AR antagonists, are they all equal ?

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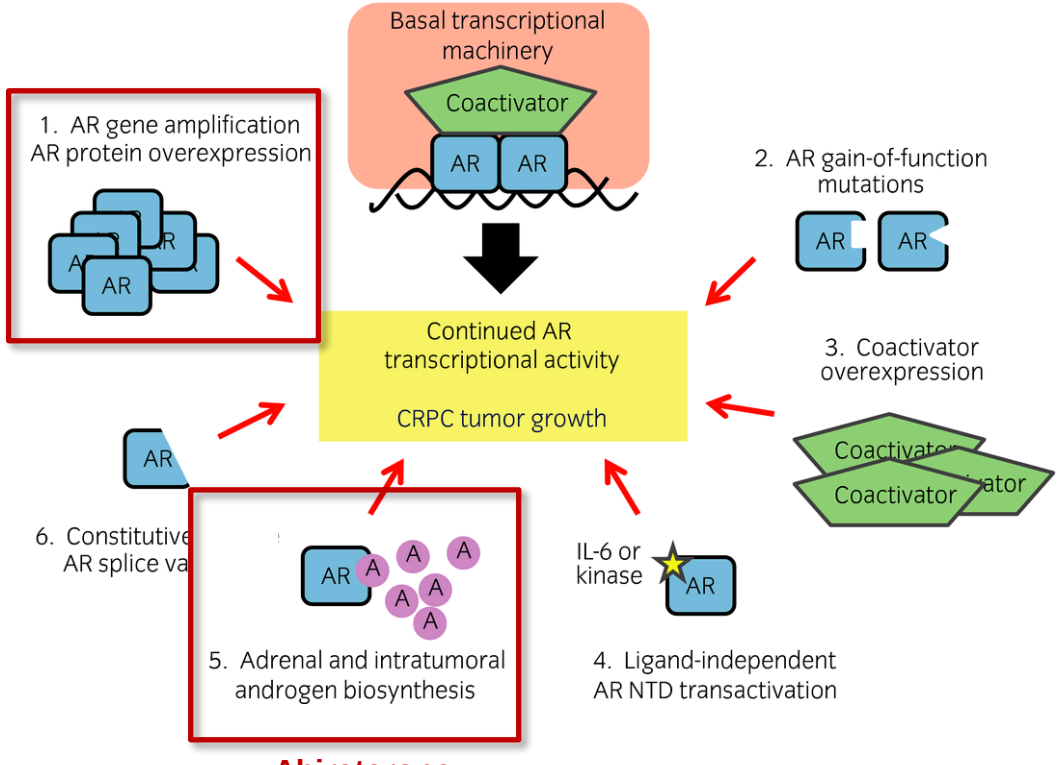
Credentials and conflict of interests

- Professor and Chairman, Division of Urology, Cliniques universitaires Saint Luc, Brussels, BE
- President, European Organization Of Research and Treatment of Cancer (EORTC)
- Investigator and paid advisor for Amgen, Astellas, Bayer, Janssen, Ferring, Pfizer, Sanofi, Myovant.
- This presentation reflects the personal view of Bertrand TOMBAL

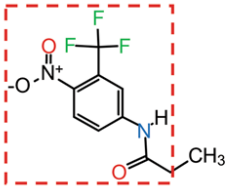
CRPC, an AR driven process

Enzalutamide
Apalutamide
Darolutamide

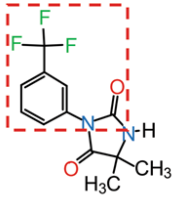


Abiraterone
(ODM-208)
(PRL-02)

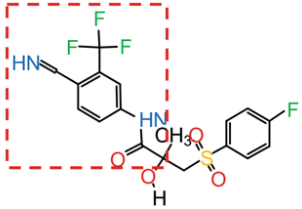
Imamura Y et al. Int J Urol 2016;23:654-65



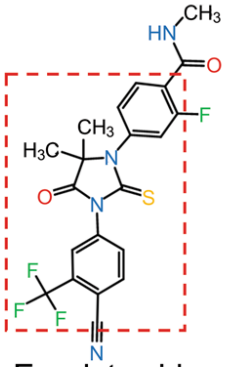
Flutamide



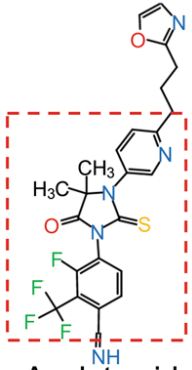
Nilutamide



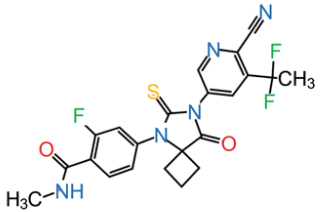
Bicalutamide



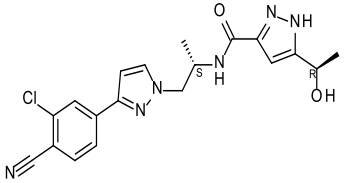
Enzalutamide



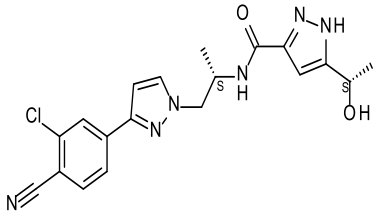
Apalutamide



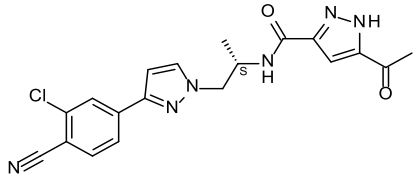
Darolutamide



(*S,R*)-darolutamide



(*S,S*)-darolutamide



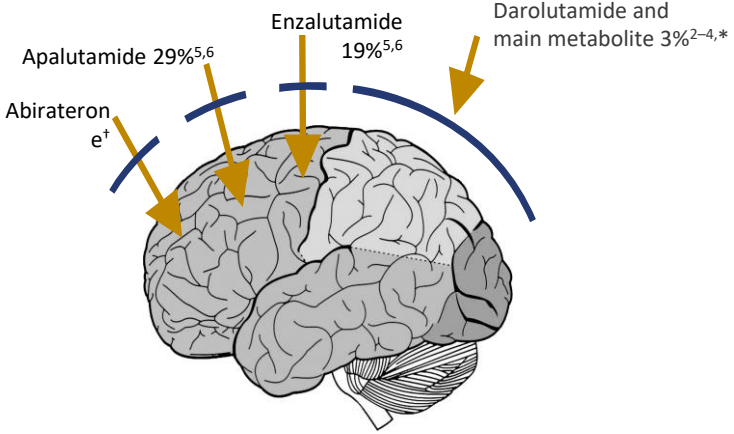
keto-darolutamide

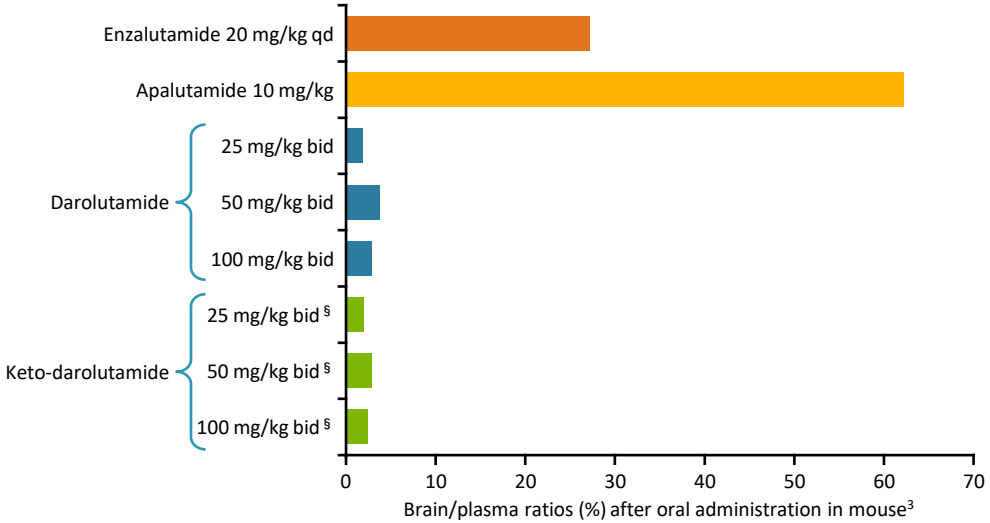
- Darolutamide is a 1:1 mixture of two pharmacologically active diastereomers ((*S,R*)-darolutamide and (*S,S*)-darolutamide), that interconvert via its pharmacologically active metabolite (keto-darolutamide)

The red dotted box indicates the shared structure between drugs. Drug structure resources from PubChem (https://pubchem.ncbi.nlm.nih.gov/search/search.cgi). Adapted from Chen Y, et al. .Cell Death Dis. 2022 Jul 21;13(7):632.

Darolutamide Demonstrates Low Blood–Brain Barrier Penetration in Preclinical Studies[1–4]

- Darolutamide has a low brain–plasma ratio in murine models[2–4,*]
- Reduced brain exposure may confer a lower risk of seizure with darolutamide[1–3]





*In preclinical studies. AR, androgen receptor; CNS, central nervous system; CYP, cytochrome P450; DDI, drug–drug interaction. 1. Moilanen A et al. Sci Rep 2015;5:12007. 2. Zurth C et al. Presented at: ASCO-GU. February 8–10, 2018. San Francisco, CA, USA. Poster 345. 3. Fizazi K et al. Lancet Oncol 2014;15:975–985. 4. Moilanen A et al. European Cancer Congress 2013. Abstract E17-2119. 5. Bayer. Data on file.

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AR antagonists, are they all equals ?

Table 2 Antiproliferative Effect of Darolutamide Compared With Other Androgen Receptor Antagonists[12,40]

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

Abbreviations: AR = androgen receptor; hAR = human androgen receptor; VCaP = vertebral cancer of the prostate.
[a]Competitive AR binding assays.
[b]Transactivation assays in AR-HEK293 cells stably expressing full-length hAR and an androgen-luciferase reporter gene construct.
[c]Xenograft model in vivo using VCaP cell line grown with a submaximal concentration of mibolerone (a synthetic androgen).

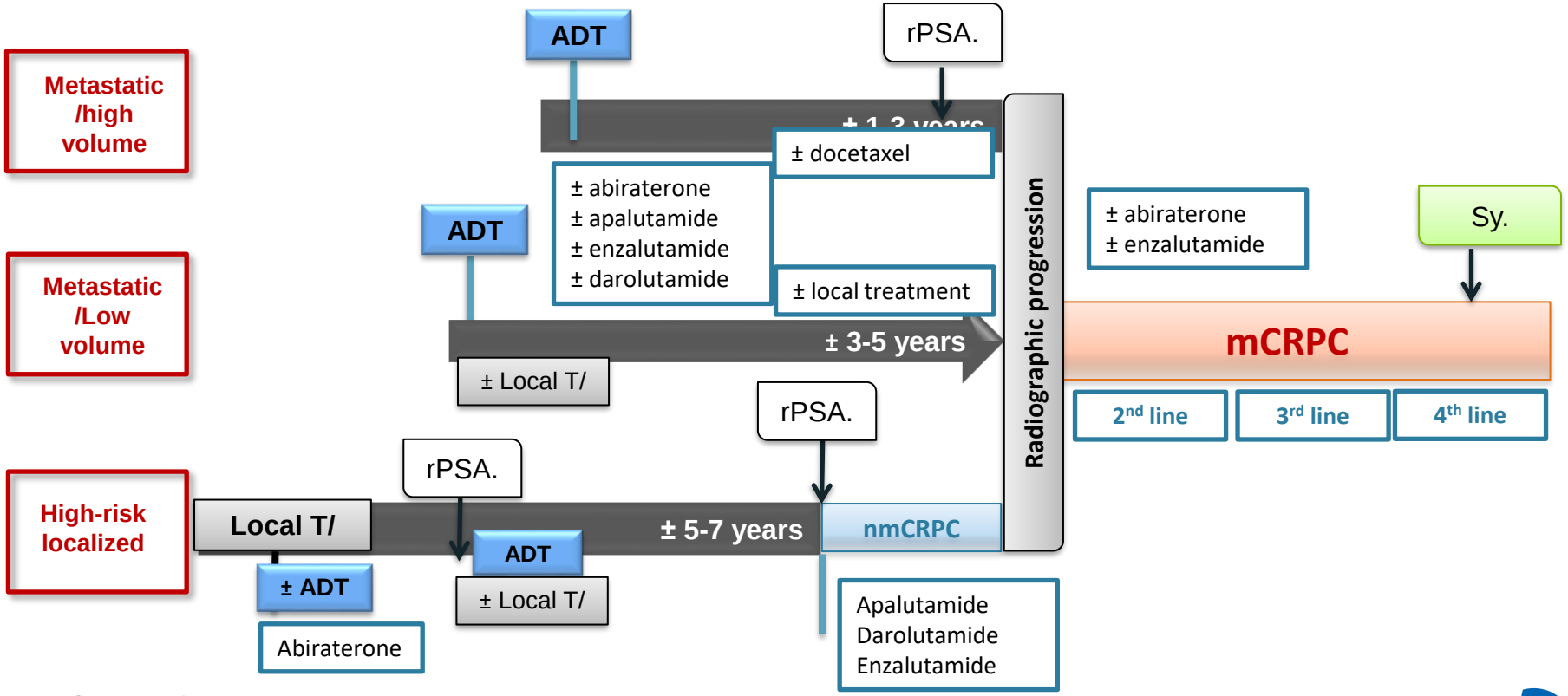
Table 3 Antagonism of Mutant Androgen Receptors Linked to Resistance to ADT[12]

Compound	Antagonism wtAR, nM	Antagonism AR (F877L) IC50, nM	Antagonism AR (T878A) IC50, nM	Antagonism AR (W742L) IC50, nM
Darolutamide	65	66	1782	1500
Keto-darolutamide	25	51	700	1160
Bicalutamide	150	218	957	Agonist
Enzalutamide	155	Agonist	296	> 10,000
Apalutamide	168	Agonist	1130	> 10,000

Abbreviations: ADT = androgen-deprivation therapy; AR = androgen receptor; wtAR = wild type AR.
Adapted with permission from Moilanen AM, Riikonen R, Oksala R, et al. Discovery of ODM-201, a new generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Sci Rep *2015; 5:12007.*

Fizazi, Smith and Tombal, Clin Genitourin Cancer. . 2018 Oct;16(5):332-340.

Advanced PCa in 2022



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ADT: androgen deprivation therapy; RT: radiotherapy;PSA: prostate-specific antigen; rPSA: PSA recurrence; pRX: progr.: radiological progression; SRE: skeletal-related events: T/: treatment; Sy; Symptoms, SRE and deterioration of HR-QoL

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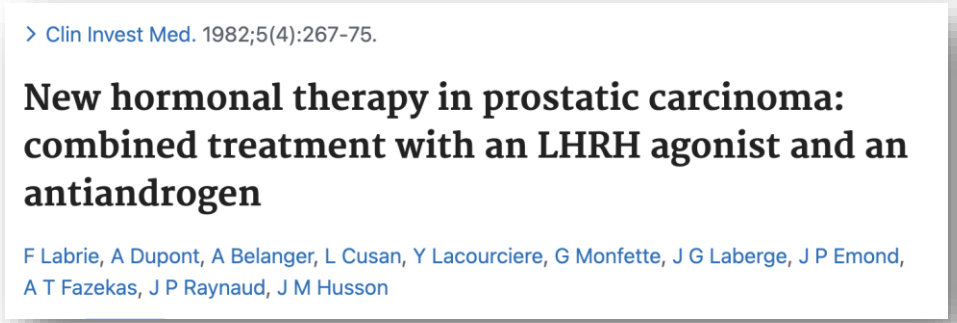

> Clin Invest Med. 1982;5(4):267-75.

New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen

F Labrie, A Dupont, A Belanger, L Cusan, Y Lacourciere, G Monfette, J G Laberge, J P Emond, A T Fazekas, J P Raynaud, J M Husson

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Published: 18 July 2017

Prostate cancer

STAMPEDE, LATITUDE and Fernand Labrie's legacy

Bertrand Tombal & Robert J. van Soest

Nature Reviews Urology **14**, 588–590 (2017) | Cite this article

1743 Accesses | **5** Citations | **16** Altmetric | Metrics

- Labrie's legacy: if you have high-risk PCA you need maximal androgen blockade with one the modern AR pathway inhibitors

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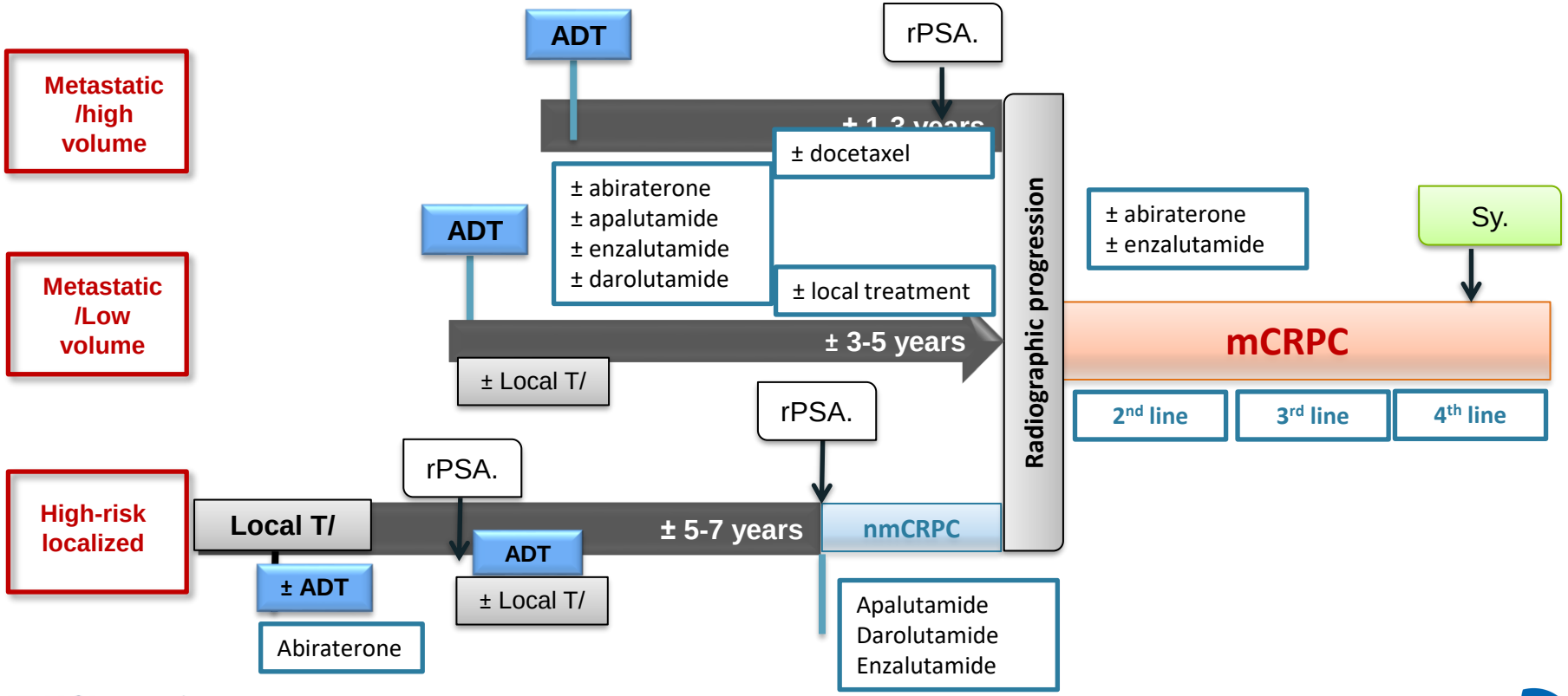
Advanced PCa in 2022



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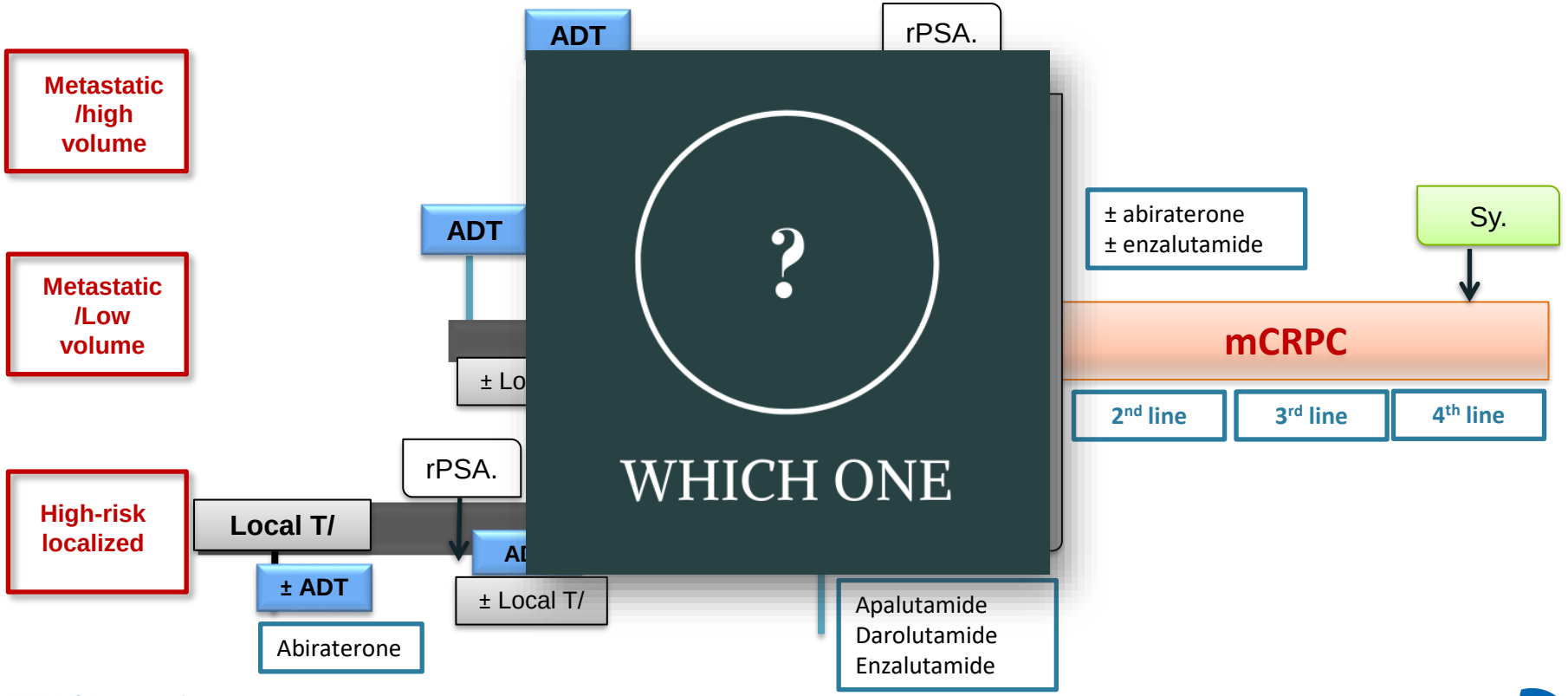
Advanced PCa in 2022



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- Market authorisation, availability and affordability.
- Efficacy.
- Mode of administration and convenience
- Side-effect profile
- Patient profile
- Drug-drug interactions

The conundrum of EMA authorization and local reimbursement…

DRUG	mHSPC	High-risk nmCRPC	mCRPC
Abiraterone*	Only High risk	no	yes
Apalutamide	yes	yes	no
Darolutamide	Yes, but with docetaxel	yes	no
Enzalutamide	yes	yes	yes

- Level 3 evidence FFS/OS from Stampede but no label extension

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Drug approved for ARpI naive mCPRC in 2022

	HR	95% CI; *P* value
Abiraterone/P vs. placebo/P (post-docetaxel)[1]	0.74	0.64–0.86; *P*<0.001
Abiraterone/P vs. placebo/P (pre-docetaxe)[2]	0.81	0.70–0.93; *P*=0.003
Enzalutamide vs. placebo (post-docetaxe)[3]	0.81	0.53–0.75; *P*<0.001
Enzalutamide vs. placebo (pre-docetaxe)[4]	0.81	0.60–0.84; *P*=0.001

CRPC: castration-resistant prostate cancer; DOC: docetaxel; P: prednisone; q3w: every 3 weeks; ARTA: abiraterone or enzalutamide

1. Fizazi K et al. Lancet Oncol 2012;13:983-92; 2. Ryan C et al. Lancet Oncol 2015;16:152-60; 3. Scher HI et al. N Engl J Med 2012;367:1187-97; 4. Beer C et al. N Engl J Med 2014;371:424-33; 5. Tannock IF et al. N Eng J Med 2004;2351:1502-12; 6. de Bono JS et al. Lancet 2010;76: 1147-54; 7. Kantoff PW et al. N Engl J Med 2010;363:411-22; 8. Parker et al. N Engl J Med 2013;369:213-23; 9. Hussain M. et al N Engl J Med 2020; 383:2345-2357

Drugs approved for nmCRPC in 2022

MFS/FFS endpoint	n	HR for MFS	95% CI; P value	OS	95% CI; P value
Apalutamide[1] (SPARTAN)	1207	0.28	0.23–0.35; <0.001	0.78[4]	0.64–0.96; 0.016
Enzalutamide[2] (PROSPER)	1401	0.29	0.24–0.35; <0.001	0.73[5]	0.61–0.89; 0.001
Darolutamide[3] (ARAMIS)	1509	0.41	0.34–0.50; <0.001	0.69[6]	0.53–0.88; 0.003

*High-risk according to PSA DT.

1. Smith MR, et al. N Engl J Med. 2018;378(15):1408–1418; 2. Hussain M, et al. N Engl J Med. 2018;378(26):2465–2474;
3. Fizazi K, et al. N Engl J Med. 2019;380(13):1235–1246; 4. Smith MR, et al. Eur Urol. 2020;S0302–2838(20):30628–X;
5. Sternberg CN, et al. J Clin Oncol. 2020;38(suppl 15):5515; 6. Fizazi K, et al. N Engl J Med. 2020;383(11):1040–1049.

AR, androgen receptor; CI, confidence interval; DT, doubling time; FFS, failure-free survival; HR, hazard ratio; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen.

Drugs approved for mHSPC in 2022

Agent	Study	n	HR (95%CI)	p
Abiraterone /P	LATITUDE[1]	1199	0.62 (0.51 - 0.76)	<0.001
	STAMPEDE ITT[2]	1917	0.63 (0.52 - 0.76)	<0.001
	PEACE 1 ITT[3]	1172	0.82 (0.69-0.98)	0.030
	PEACE 1 Docetaxel[3]	710	0.75 (0.59-0.95)	0.017
Apalutamide	Titan[4]	1052	0.65 (0.53 - 0.79)	<0.001
Enzalutamide	ENZAMET[5]	1125	0.67 (0.52 - 0.86)	0.002
	ARCHES[6]	1150	0.66 (0.53-0.81)	<0.0001
Darolutamide	ARASENS Docetaxel[7]	1306	0.68 (0.57-0.80)	<0.001

ITT: Intent to treat; HR: hazard ration; CI: confidence interval

1) Fizazi, K. et al. 2017 27;377(4):352-360; 5) James, N. D. et al.. NEJM 2017 27;377(4):338-351; 3) Fizazi K et al. ESMO 2021; 4)Chi K. et al. JCO 2021 39(20):2294-2303, 5) Davis ID. Et al. NEJM 2019 11;381(2):121-131. 6) Amstrong A. et al An. Onc. (2021) 32 (suppl_5): S1283-S1346., 10) Smith et al. NEJM 2022 Feb 17. doi: 10.1056/NEJMoa2119115, 7) Parker et al.; Lancet. 2018 Dec 1;392(10162):2353-2366.

- Market authorisation, availability and affordability.
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Convenience…

Abiraterone	• 2 times 500 mg tablets without food (No food should be eaten for at least 2 hours before and for 1 hour after). With prednisone 5 mg BID in mCRPC and 5 mg OD in mHNPC . • Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly. Measure ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter.

Zytiga ® Summary of Product Characteristics (SmP); Xtandi®, Erleada®, Nubequa® Summary of Product Characteristics (SmP) ;

Abiraterone and the prednisone Paradox

		mHNPC[1]	mCRPC[2]
Prednisone dose		5 mg OD	5 mg BID
Hypertension	All grade (%)	37	17
	≥ G3 (%)	20	2
Hypokalaemia	All grade (%)	20	22
	≥ G3 (%)	10	4

1) Fizazi, K. et al. 2017 27;377(4):352-360; 2) Ryan et al, N Engl J Med. . 2013 Jan 10;368(2):138-48.

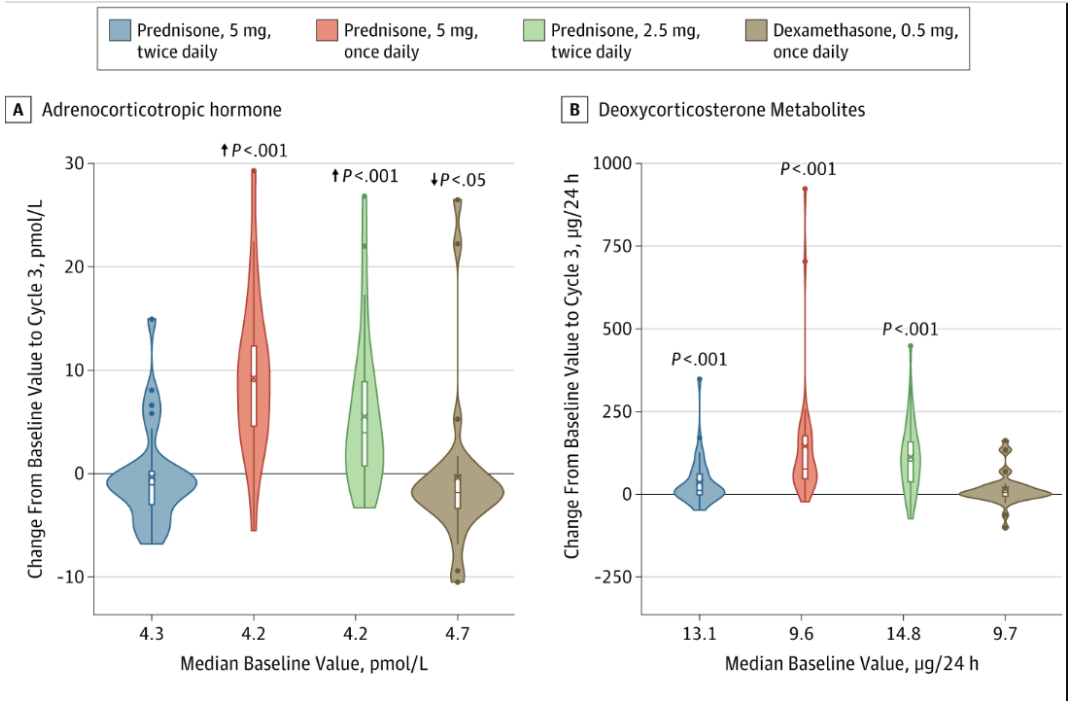
Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for MCRPC: A Randomized, Open-label Phase 2 Study

Table. Primary End Point: Mineralocorticoid Excess Adverse Events During the First 24 Weeks

Variable	Treatment Group[a]			
	Prednisone, 5 mg, Twice Daily (n = 34)[b]	Prednisone, 5 mg, Once Daily (n = 38)[b]	Prednisone, 2.5 mg, Twice Daily (n = 35)[b]	Dexamethasone, 0.5 mg, Once Daily (n = 37)[b]
Met the primary end point[c]				
No. (%)	24 (71)	14 (37)	21 (60)	26 (70)
95% CI	(54-83)	(23-53)	(44-74)	(54-83)
Investigator reported an adverse event				
Grade ≥2 hypertension and grade ≥1 hypokalemia, No. (%)	2 (6)	1 (3)	3 (9)	2 (5)
Grade ≥2 hypertension alone, No. (%)	7 (21)	18 (47)	10 (29)	6 (16)
Grade ≥1 hypokalemia alone, No. (%)	1 (3)	5 (13)	1 (3)	3 (8)

Attard et al. JAMA Oncol. . 2019 Aug 1;5(8):1159-1167.

Assessment of the Safety of Glucocorticoid Regimens in Combination With Abiraterone Acetate for MCRPC: A Randomized, Open-label Phase 2 Study



Attard et al. JAMA Oncol. . 2019 Aug 1;5(8):1159-1167.

Convenience…

Abiraterone	• 2 times 500 mg tablets without food (No food should be eaten for at least 2 hours before and for 1 hour after). With prednisone 5 mg BID in mCRPC and 5 mg OD in mHNPC . • Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly. Measure ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter.
Apalutamide	• The recommended dose is 240 mg (four 60 mg tablets) as an oral single daily dose • is not recommended in patients with a history of seizures or other predisposing factors.
Enzalutamide	• Four 40 mg capsules (160 mg) orally with or without food. • No additional tests, except if is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring. • Relative contra-indications: patients who had a seizure, with predisposing factors for seizure, or using concomitant medications that may lower the seizure threshold.
Darolutamide	• The recommended dose is s 600 mg darolutamide (two tablets of 300 mg) taken twice daily.

Zytiga ® Summary of Product Characteristics (SmP); Xtandi®, Erleada®, Nubequa® Summary of Product Characteristics (SmP) ;

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AE leading to permanent discontinuation of a trial agent

mHNPC

In % of patients discontinuing for AE	Active drug	Comparator
Abiraterone (Latitude)[1]	12	10
Apalutamide (Titan)[2]	8.0	5.3
Enzalutamide (Arches)[3]	7.2	5.2
Darolutamide (Arasens)[4]	13.6	10.6

nmCRPC

In % of patients discontinuing for AE	Active drug	Comparator
Apalutamide (Spartan)[5]	15	7.3
Enzalutamide (Prosper)[6]	17	9
Darolutamide (ARAMIS)[7]	8.9	8.7

ITT: Intent to treat; HR: hazard ration; CI: confidence interval

1) Fizazi, K. et al. 2017 27;377(4):352-360; 2)Chi K. et al. JCO 2021 39(20):2294-2303, 8) Davis ID. Et al. NEJM 2019 11;381(2):121-131. 3) Amstrong A. et al An. Onc. (2021) 32 (suppl_5): S1283-S1346., 4) Smith et al. NEJM 2022 Feb 17. doi: 10.1056/NEJMoa2119115, 5) 1.Sternberg CN, et al. NEJM 2020;382:2197–2206, 2. Smith MR et al. Eur Urol 2020;S0302-2838(20)30628-X [Epub ahead of print], 3. Fizazi K, et al. NEJM 2020; 383(11):1040–1049

Can we say that a drug is better tolerate?

Patients have similar characteristics at baseline in the three trials.

Characteristic	nmCRPC		
Trial	SPARTAN	PROSPER	ARAMIS
Tested drug	Apalutamide	Enzalutamide	Darolutamide
ClinicalTrials.gov	NCT01946204	NCT02003924	NCT02200614
Publication (reference)	2018 (18)	2018 (17)	2019 (16)
All patients,[b] *n*	1201	1395	1508
In placebo arm,[b] *n*	398	465	554
Follow-up, median [months]	20	17	18
Scheduled study visits over median follow-up,[c] *n*	12	6	6
Patient characteristics			
Age, median (range) years	74 (52–97)	73 (53–92)	75 (50–92)
Excellent performance status (ECOG-PS 0), %	77.8	81.6	70.6
Disease characteristics			
PSA, median, ng/ml	8.0	10.2	9.7
PSA doubling time, median, months	4.5	3.6	4.7
Cancer diagnosis to enrollment, median years	7.9	–	7.0
High-volume disease, %	0	0	0
Bone-sparing agent use, %	10	10	6

Adverse event reporting differs widely between trials

	nmCRPC		
Characteristic	SPARTAN	PROSPER	ARAMIS
AE methods			
CTCAE version	4.0	4.03	4.03
Risk cut-off for AEs[a]	≥ 15%	≥ 5%	≥ 5%
AEs of interest,[b] *n*	5	7	14
AEs reported,[c] *n*	13	23	26
AE rates reported[d]	Yes	No	Yes
Attribution reported[e]	Yes	No	No
AEs in placebo arm			
Fatigue, Absolute risk (95% CI), %	21.1 (17.4–25.4)	13.8 (10.9–17.2)	8.7 (6.6–11.3)
Hypertension, Absolute risk (95% CI), %	19.8 (16.2–24.0)	5.2 (3.5–7.6)	5.2 (3.7–7.4)
Any AE, Absolute risk (95% CI), %	93.2 (90.3–95.3)	77.4 (73.4–81.0)	76.9 (73.2–80.2)
Any grade 3–4 AE, Absolute risk (95% CI), %	34.2 (29.7–39.0)	23.4 (19.8–27.5)	19.5 (16.4–23.0)
Relative risk of all grade 3–4 AEs[f] (95% CI)	1.00 (Reference)	0.44 (0.22–0.88)	0.45 (0.23–0.86)
AEs by drug *vs.* placebo			
Fatigue, Relative risk (95% CI)	1.44 (1.16–1.79)	2.37 (1.85–3.03)	1.39 (1.01–1.92)
Hypertension, Relative risk (95% CI)	1.25 (0.99–1.58)	2.32 (1.51–3.56)	1.26 (0.82–1.93)

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Drago J. et al J. Natl Cancer Inst. 2020 Aug 28; DOI: 10.1093/jnci/djaa134

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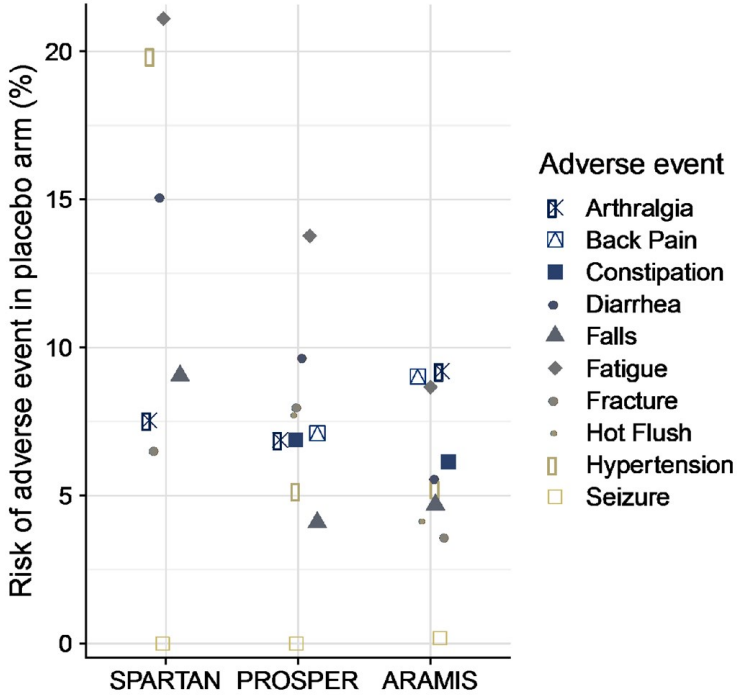
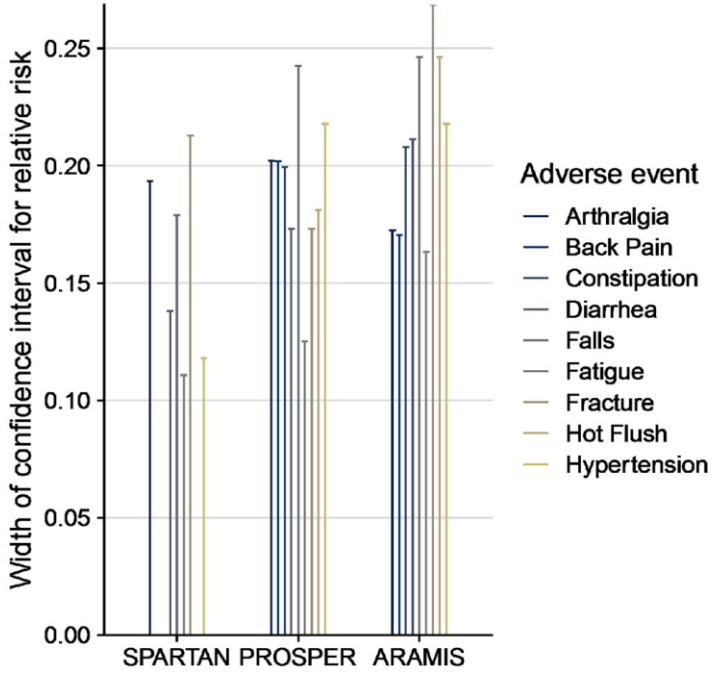
Can we say that a drug is better tolerate?

Absolute rate of adverse event in the placebo groups differs between trials



Lower event numbers decrease confidence in relative risk measure.



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Drago J. et al J. Natl Cancer Inst. 2020 Aug 28; DOI: 10.1093/jnci/djaa134

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Can we say that a drug is better tolerate?

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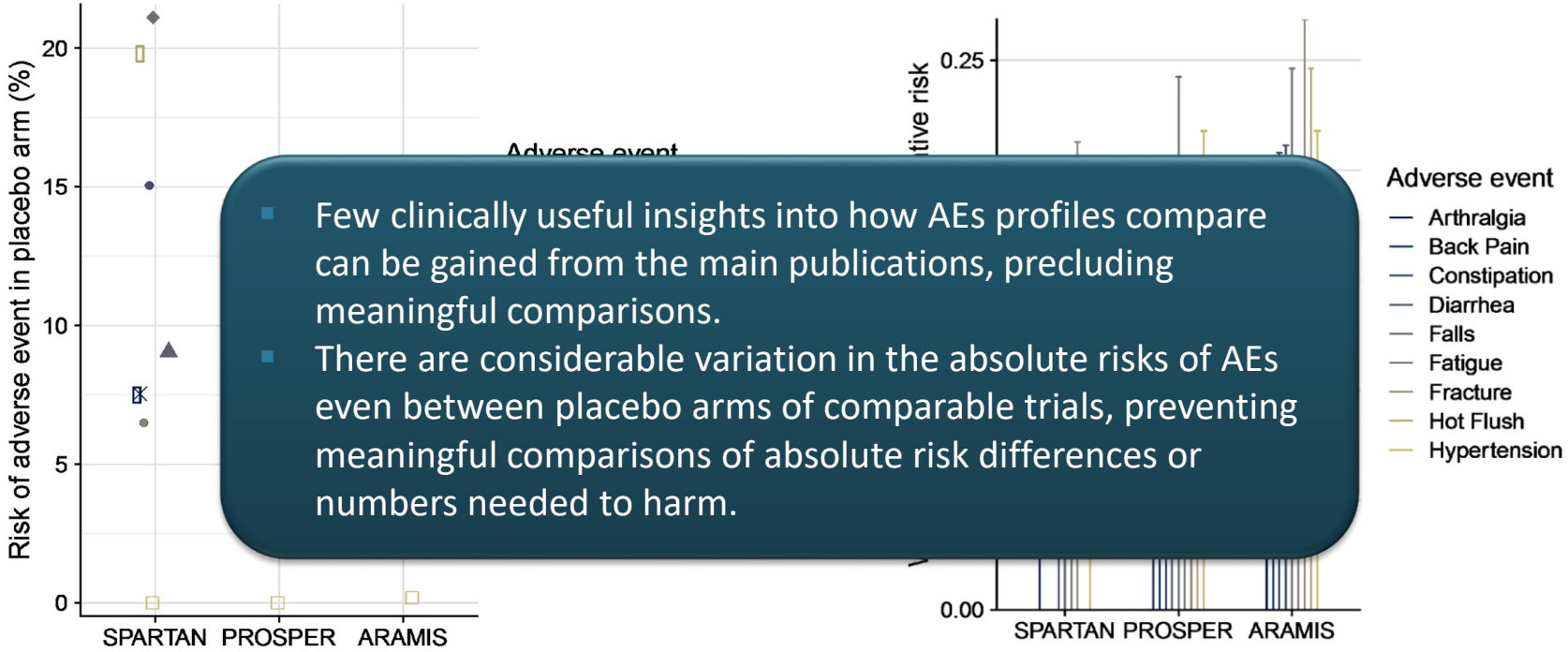

- Few clinically useful insights into how AEs profiles compare can be gained from the main publications, precluding meaningful comparisons.
- There are considerable variation in the absolute risks of AEs even between placebo arms of comparable trials, preventing meaningful comparisons of absolute risk differences or numbers needed to harm.

Drago J. et al J. Natl Cancer Inst. 2020 Aug 28; DOI: 10.1093/jnci/djaa134

Side Effect profile of abiraterone

Adverse Event	Abiraterone Group (N = 597)			Placebo Group (N = 602)		
	number of patients (percent)					
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Graded adverse events†						
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)
Hypokalemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)
ALT increased	98 (16)	31 (5)	2 (<1)	77 (13)	8 (1)	0
Hyperglycemia	75 (13)	26 (4)	1 (<1)	68 (11)	18 (3)	0
AST increased	87 (15)	25 (4)	1 (<1)	68 (11)	9 (1)	0
Bone pain	74 (12)	20 (3)	0	88 (15)	17 (3)	0
Cardiac disorder						
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0
Anemia	54 (9)	12 (2)	3 (1)	85 (14)	26 (4)	1 (<1)
Back pain	110 (18)	14 (2)	0	123 (20)	19 (3)	0
Fatigue	77 (13)	10 (2)	0	86 (14)	14 (2)	0
Spinal-cord compression	14 (2)	12 (2)	0	12 (2)	7 (1)	3 (<1)

Fizazi, K. et al. 2017 27;377(4):352-360

Side Effect profile of abiraterone

Adverse Event	Abiraterone Group (N = 597)			Placebo Group (N = 602)		
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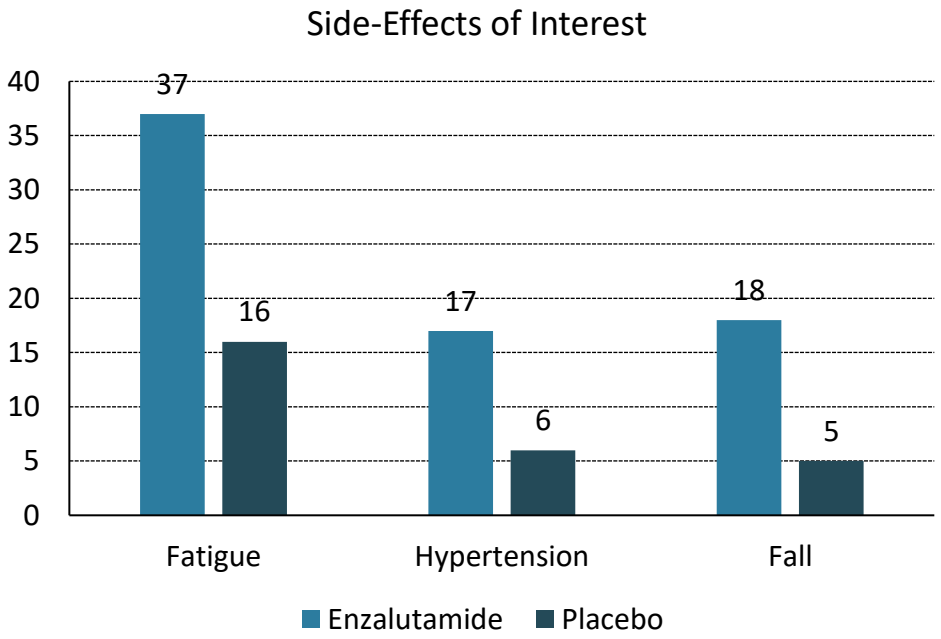
Cardiac disorder						
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0
Anemia	54 (9)	12 (2)	3 (1)	85 (14)	26 (4)	1 (<1)
Back pain	110 (18)	14 (2)	0	123 (20)	19 (3)	0
Fatigue	77 (13)	10 (2)	0	86 (14)	14 (2)	0
Spinal-cord compression	14 (2)	12 (2)	0	12 (2)	7 (1)	3 (<1)

Fizazi, K. et al. 2017 27;377(4):352-360

Side Effect profile and relative contra-indications of Enzalutamide (from PROSPER).

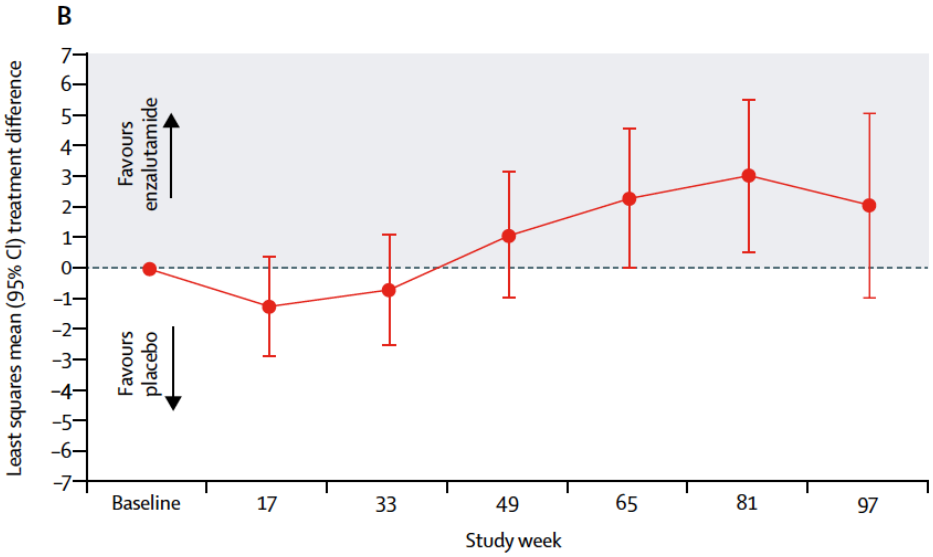
	Enzalutamide (N=930)		Placebo (N=465)	
Grade (n,(%)	All	≥3	All	≥3
Fatigue	348 (37)	38 (4)	73 (16)	3 (1)
Hypertension	161 (17)	54 (6)	27 (6)	10 (2)
Asthenia	94 (10)	16 (2)	32 (7)	1 (<1)
Back pain	120 (13)	4 (<1)	38 (8)	1 (<1)
Dizziness	112 (12)	5 (1)	27 (6)	0
Diarrhea	112 (12)	5 (1)	47 (10)	2 (<1)
Nausea	125 (13)	4 (<1)	42 (9)	0
Hot flush	132 (14)	1 (<1)	38 (8)	0
Fall	164 (18)	22 (2)	25 (5)	4 (1)
Arthralgia	119 (13)	1 (<1)	36 (8)	1 (<1)
Constipation	121 (13)	3 (<1)	39 (8)	2 (<1)
Hematuria	97 (10)	29 (3)	41 (9)	17 (4)
Headache	103 (11)	4 (<1)	23 (5)	0
Decreased appetite	108 (12)	4 (<1)	22 (5)	2 (<1)



Sternberg CN, et al. N Engl J Med 2020;382:2197–2206

In PROSPER, enzalutamide maintains QoL measure by Total FACT-P score

Treatment difference in least squares mean change from baseline

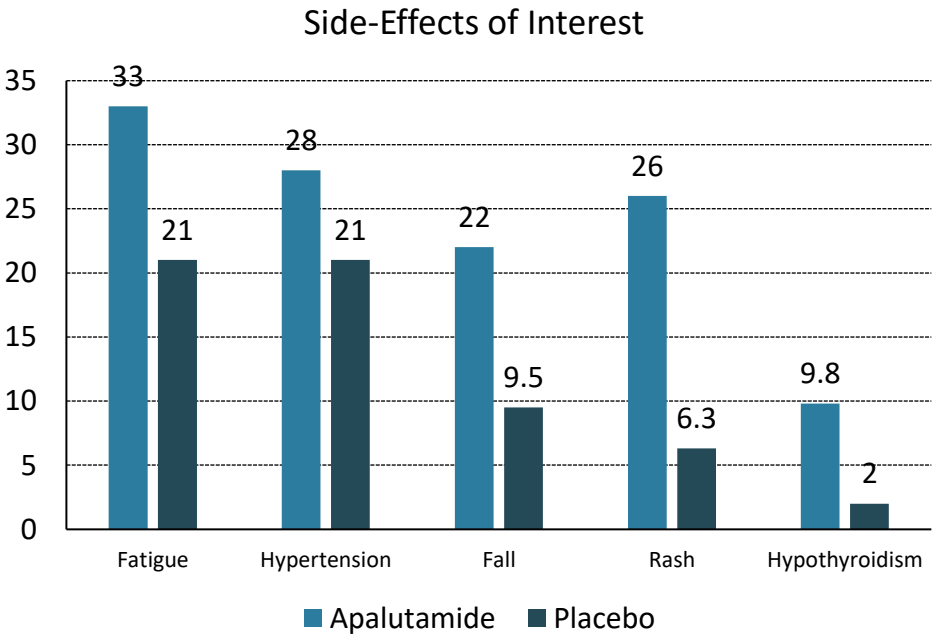


Number at risk							
Enzalutamide	..	815	718	621	522	427	354
Placebo	..	403	329	239	183	139	90

FACT-P: Functional Assessment of Cancer Therapy-Prostate.
B. Tombal et al. Lancet Oncol. 2019 20(4); 556-569, 2019

Side Effect profile apalutamide (from SPARTAN)

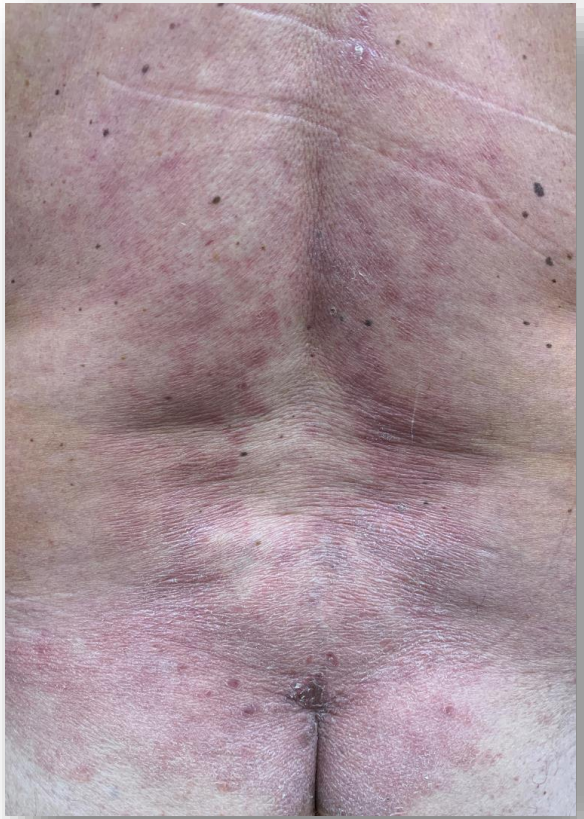
	Apalutamide (n = 803)		Placebo (n = 398)	
Any AE, n (%)	781 (97)		373 (94)	
Grade 3 or 4	449 (56)		145 (36)	
Any serious	290 (36)		99 (25)	
leading to discontinuation	120 (15)		29 (7.3)	
leading to death	24 (3.0)		2 (0.5)	
AE of Interest Grade (n (%))	All	3–4	All	3–4
Fatigue (%)	33	0.9	21	0.3
Hypertension (%)	28	16	21	12
Diarrhea (%)	23	1.5	15	0.5
Skin Rash	26	5.2	6.3	0.3
Fall (%)	22	2.7	9.5	0.8
Nausea (%)	20	0	16	0
Arthralgia (%)	20	0.4	8.3	0
Weight decreased (%)	20	1.5	6.5	0.3
Back pain (%)	18	1.4	15	1.5
Hot flush (%)	15	0	8.5	0
Hypothyroidism	9.8	0	2	0

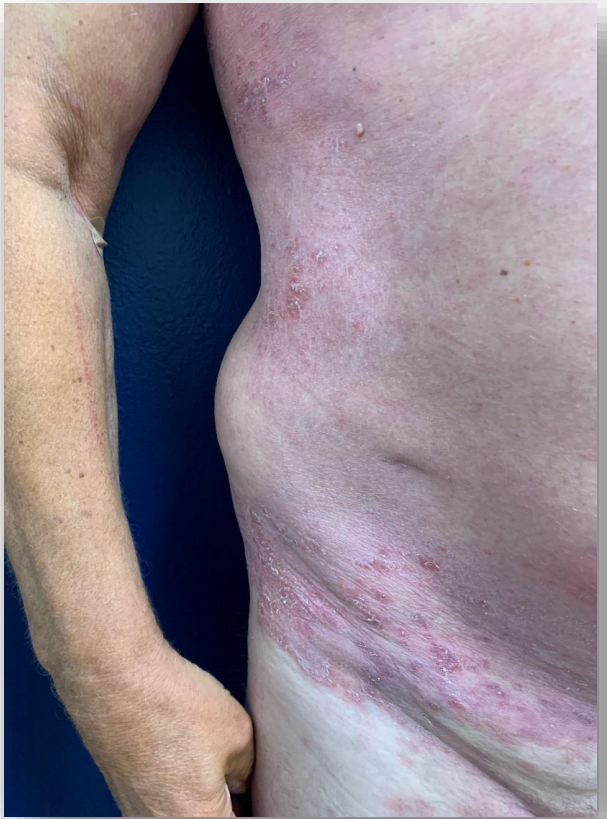


AE = adverse event;

Smith MR et al. *Eur Urol* 2020;S0302-2838(20)30628-X [Epub ahead of print]

Apalutamide Rash





Enzalutamide and Apalutamide: In Vitro Chemical Reactivity Studies and Activity in a Mouse Drug Allergy Model

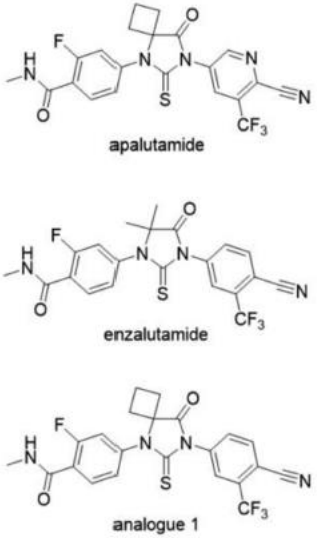
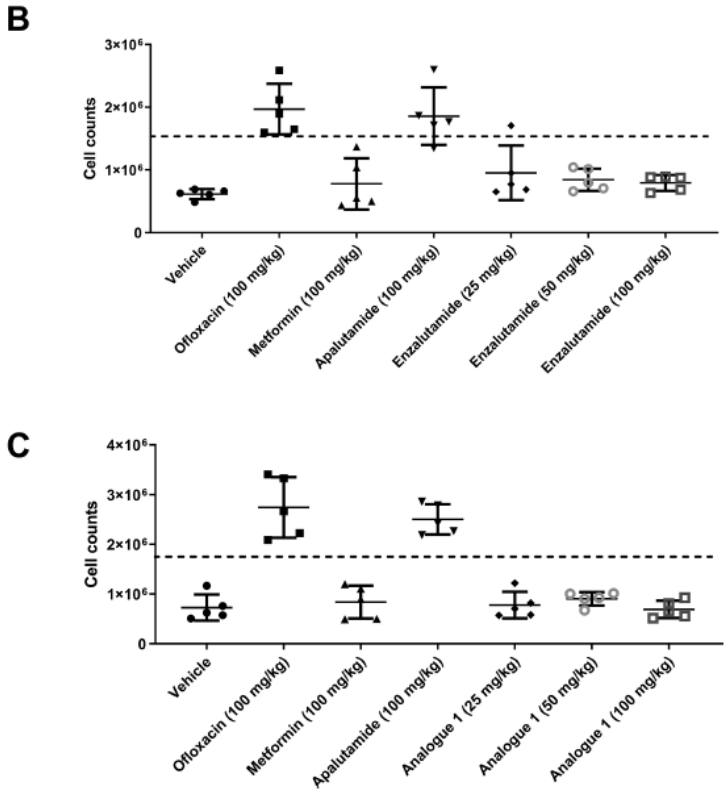


Figure 1. Structures of apalutamide, enzalutamide, and analogue 1.



Ji et al. Chem Res Toxicol. . 2020 Jan 21;33(1):211-222.

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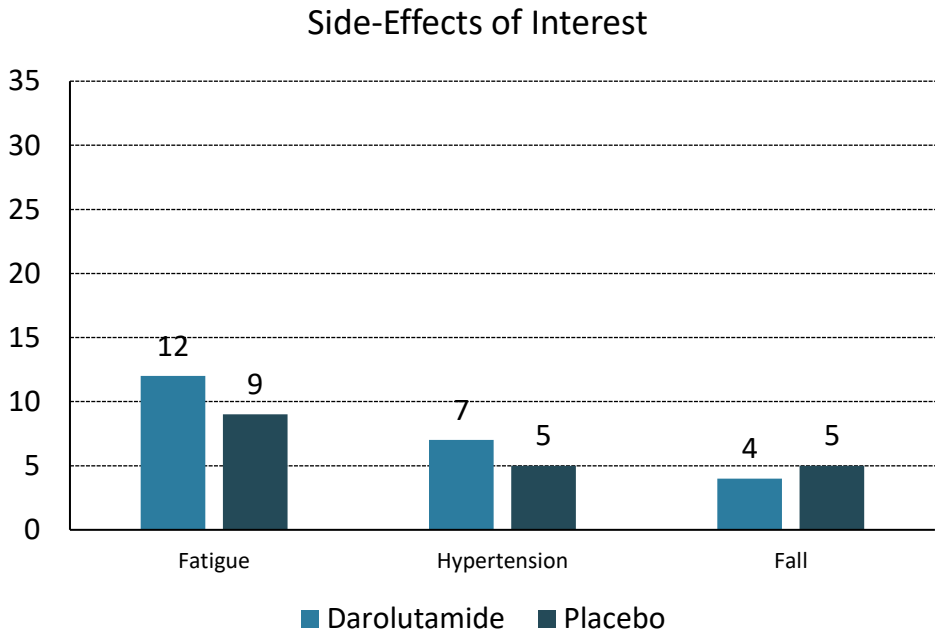
The trade-off is that the active drugs are started earlier with a potential risk of increasing toxicity.

Adverse event, n (%)	ARAMIS[1] Darolutamide N=954 All Gra.	Darolutamide N=954 Gra.≥3	Placebo N=554 All Gra.	Placebo N=554 Gra.≥3
Any	83	25	77	20
Serious	25	16	20	13
Leading to discontinuation	9	3	9	4
Associated with death	4		3	
Adverse events of interest				
Fatigue	12	<1	9	<1
Hypertension	7	3	5	2
Fall	4	<1	5	<1
Fracture	4	<1	4	<1
Nausea	5	<1	6	0 (0)
Diarrhea	7	0	6	<1
Seizure	<1	0	<1	0
Rash				
Hypothyroidism				



Gra: grade; 1. Fizazi K, et al. N Engl J Med. 2019. DOI:10.1056/NEJMoa1815671

- Market authorisation, availability and affordability.
- Efficacy.
- Mode of administration and convenience
- Side-effect profile
- Patient profile
- Drug-drug interactions

What is your preferred choice between Abiraterone and Enzalutamide at any time in the treatment sequence in men with mCRPC if all options are available in case of the following medical situations?

	Enzalutamide	Abiraterone	Either
Stable brain metastases	6%	73%	10%
History of falls	2%	94%	4%
Baseline significant fatigue	6%	88%	6%
Baseline significant neurocognitive impairment	4%	84%	10%
Long QTc-syndrome or men on not replaceable drugs with potential QT prolongation	27%	31%	24%
Diabetes mellitus requiring prescription drug therapy	84%	6%	10%
Cardiac ejection fraction below 45-50%	63%	6%	27%
Active liver dysfunction	68%	8%	14%

Gillessen S et al. Eur Urol. 2018 Feb;73(2):178-211.

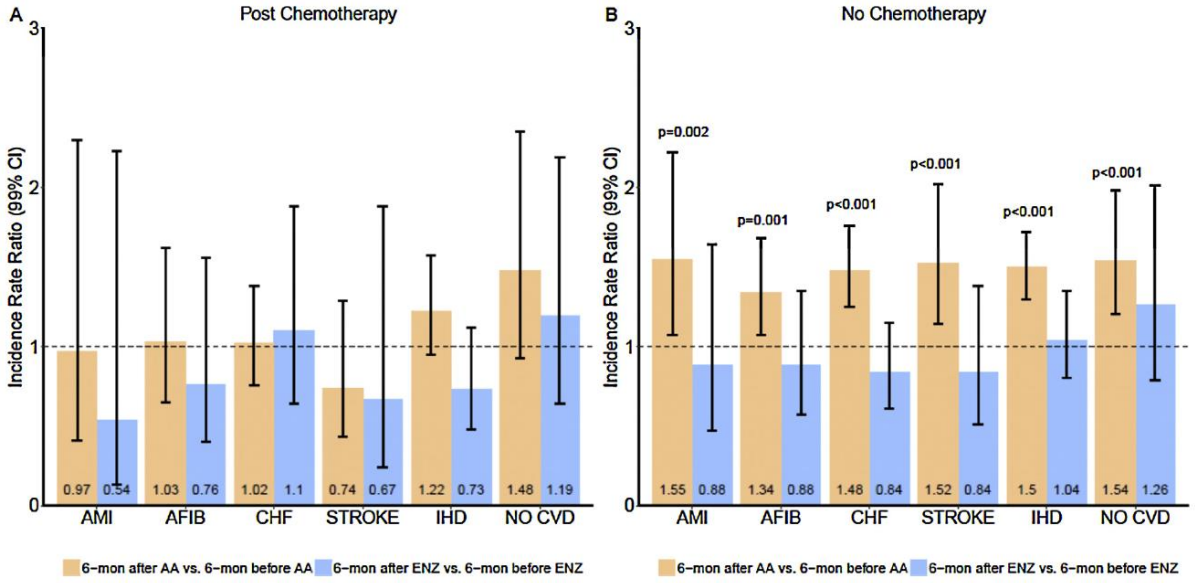
CV exclusions criteria

Study	Criteria
STAMPEDE[1]	Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment. History of MI 5%, Cerebrovascular disease 2%, angina 4%, congestive heart failure >1%
Latitude[2]	Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of <50% at baseline
ENZAMET[3]	Significant CV disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (NYHA functional capacity class II or greater, Refer to Appendix 6), ongoing arrhythmias of Grade >2 [NCI CTCAE, version 4.03], thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
TITAN[4]	Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism), or clinically significant ventricular arrhythmias within 6 months prior to randomization

1)James, N. D. et al.. NEJM 2017 27;377(4):338-351; 2)Fizazi, K. et al. 2017 27;377(4):352-360;3) Chi K. et al. NEJM 2019 4;381(1):13-24; 4) Davis ID. Et al. NEJM 2019 Jun 2. doi: 10.1056; 8)

Clinical outcomes among patients treated with abiraterone acetate for advanced prostate cancer with pre-existing cardiovascular conditions.

- Population-based study from SEER-Medicare treated with AA in 2011-2014.
- The primary endpoints were 6-month overall mortality and changes in hospitalization rates following AA initiation.
- 2845 patients with Abiraterone acetate and 1031 with Enzalutamide, 67% having at least one pre-existing CVD.



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Lu-Yao G. et al, Eur Urol. 2019 Aug 2. pii: S0302-2838(19)30585-8. doi: 10.1016/j.eururo.2019.07.031.
AA = abiraterone; AMI = acute myocardial infarction; AFIB = atrial fibrillation; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; ENZ = enzalutamide; IHD = ischemic heart disease.

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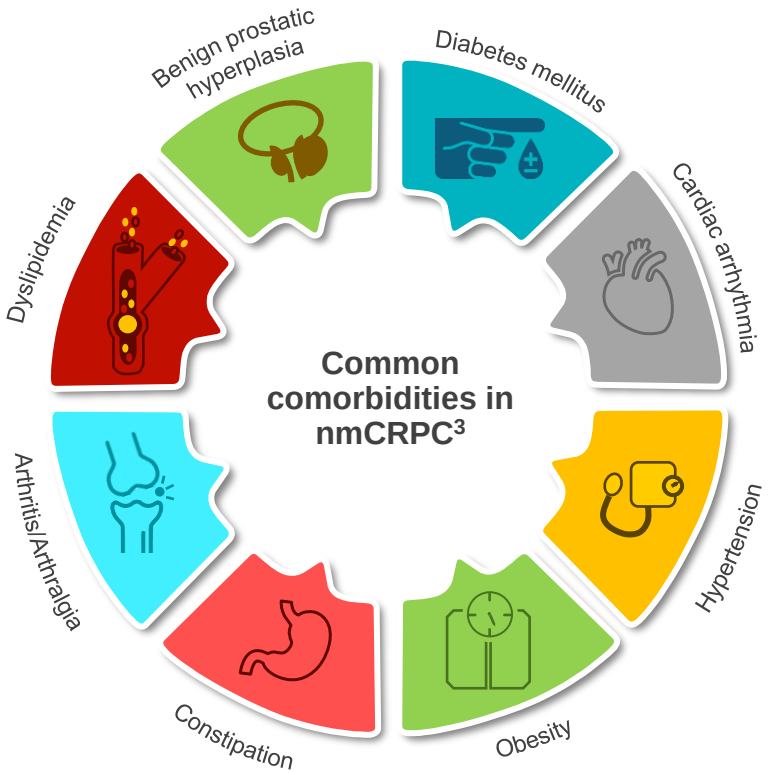
- Market authorisation, availability and affordability.
- Efficacy.
- Mode of administration and convenience
- Side-effect profile
- Patient profile
- Drug-drug interactions

Always ask your pharmacist to check for drug-drug-interaction.



Almost all patients with nmCRPC have comorbidities that are managed with concomitant medications[2,3]

Examples of medications for common comorbidities in patients with nmCRPC[3]

Cardiovascular disease

- **Atenolol** (OATP1B1 substrate)
- **Losartan** (CYP2A4/CYP2C9 substrate)
- **Clopidogrel** (strong CYP2C8 inhibitor)
- **Rivaroxaban** (CYP3A substrate)
- **Rosuvastatin** (BCRP/OATP1B1 substrate)
- **Gemfibrozil** (strong CYP2C8 inhibitor)
- **Propranolol** (CYP2C19 substrate)
- **Amlodipine** (CYP3A4 substrate)
- **Digoxin** (P-gp substrate)
- **Propafenone** (CYP3A4 substrates)

Pain and Inflammation

- **Fentanyl, oxycodone** (CYP3A4/P-gp substrates)

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1. Mateo J, et al. *Eur Urol*. 2019;75(2):285-293. 2. Pirschel C. ONSVoice. https://voice.ons.org/news-and-views/comorbidities-in-cancer-patient-care. Published January 30, 2017. Accessed May 14, 2019. 3. Shore N, et al. *Target Oncol*. 2019;14:527-539.

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Clinically Relevant Drug-Drug Interactions

A. Effects of enzalutamide, apalutamide, or darolutamide on the exposure of CYP enzyme or transporter substrates

Enzyme/transporter	Apalutamide [13, 14]	Enzalutamide [11, 12]	Darolutamide [23]	Examples of drugs [4, 29, 30, 32, 33]
	Effect on substrate exposure			
CYP3A4	↓	↓	–	**Analgesics:** fentanyl, oxycodone **Anticoagulants:** rivaroxaban **Antihypertensives / CV agents:** amlodipine, amiodarone, dronedarone, felodipine, nisoldipine, ranolazine **Antiplatelet agents:** ticagrelor **CNS drugs:** alprazolam, buspirone, donepezil, midazolam, quetiapine, triazolam **Lipid-modifying agents:** lovastatin, simvastatin **Urological agents:** avanafil, darifenacin, dutasteride, oxybutynin, solifenacin, tamsulosin, tolterodine, vardenafil
CYP2C9	↓	↓	–	**Anticoagulants**: warfarin **Antidiabetics:** glimepiride **Antihypertensives:** losartan **Anti-inflammatories:** celecoxib **Lipid-modifying agents:** fluvastatin
CYP2C19	↓	↓	–	**Beta-blockers:** propanolol **CNS drugs:** diazepam **PPIs**: lansoprazole, omeprazole, rabeprazole
UGT	↓	↓†	–	**Analgesics:** buprenorphine **Antiretrovirals:** zidovudine **CNS drugs:** morphine **Anti-epileptics:** valproic acid
P-gp	↓	↑↓	–	**Analgesics:** fentanyl, oxycodone **Anticoagulants:** dabigatran etexilate **CV agents:** digoxin, ranolazine
BCRP	↓	↑↓	↑‡	**CV agents:** furosemide **Lipid-modifying agents:** atorvastatin, rosuvastatin, fluvastatin **DMARDs:** sulfasalazine
OATP1B1	↓	–	↑	**Hypertension/CV agents:** atenolol **Lipid-modifying agents:** atorvastatin, pitavastatin, rosuvastatin, pravastatin **Antidiabetics:** glyburide, nateglinide, repaglinide

B. Effects of CYP enzyme or drug transporter inhibitors and inducers on the exposure of enzalutamide, apalutamide, or darolutamide

Enzyme/transporter	Apalutamide [13, 14]	Enzalutamide [11, 12]	Darolutamide [23]	Examples of drugs [4, 29, 30, 32, 33]
	Effect on exposure of apalutamide, enzalutamide or darolutamide			
Inhibitors				
CYP3A4	↑	–	↑§	**Antibiotics:** clarithromycin, erythromycin **Antifungals:** itraconazole, ketoconazole **Antihypertensives:** diltiazem, verapamil **Antiretrovirals:** indinavir, nelfinavir, ritonavir
CYP2C8	↑	↑	–	**Antibiotics (systemic):** trimethoprim **Antiplatelet agents:** clopidogrel, gemfibrozil
Inducers				
CYP3A4	–	↓‖	↓¶	**Anti-epileptics:** carbamazepine, phenobarbital **Antibiotics (systemic):** rifampicin
P-gp	–	–	↓¶	**Anti-epileptics:** carbamazepine, phenobarbital **Antibiotics (systemic):** rifampicin **Systemic corticosteroids:** dexamethasone

Shore N, et al. Target Oncol. 2019 Oct;14(5):527-539.

ARpI intensification in patients treated with ADT + docetaxel.

Study (docetaxel subgroup)	drug	n	% total	HR PFS (95% CI)	HR OS (p)	Timing docetaxel
ENZAMET[1]	Enzalutamide	503	44%	0.48 (0.37–0.62)	0.90 (0.62–1.31)	concomitant
ARCHES[2]	Enzalutamide	104	21%	0.52 (0.30-0.89)	0,74 (0.46-1.20)	sequential
TITAN[3]	Apalutamide	113	17%	0.47 (0.22–1.01)	1.12 (0.59–2.12)	sequential
PEACE 1[4]	Abiraterone	710	60%	0.50 (0.40–0.62)	0.75 (0.59-0.95)	concomitant
ARASENS[5]	Darolutamide	1305	100%		0.68 (0.57-0.80)	concomitant

ITT: Intent to treat; HR: hazard ration; CI: confidence interval

1) Davis ID. Et al. NEJM 2019 11;381(2):121-131, 2) Amstrong A. et al An. Onc. (2021) 32 (suppl_5): S1283-S1346., 3) Chi K. et al. JCO 2021 39(20):2294-2303, 4)) Fizazi K et al. ESMO 2021, 5) Smith et al. NEJM 2022 Feb 17. doi: 10.1056/NEJMoa2119115

Phase Ib Study of Enzalutamide in Combination with Docetaxel in Men with Metastatic Castration-Resistant Prostate Cancer

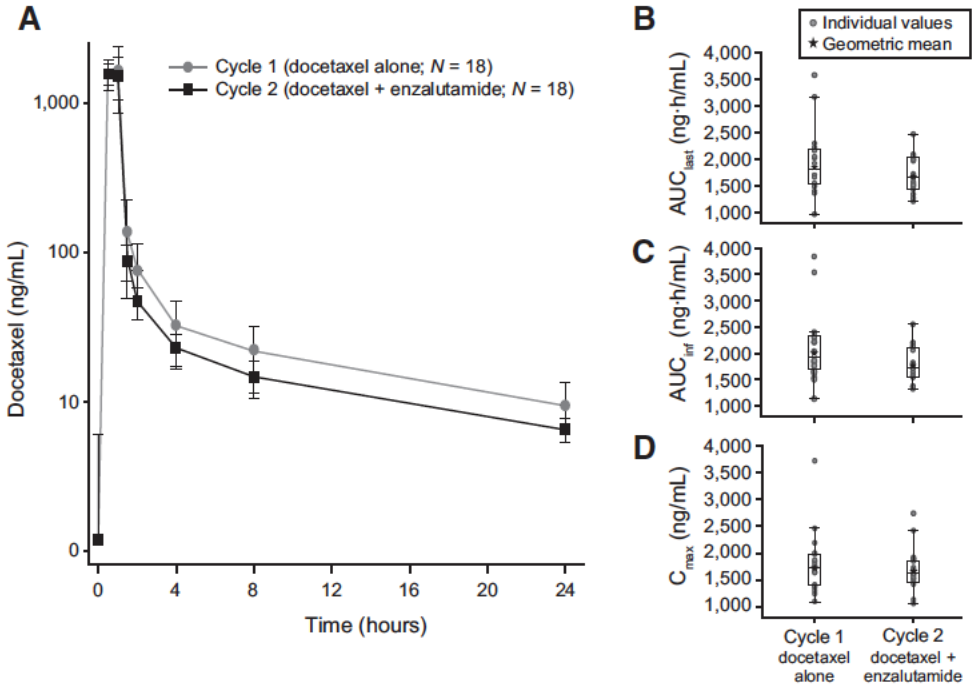

Figure 1.
Individual and mean docetaxel PK by treatment cycle. **A,** mean ± SD plasma docetaxel concentration in cycle 1 (docetaxel alone) and cycle 2 (with enzalutamide administration). Insets show individual values and geometric mean for docetaxel (**B**) AUC_{last}, (**C**) AUC_{inf}, and (**D**) C_{max}. Box plots indicate median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range.

Morris M et al. Clin Cancer Res. 2016 Aug 1;22(15):3774-81.

AR antagonists, are they all equal ?

- Licensing, availability and affordability are key drivers.
- The four available agents are equivalent in term of efficacy.
- Convenience of administration and monitoring clearly favour AR antagonists.
- In absence of direct comparison, it is difficult to ascertain which one is better tolerate. If relying on difference vs. placebo, darolutamide is attractive.
- Be careful of patients not well evaluated in clinical trials (e.g. CV disease).
- In the end, your EMR or your pharmacist may select the drug base on DDI profile