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CLINICAL REVIEW OF nmCRPC: KEY TRIALS AND ENDPOINTS

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nmCRPC, non-metastatic castration resistant prostate cancer

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INTRODUCTION

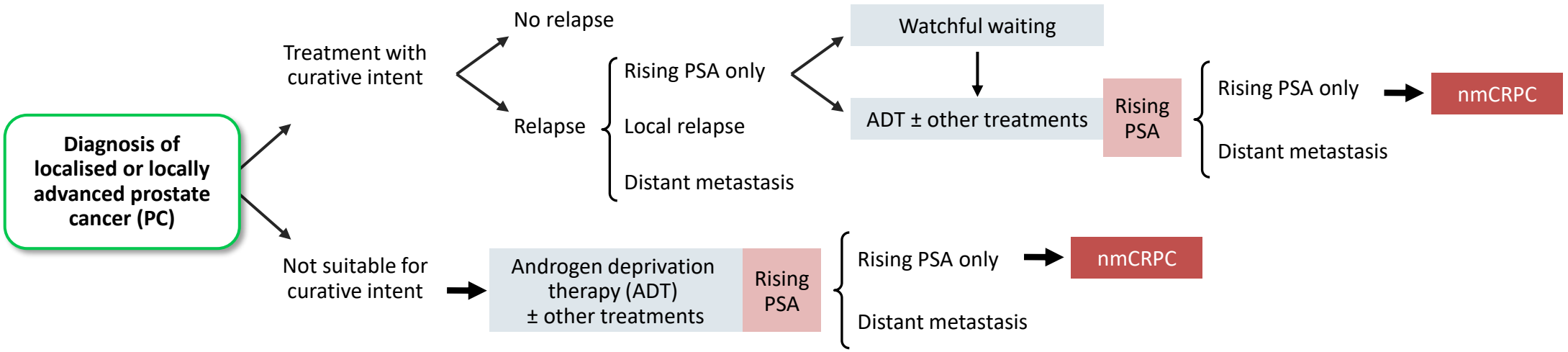
- Non-metastatic castration-resistant prostate cancer **(nmCRPC) is characterised by rising** levels of prostate-specific antigen **(PSA)** despite castration levels of testosterone, **the absence of radiographic progression, and the absence of distant metastases** (as determined by imaging)
- **Many years may elapse between detection of rising PSA levels and metastasis or death**
  - During this long survival period, patients may receive multiple therapies which could affect an overall survival (OS) endpoint
  - Metastasis-free survival (MFS) has therefore emerged as an FDA-accepted endpoint for nmCRPC clinical trials
- **Apalutamide (APA) was the first drug approval in nmCRPC**, and represents the first use of MFS as a primary endpoint to support drug approval
  - Approval was based on data from the SPARTAN trial
- Subsequently, **enzalutamide (ENZA) and darolutamide (DARO)** were also **approved by the FDA for patients with nmCRPC** on the basis of the MFS endpoints in the PROSPER and ARAMIS trials
- Here we review data from these key trials

Beaver J, et al. N Engl J Med. 2018;378:2458-60; www.accessdata.fda.gov/. Accessed 15 January 2021

THE M0 CRPC PATIENT

- Patients with nmCRPC are a heterogeneous population

Disease evolution patterns to the clinical states of nmCRPC

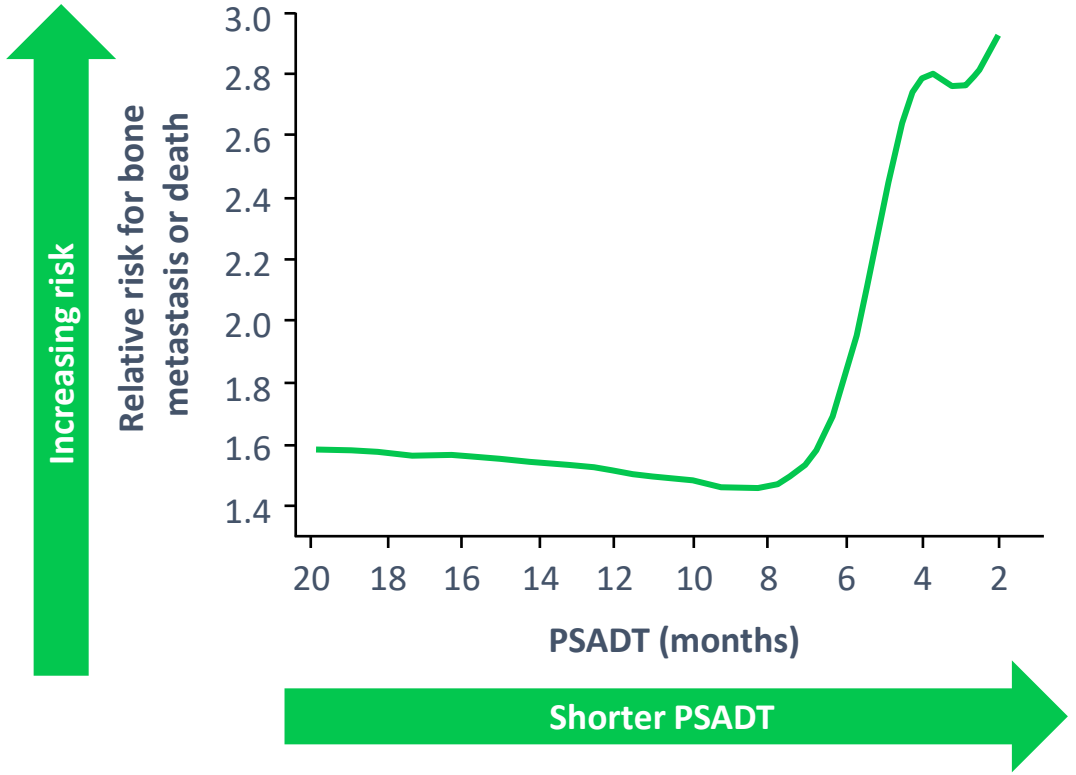


nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate specific antigen

Mateo J, et al. Eur Urol. 2019;75:285-93

STUDY POPULATION AND DESIGN: SPARTAN, PROSPER, AND ARAMIS

Patients with a (PSADT) ≤10 months
were included in all trials; these patients are at significant risk of metastases or death



PSADT, prostate specific antigen doubling time

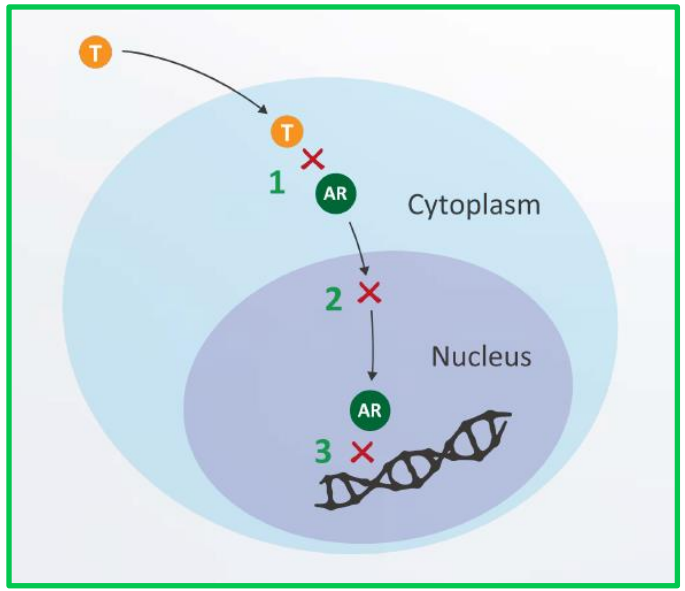
Smith MR, et al. J Clin Oncol. 2013;31:3800-6

HIGH-RISK nmCRPC: TREATMENT

- APA, DARO, and ENZA are androgen receptor (AR)-signalling inhibitors

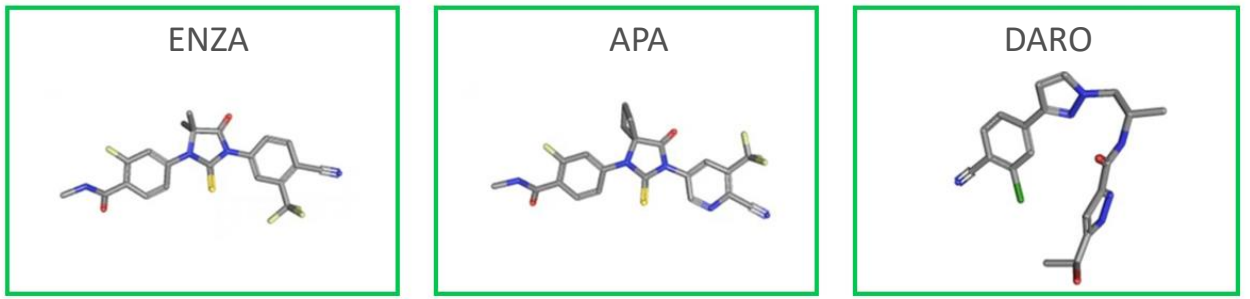
Mechanism of action[1,2]

1. Inhibit androgen binding to AR
2. Inhibit nuclear translocation of AR
3. Inhibit AR binding to DNA



Structure

- DARO is structurally distinct from APA and ENZA, and is characterised by low blood–brain barrier penetration[2,3,4]
  - This could result in less central nervous system toxicity and improved tolerability



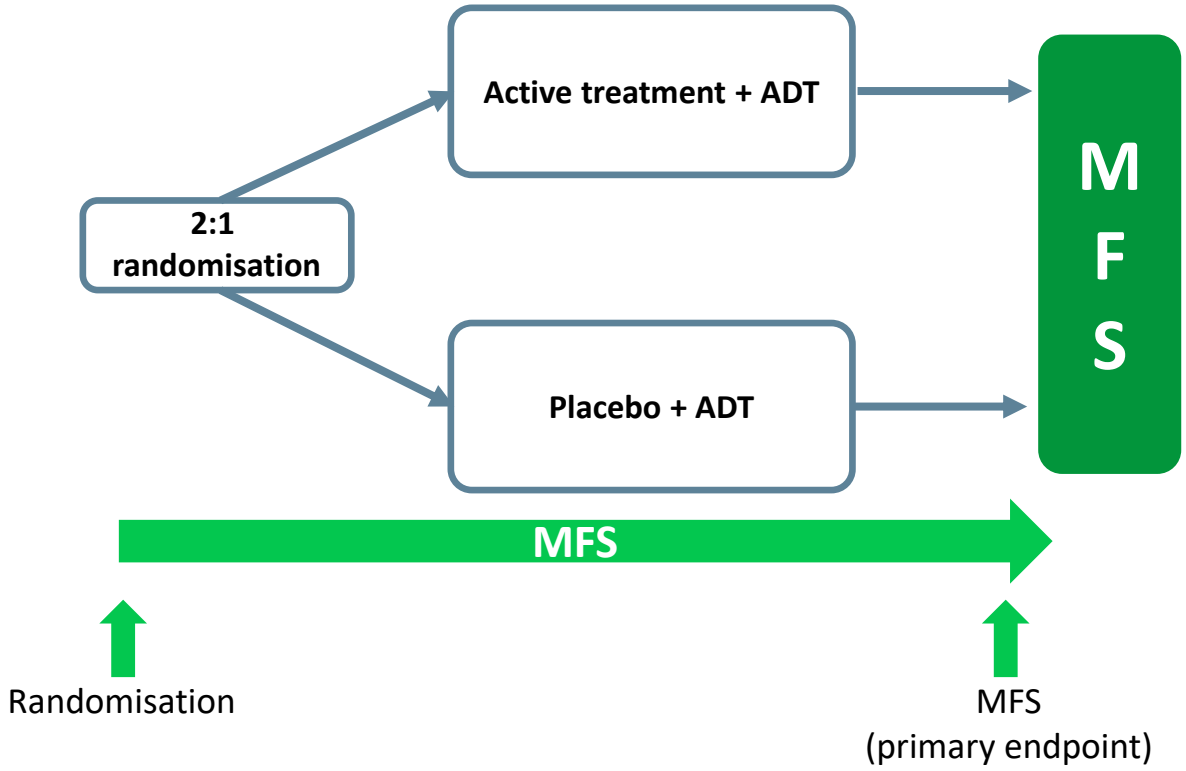
APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide

1. Tran C, et al. Science 2009;324:787-90; 2. Fizazi K, et al. Clinical Genitourinary Cancer 2018; 16: 322-40; 3. Zurth C, et al. J Clin Oncol. 2018;36 suppl 6S:345 (ASCO GU 2018 presentation); 4. Zurth C, et al. J Clin Oncol. 2019;37 suppl 7S:156 (ASCO GU 2019 presentation)

Images from PubChem database: https://pubchem.ncbi.nlm.nih.gov/

STUDY POPULATION AND DESIGN: SPARTAN,[1] PROSPER,[2] AND ARAMIS[3]

Each trial had a similar 2-arm, randomised-study design



SPARTAN	PROSPER	ARAMIS
APA	ENZA	DARO

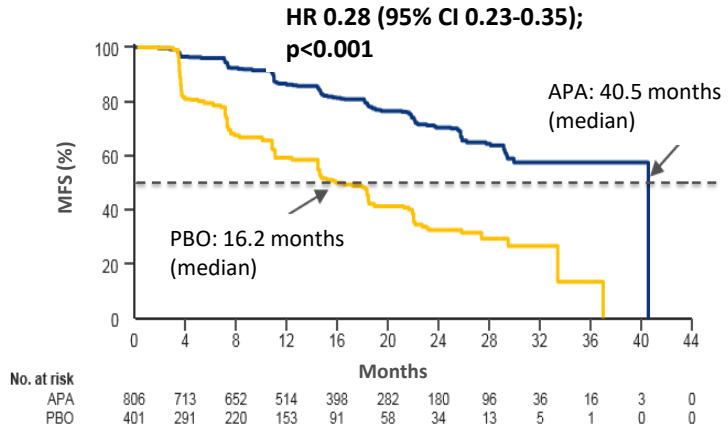
ADT, androgen deprivation therapy; APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide; MFS, metastasis-free survival

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

PRIMARY ENDPOINT: MFS

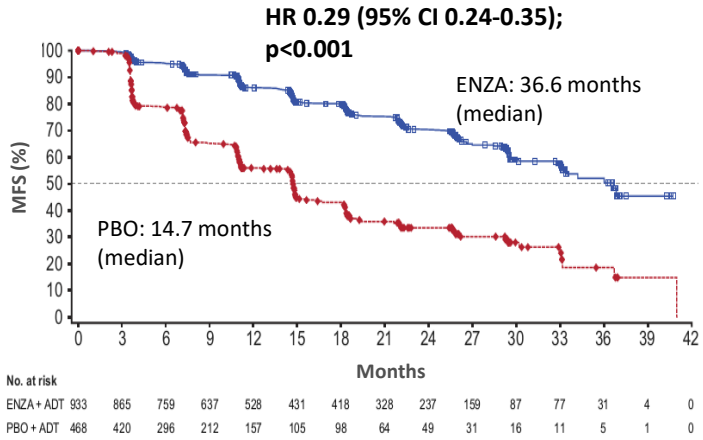
SPARTAN[1]

72% risk reduction



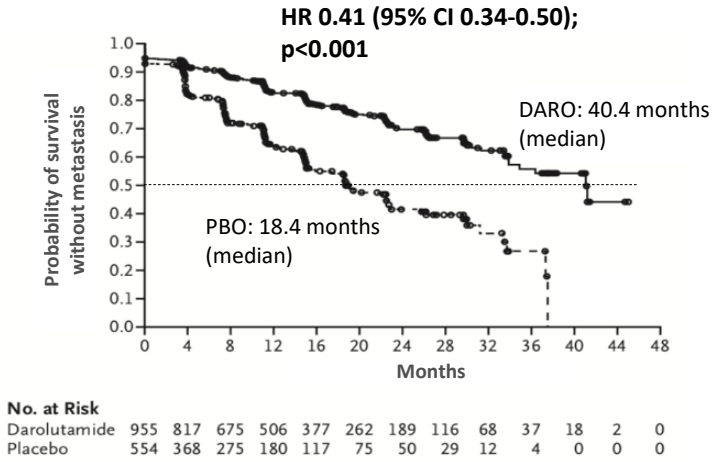
PROSPER[2]

71% risk reduction



ARAMIS[3]

59% risk reduction



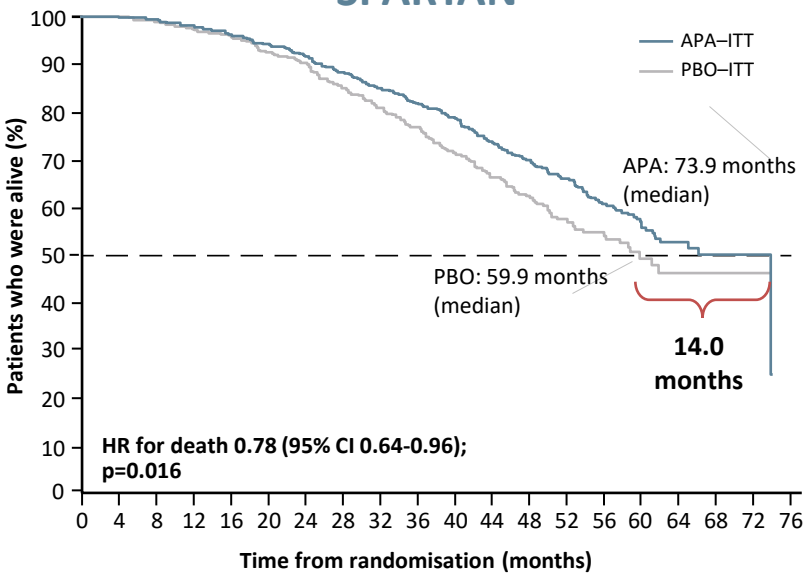
	SPARTAN		PROSPER		ARAMIS	
MFS	**APA (n=806)**	**PBO (n=401)**	**ENZA (n=933)**	**PBO (n=468)**	**DARO (n=955)**	**PBO (n=554)**
Median, months	40.5	16.2	36.6	14.7	40.4	18.4
Δ MFS, months	24.3		21.9		22.0	
95% CI	NR-NR	14.59-18.4	33.1-NR	14.2-15.0	34.3-NR	15.5-22.3
HR (95% CI)	0.28 (0.23-0.35)		0.29 (0.24-0.35)		0.41 (0.34-0.50)	
p value	<0.001		<0.001		<0.001	

APA, apalutamide; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; MFS, metastasis-free survival; NR, not reached; 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

SECONDARY ENDPOINT: OS – FINAL ANALYSIS

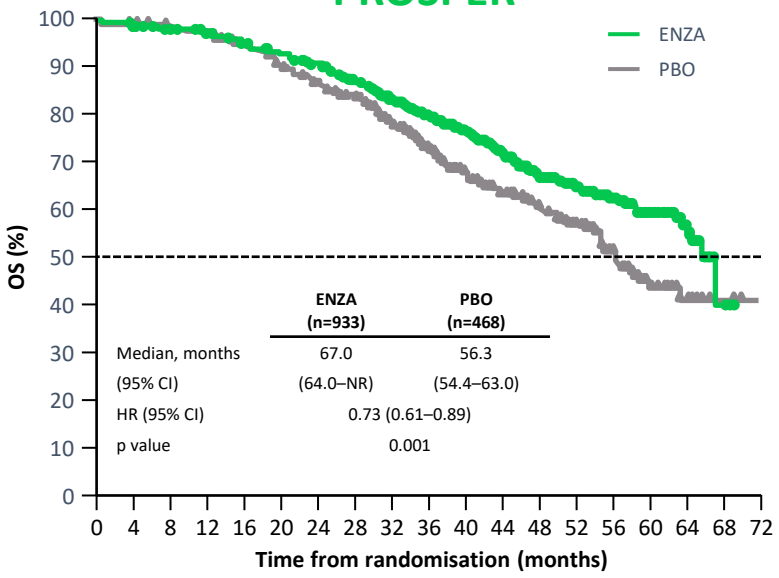
SPARTAN[1]



No. of patients at risk

APA	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0
PBO	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0

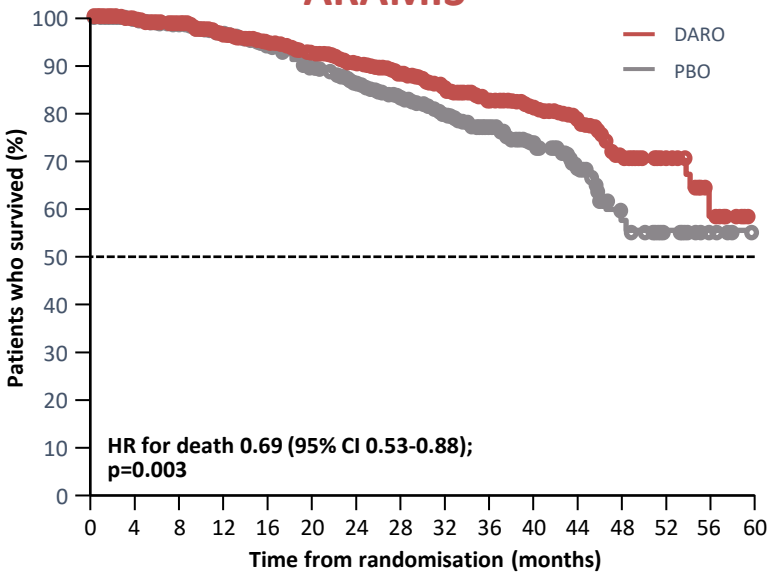
PROSPER[2]



No. of patients at risk

ENZA	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0
PBO	468	467	459	444	428	404	381	363	321	274	219	177	140	106	64	30	16	3	0

ARAMIS[3]



No. of patients at risk

DARO	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0
PBO	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0

	SPARTAN		PROSPER		ARAMIS	
OS	**APA (n=806)**	**PBO (n=401)**	**ENZA (n=933)**	**PBO (n=468)**	**DARO (n=955)**	**PBO (n=554)**
Median follow-up, months	52.0		48.0		29.0	
Median, months	73.9	59.9	67.0 (95% CI 64.0-NR)	56.3 (95% CI 54.4-63.0)	NR	NR
Δ OS, months	14.0		10.7		–	
HR	0.78		0.73		0.69	
p value	0.016		0.001		0.003	

CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; ITT, intention to treat; NR, not reached; PBO, placebo

1. Smith MR, et al. Eur Urol. 2021;79:150-8; 2. Sternberg CN, et al. N Engl J Med. 2020;382:2197-206; 3. Fizazi K, et al. N Engl J Med. 2020;383:1040-9

SAFETY

Safety	SPARTAN[1,2]		PROSPER[3]		ARAMIS[4]	
	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, %	120 (15)	29 (7.3)	158 (17)	41 (9.0)	85 (8.9)	48 (8.7)
Grade 3 or 4 AEs, n (%)	449 (56)	145 (36)	446 (48)	126 (27)	251 (26.3)	120 (21.7)
AE leading to death, n (%)	24 (3)	2 (0.5)	51 (5)	3 (1)	38 (4.0)[a]	19 (3.4)[a]
AE of special interest, EAIR for any grade per 100 patient-years						
Fatigue	32.3[b]	27.2[b]	19	17	8.3	7.4
Hypertension	36.3[b]	38.7[b]	7	5	4.9	5.8
Rash	19.0	8.7	2	2	2.0	1.0
Falls	12.0	9.6	9	4	3.3	4.3
Fractures	9.5	8.3	9	5	3.4	3.2
Mental impairment disorder[c]	3.9[b]	3.4[b]	3	2	1.3	1.6

AEs with EAIR that was ≥3 events per 100 patient-years higher in the treatment group than in the control group[d]

[a] Reported as Grade 5 adverse event; [b] Data taken from first interim analysis as not reported in final analysis[1]; [c] 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: MedRA High Level Group Term Presented for information, safety comparisons across trials should not be made; [d] Based on criteria applied in the PROSPER study analysis[3]

AE, adverse event; APA, apalutamide; DARO, darolutamide; EAIR, exposure-adjusted incidence rate; ENZA, enzalutamide; NR, not reported; PBO, placebo

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Smith MR, et al. Eur Urol. 2021;79:150-8; 3. Sternberg CN, et al. N Engl J Med. 2020;382:2197-206; 4. Fizazi K, et al. N Engl J Med. 2020;383:1040-9

DO THE SAFETY PROFILES DIFFER?

- Conclusions should not be drawn by comparing safety data from different trials due to differences in the clinical trial design and populations
- Recent analyses have attempted to compare safety profiles across the 3 AR-signalling inhibitors:

Author	Title	Conclusions	Limitations
Drago et al, ASCO GU 2020[1]	Adverse event profiles of APAL, ENZA, and DARO in SPARTAN, PROSPER, and ARAMIS: How confident are we about which drug is safest?	While conducted in similar patient populations, these trials had remarkable differences in AE reporting and in absolute AE risks between PBO arms.	Rather than indicating better safety, low absolute AE numbers decrease confidence in AE profiles. Published data are insufficient to differentiate the AE profiles of these agents in nmCRPC.
Jiang et al, ASCO 2020[2]	Safety outcomes of DARO versus APAL and ENZA in nmCRPC: Matching-adjusted indirect comparisons.	After adjusting for trial differences, DARO showed favorable safety profile in fall, dizziness, mental-impairment, hypertension, rash, fatigue, and fracture.	Patient-level data used from ARAMIS and compared to published trial data for PROSPER and SPARTAN: 1. Only known baseline factors that were consistently reported across trials were included among the matching covariates in the MAICs 2. As with any comparison of non-randomised treatment groups, such comparisons are subject to potential bias due to unobserved or unmeasurable confounding factors, 3. The results of the study may not be generalisable beyond the study sample
George et al, ESMO 2020[3]	DARO, ENZA and APAL, the risk of adverse events in patients with nmCRPC: Number needed to harm	NNH can help contextualize the risk of AEs. Findings show a consistent trend of higher NNH for DARO compared to APAL and ENZA, and that AE profile may be noteworthy for healthcare systems as well as patients	Prospective comparative trials are needed to further confirm these findings.

- Ultimately, **randomised head-to-head trials are required in order to truly compare safety profiles**
  - **DaroAcT Trial (NCT04157088)** – directly comparing DARO and ENZA to assess differences in physical and cognitive function; expected to complete 2022

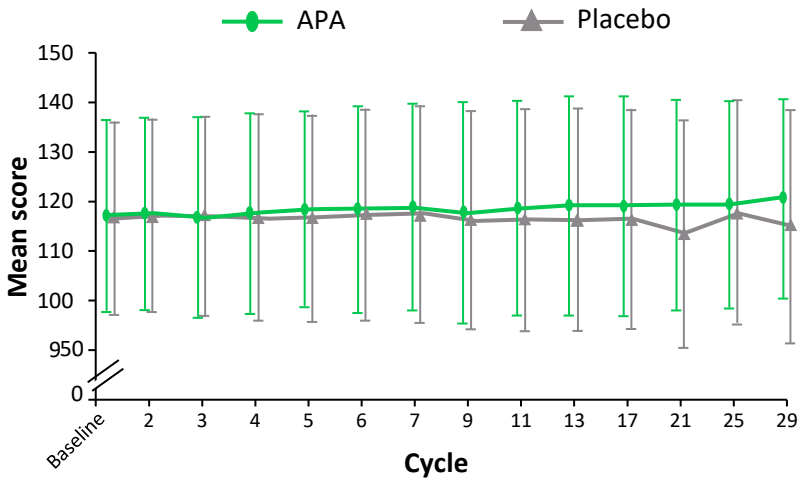
AE, adverse event; APAL, apalutamide; AR, androgen receptor; DARO, darolutamide; ENZA, enzalutamide; MAIC, matched-adjusted indirect comparison; nmCRPC, non-metastatic castration-resistant prostate cancer; NNH, number needed to harm; PBO, placebo

1. Drago J, et al. J Clin Oncol. 2020;38 suppl:318 (ASCO GU 2020 poster presentation); 2. Jiang S, et al. J Clin Oncol. 2020;38 suppl:5561 (ASCO 2020 poster presentation); 3. George D, et al. Ann Oncol. 2020;31 suppl 4: S507-S549 (ESMO 2020 poster presentation)

TREATMENT IS ASSOCIATED WITH MAINTENANCE OF HRQoL

SPARTAN[1]

FACT-P

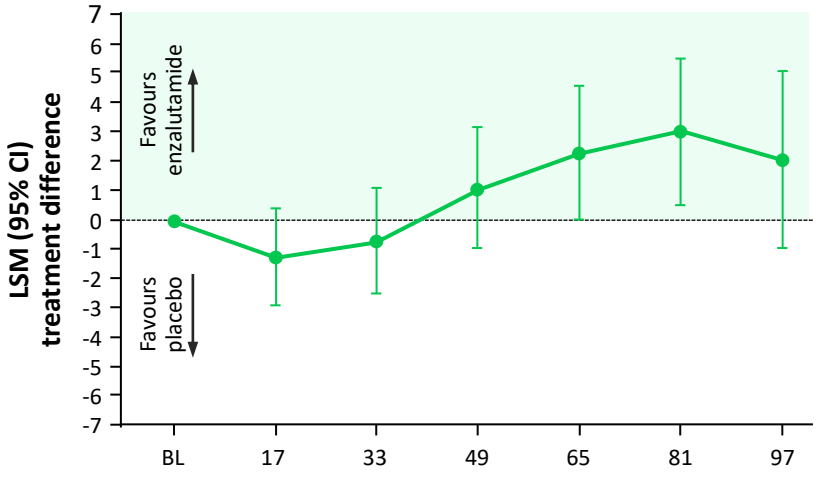


Patients in each cycle

APA	797	781	767	742	717	695	676	649	614	590	456	352	257	167
Placebo	395	389	379	371	350	301	283	265	221	199	136	83	54	35

PROSPER[2]

FACT-P

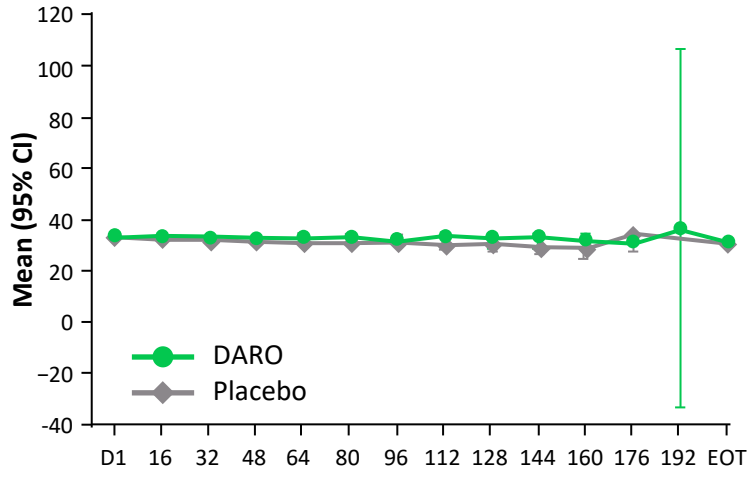


No. at risk

ENZA –	815	718	621	522	427	354
Placebo –	403	329	239	183	139	90

ARAMIS[3]

FACT-P PCS



No. at risk

DARO	938	882	820	669	512	387	270	199	121	73	37	19	2	191
Placebo	546	501	376	269	186	119	79	52	31	15	8	1	0	253

APA, apalutamide; AUC, area under the curve; BL, baseline; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HRQoL, health-related quality of life; LSM, least squares mean; PBO, placebo; PCS, Prostate Cancer Subscale

1. Saad F et al. Lancet Oncol. 2018;19:1404-1416; 2. Tombal B, et al. Lancet Oncol. 2019;20:556-69; 3. Fizazi K, et al. J. Clin Oncol 2019; 37; no. 15_suppl: 5000-5000

CONCLUSIONS

- High-risk nmCRPC patients are at a very high-risk to develop metastatic disease within 2 years of diagnosis[1]
- Extending MFS and preserving quality of life has been an unmet need for a long time
- APA, ENZA, and DARO delay MFS and time to next-line treatment by an impressive ~2 years
  - All three molecules also significantly improve OS
- APA, ENZA, and DARO have a very good safety profile
- Quality of life is preserved and disease-related symptoms are significantly delayed with APA, ENZA, and DARO
- APA, ENZA, and DARO should be considered new standards in the treatment of nmCRPC

APA, apalutamide; ENZA, enzalutamide; DARO, darolutamide; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival

1. Mateo J, et al. European Urology 2019; 75: 285-293

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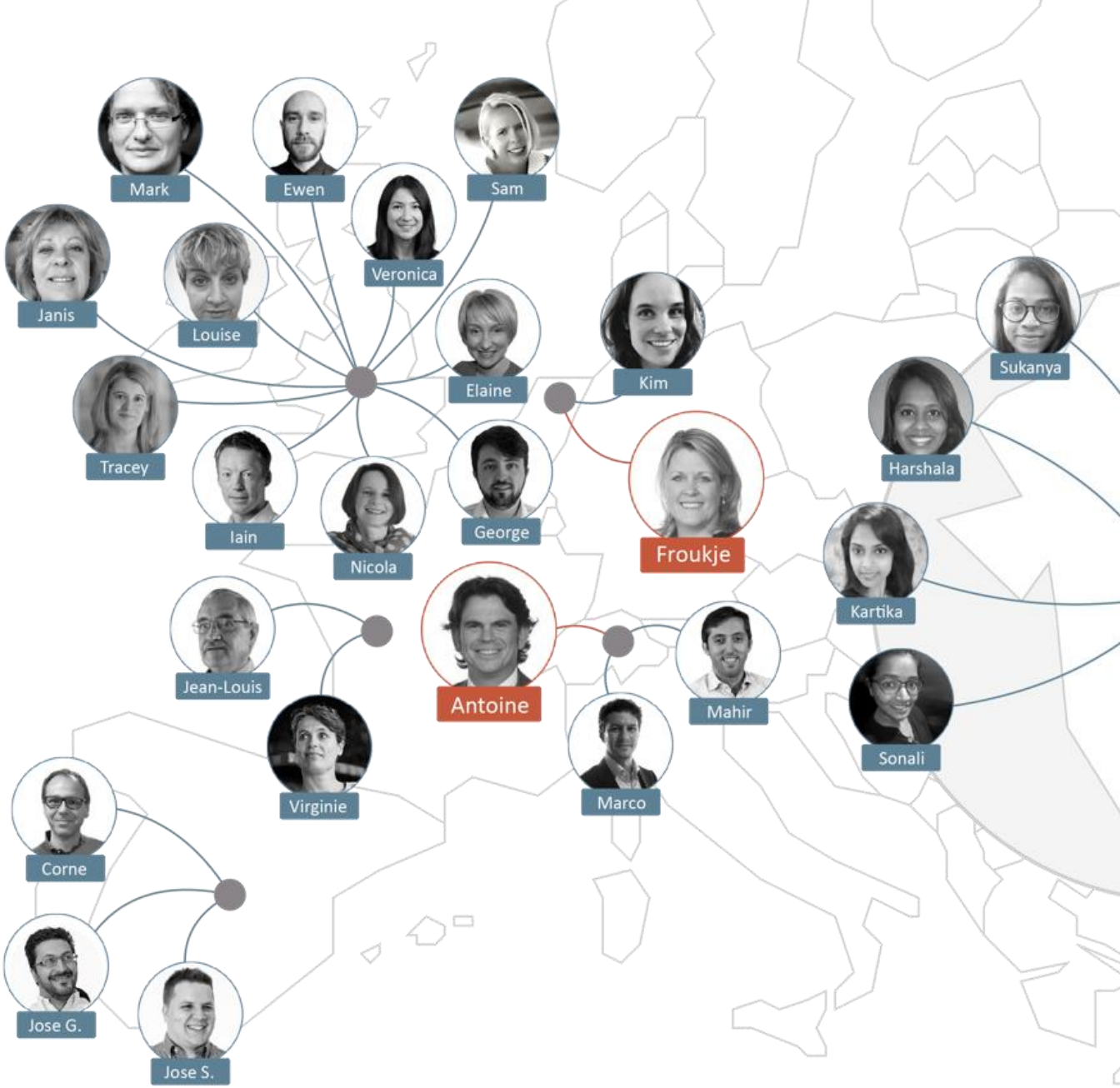

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