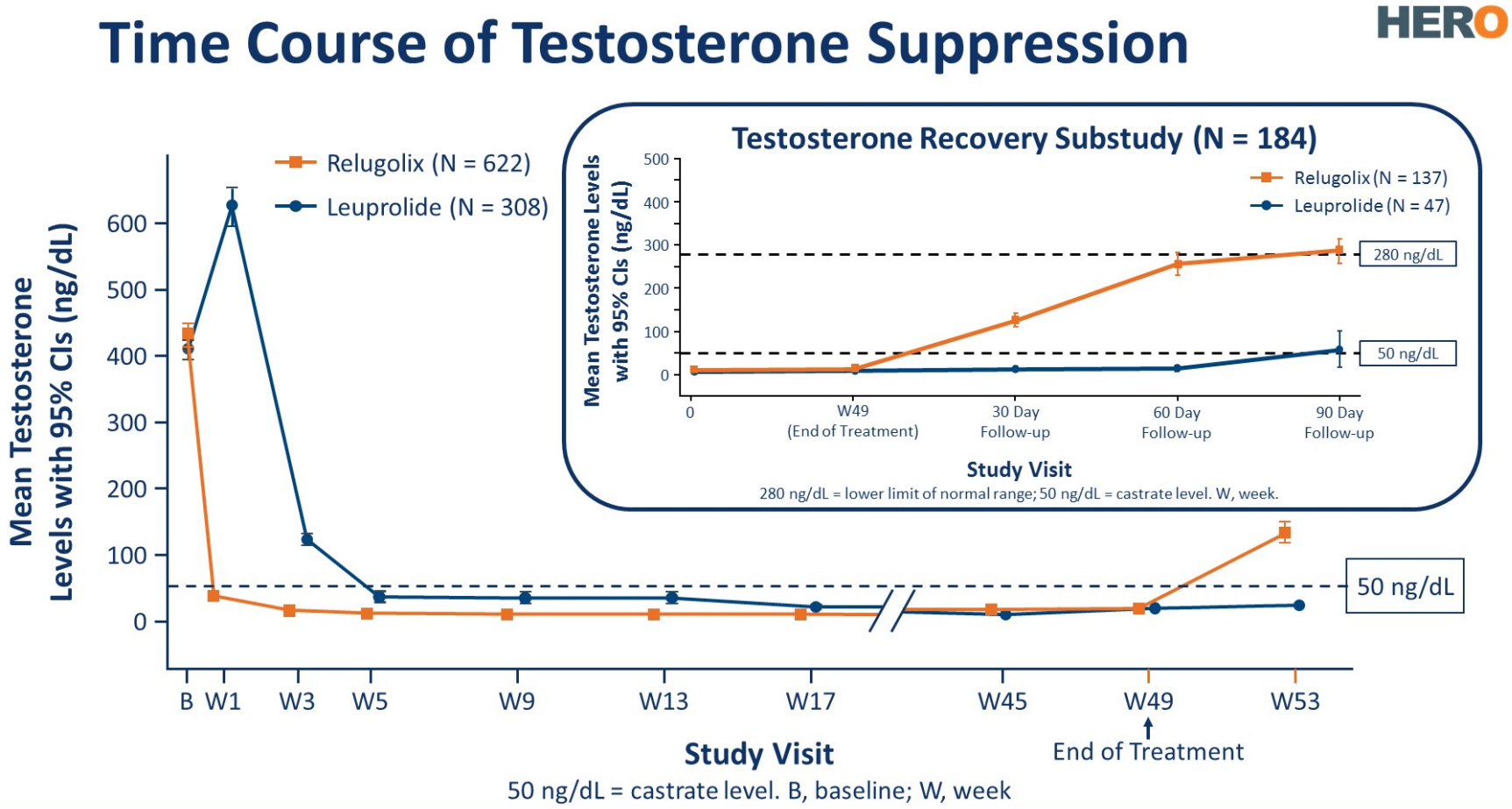
Quicker T recovery



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Practical Points: LHRH agonists and antagonists

Agonist preferred

- With abiraterone, enzalutamide, apalutamide, etc
- Without prescription drug coverage AND unable to come in for monthly injection

Antagonist preferred

- History of significant cardiovascular disease
- Side effects not well tolerated (rapid reversal)
- Inadequate T suppression with agonist

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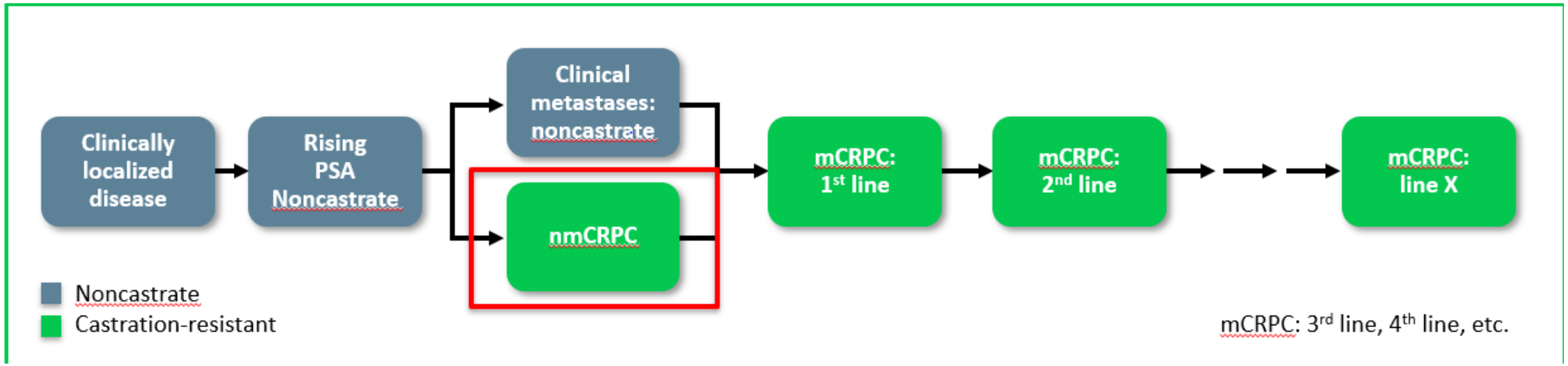
Prostate Cancer Disease States: the potential for nmCRPC



Two defining criteria of nmCRPC

- Rising PSA in the setting of castrate testosterone levels (≤ 50 ng/dL)
- No radiographically identifiable metastasis
  - By CT/bone scan

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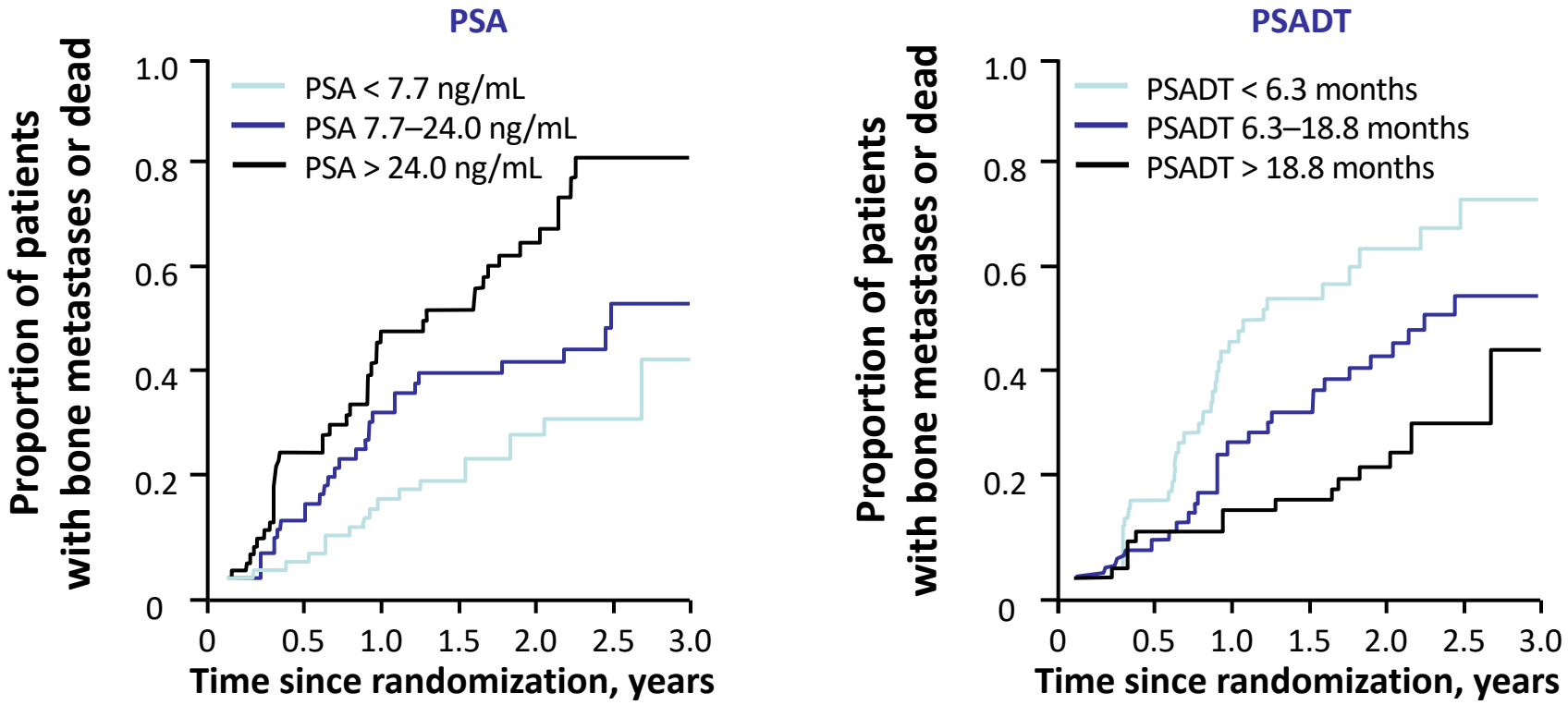
PSA and PSADT Are Associated With Shorter Time to Metastasis in non-metastatic prostate cancer



PSA, prostate specific antigen; PSADT, prostate specific antigen doubling time

Smith MR, et al. J Clin Oncol. 2005;23:2918-25

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Biochemical recurrence: current status and future aspects

- Treat with intermittent ADT if risk/ comorbidities warrant
  - JPR.7 trial – no survival difference intermittent vs continuous androgen suppression, but QOL advantage for intermittent
- Monotherapy. Duration ?
  - Klotz et al – 4 vs 10 months degarelix with similar time off
  - AFT trial of “androgen annihilation” tests monotherapy vs dual combination with AR antagonist vs triple therapy adding abiraterone. Duration is 12 months
- Need to check testosterone with rising PSA to differentiate CRPC vs recurrent HSPC
- Need to image (current = CT + bone scan, future = PET) to distinguish mCRPC from nmCRPC since treatment options differ

Courtesy of Tanya B Dorff, MD

Registrational trials of AR antagonists in nmCRPC

Agent	Apalutamide 240 mg daily	Darolutamide 600 mg BID	Enzalutamide 160 mg daily
Study name	SPARTAN[1]	ARAMIS[2]	PROSPER[3]
Design	2:1 apa/placebo	2:1 daro/placebo	2:1 enza/placebo
Number of pts	1207	1509	1401
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2	PSA DT ≤10 mo -- bPSA ≥2

1. Chi KN et al. NEJM 2019; 381:13-24
2. Fizazi K et al. NEJM 2019; 380:1235-46
3. Hussain M et al. NEJM 2018; 378:2465-74

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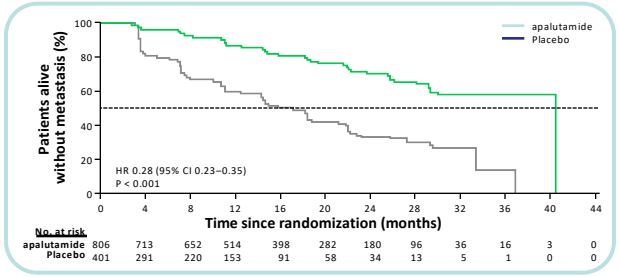
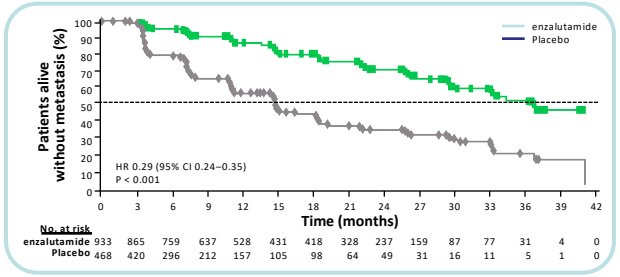
Primary Endpoint: Metastasis-Free Survival

SPARTAN[1]
apalutamide



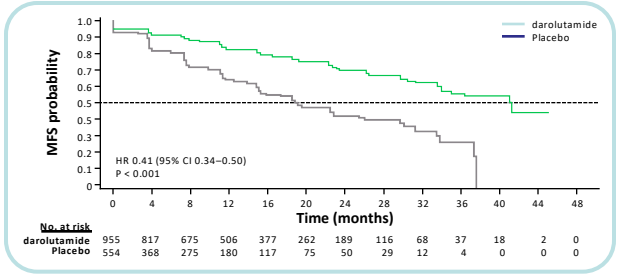
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

PROSPER[2]
enzalutamide



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month MFS benefit

ARAMIS[3]
darolutamide



- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

APA, apalutamide; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; MFS, metastasis-free survival; PBO, placebo

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Hussain M, et al. N Engl J Med. 2018;378:2465-74; 3. Fizazi K, et al. N Engl J Med. 2019;380:1235-46

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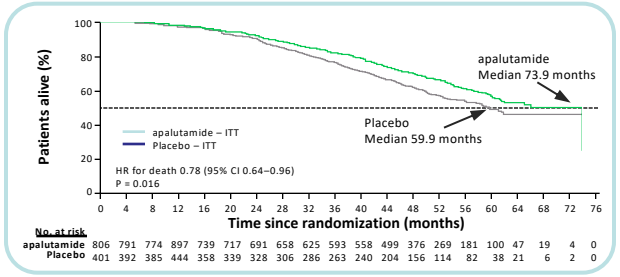
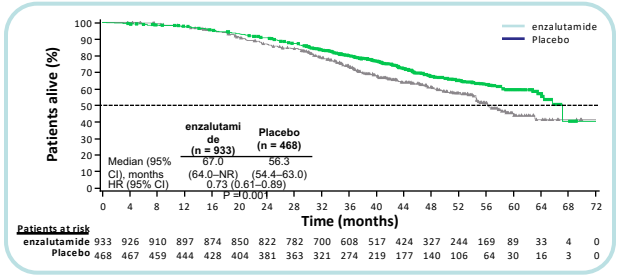
Secondary Endpoint: Final Overall Survival

SPARTAN[1]
apalutamide



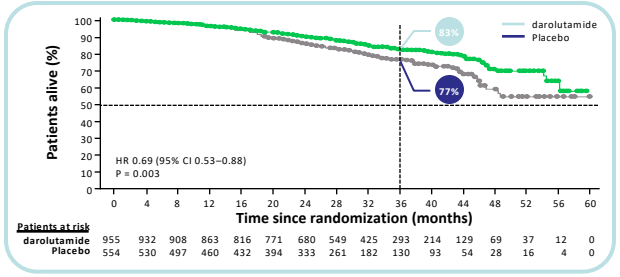
- 22% reduction in risk of death
  HR 0.78 (95% CI 0.64–0.96); P = 0.0161
- 71% of placebo patients received subsequent life-prolonging therapy

PROSPER[2]
enzalutamide



- 27% reduction in risk of death
  HR 0.73 (95% CI 0.61–0.89); P = 0.001
- 65% of placebo patients received subsequent antineoplastic therapy

ARAMIS[3]
darolutamide



- 31% reduction in risk of death
  HR 0.69 (95% CI 0.53–0.88); P = 0.003
- 55% of placebo patients received subsequent life-prolonging therapy

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached

1. Smith MR, et al. Eur Urol. 2020; https://doi.org/10.1016/j.eururo.2020.08.011; 2. Sternberg CN, et al. N Engl J Med. 2020;382: 2197-206; 3. Fizazi K, et al. N Engl J Med. 2020; 383: 1040-1049

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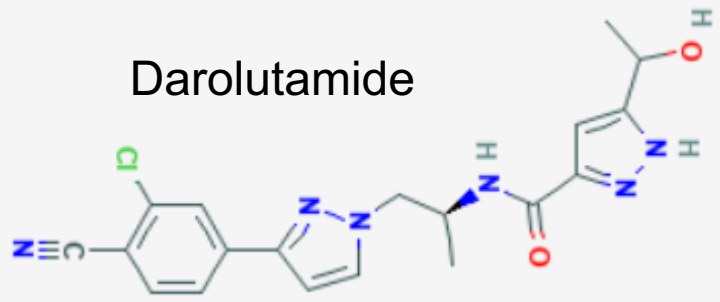
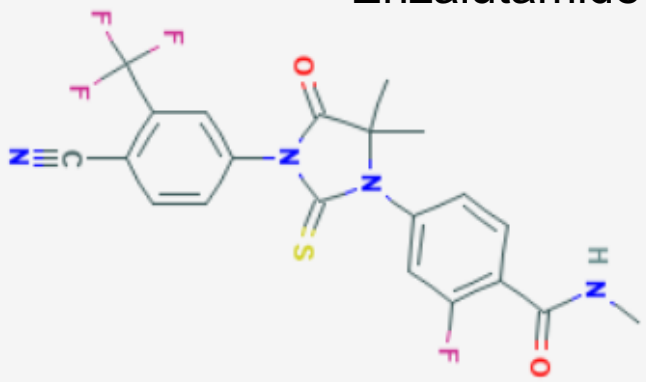
Structural differences between the AR antagonists

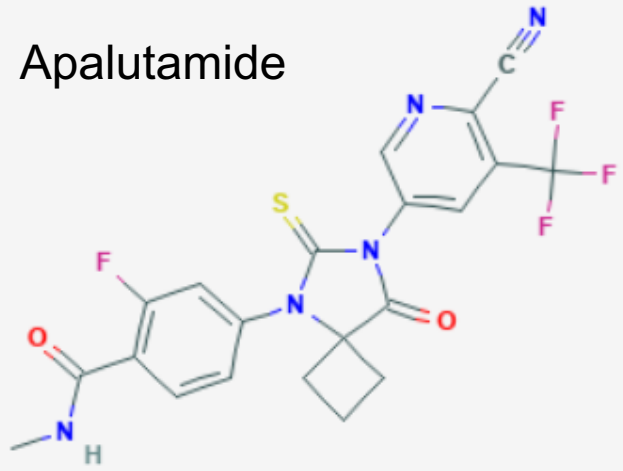
Darolutamide



Enzalutamide



Apalutamide



Compound	AR Affinity[a] Ki, nM	Antagonism hAR[b] IC50, nM	Proliferation VCaP[c] IC50, nM
Darolutamide	11	26	230
Keto-darolutamide	8.4	38	170
Enzalutamide	86	219	410
Apalutamide	93	200	420

Fizazi K et al
Clin GU Cancer
2018; 16:332-40

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Adverse Events of Interest: Hypertension is a class effect

Safety	SPARTAN[1,2,3]		PROSPER[4]		ARAMIS[5]	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 930)	PBO (n = 465)	DARO (n = 954)	PBO (n = 554)
Any AE, n (%)	781 (97)	373 (94)	876 (94)	380 (82)	818 (85.7)	439 (79.2)
Any serious AE, n (%)	290 (36)	99 (25)	372 (40)	100 (22)	249 (26.1)	121 (21.8)
AE leading to discontinuation, %	15.0	7.3	17.0	9.0	8.9	8.7
AE leading to death, n (%)	24 (3.0)	2 (0.5)	51 (5.0)	3 (1.0)	38 (4.0)	19 (3.4)
AE (all grades), %						
Fatigue	31.9†	21.4†	37	16	13.2	8.3
Hypertension	27.6†	20.9†	18.0	6.0	7.8	6.5
Rash	26.0	6.3	4	3	3.1	1.1
Falls	22.0	9.5	18.0	5.0	5.2	4.9
Fractures	18.0	7.5	18	6	5.5	3.6
Mental impairment disorder#	5.1§	3.0§	8.0	2.0	2.0	1.8

#SPARTAN: disturbance in attention, memory impairment, cognitive disorder and amnesia; PROSPER: as per SPARTAN trial with the addition of Alzheimer's disease, mental impairment, vascular dementia and senile dementia; ARAMIS trial: cognitive disorder, memory impairment and change in mental status; § Data taken from first interim analysis as placebo group not reported in final analysis[1] ; † Data taken from second interim analysis as placebo group not reported in final analysis[2]

AE, adverse event; APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide; NA, not available; PBO, placebo

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Adverse Events of Interest: falls/fractures and cognitive impairment less different between darolutamide and placebo

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Adverse Events of Interest: rash fairly unique to apalutamide. Also need to monitor thyroid with this agent

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Practical Points: choosing an AR antagonist in nmCRPC

- All 3 agents (apalutamide, darolutamide, enzalutamide) are all highly effective and well tolerated
  - In frail elderly, think hard about treating in nmCRPC (weight loss, osteoporosis, cognitive change)
  - Given lower fall/fracture and cognitive impairment, consider darolutamide
- Darolutamide seems to have the cleanest toxicity profile when compared against its placebo comparator arm
  - Definitely preferred in patients with history of seizure or risk factor for seizure
  - Downside: BID dosing
- Insurance coverage may dictate choice

Courtesy of Tanya B Dorff, MD

Case 1: A 68-Year-Old Man Who Received Darolutamide

- A retired police officer, with prostate cancer diagnosed at age 68 due to abnormal DRE although PSA was only 2.
- Biopsy revealed Gleason 4+5 adenocarcinoma, and radical prostatectomy confirmed T3bN1 Gleason 5+4
- PSA failed to nadir, measured 0.77 at 2 months post op. Imaging revealed no evidence of metastatic disease.
- He was treated with ADT (Degarelix – has CAD) and PSA decreased to 0.08 after 3 months but then he developed early castration resistance with PSA rising to 0.539, 1.49 and then 2.16. PSA doubling time was <3 months.
- He was started on darolutamide, and PSA nadired to undetectable but then rose 6 months later. After 20 months, he developed metastatic disease.

Courtesy of Tanya B Dorff, MD

Case 2: A 69-Year-Old Man Who Received Apalutamide

- A 69-year-old Hispanic gentleman followed for rising PSA for many years,
- Patient had 4 negative biopsies in the past including one when PSA was 103.5 – finally PSA reached 292 and MRI fusion biopsy at our institutions revealed 4+3 adenocarcinoma.
- Imaging was positive for enlarged pelvic lymph nodes, but negative for distant metastatic disease.
- He was treated with ADT + IMRT and achieved a PSA nadir of 0.05 After completing 2 years ADT, he was transitioned to surveillance.
- PSA began rising despite failure of testosterone recovery.
- When PSA reached 2.4 with testosterone of 23 about 3 years after completing primary treatment, we initiated apalutamide.

Courtesy of Tanya B Dorff, MD

Case 2 Continued: 69-Year-Old Man

- He developed rash after 2 months on treatment – this was on his arms, legs, chest, abdomen and back and patient complained of mild itching.
- Apalutamide was held and he took diphenhydramine hydrochloride and topical hydrocortisone administered as needed for itching.
- After about 1 week, the rash was 80% better, and he resumed apalutamide at full dose. His rash did not recur.
- PSA dropped to undetectable level by 3 months on treatment, and stayed there for 1 year before slowly rising; it remans <0.03 but detectable on ultrasensitive assay at 0.018.

Courtesy of Tanya B Dorff, MD