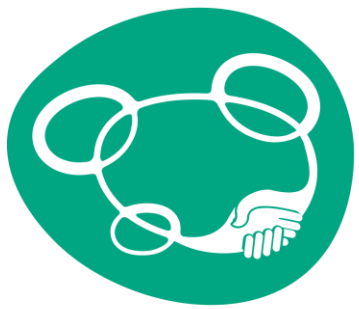

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OVERVIEW OF SAFETY CONSIDERATIONS FOR NEXT-GENERATION ANDROGEN RECEPTOR INHIBITORS FOR nmCRPC: THE ROLE OF THE NURSE

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nmCRPC, non-metastatic castration-resistant prostate cancer

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nmCRPC: WHAT DO WE KNOW?

- **Non-metastatic castration-resistant prostate cancer (nmCRPC) is the earliest form of castration-resistant disease**
- nmCRPC is characterised by a **prostate-specific antigen (PSA) concentration of ≥2 ng/mL** (≥25%) over the nadir, despite **castrate levels of testosterone (<50 ng/dL)**, in patients with **no radiographic evidence of metastatic disease**
- Patients with nmCRPC have a **significant risk of progressing to metastatic CRPC**
- **Metastatic CRPC carries a poor prognosis**, with shorter overall survival (OS) and reduced health-related quality of life (QoL)
- Since nmCRPC patients are mostly asymptomatic from their disease, treatment should delay development of metastases as well as maintaining QoL
- **Therapeutic benefit should be balanced against the potential risk of adverse events (AEs)**

Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

nmCRPC TREATMENT LANDSCAPE

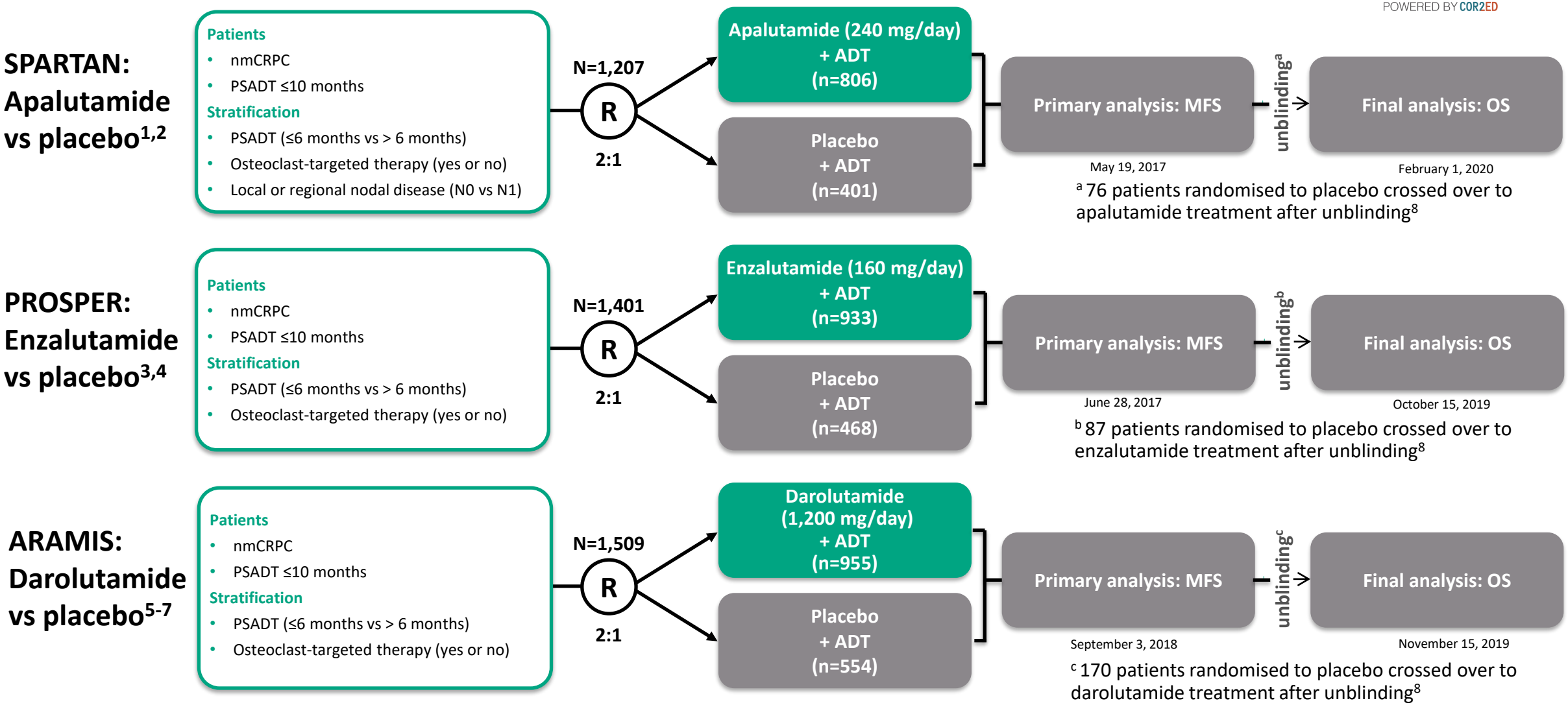
- The nmCRPC treatment landscape has been transformed by the approval of three next-generation oral androgen receptor (AR) inhibitors:[a]
  - **Apalutamide**
    - Approved in 2018 based on the Phase 3 SPARTAN trial[1]
  - **Enzalutamide**
    - Approved in 2018 based on the Phase 3 PROSPER trial[2]
  - **Darolutamide**
    - Approved in 2019 based on the Phase 3 ARAMIS trial[3]

[a] Androgen deprivation therapy (ADT) should be given in conjunction with next-generation AR inhibitors

nmCRPC, non-metastatic castration-resistant prostate cancer

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. 2019;380:1235-46

STUDY DESIGNS: SPARTAN, PROSPER, ARAMIS

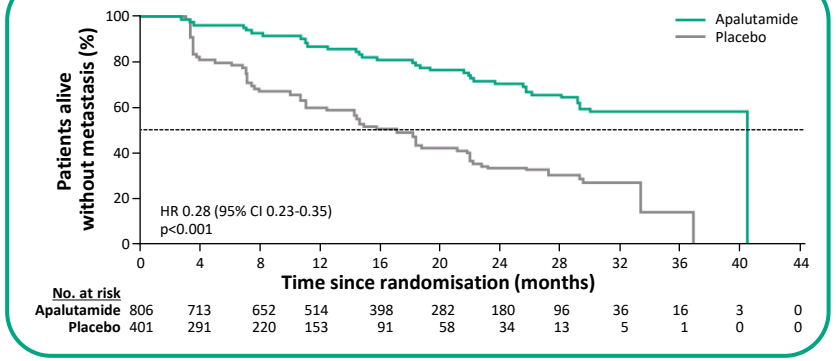


ADT, androgen deprivation therapy; b.i.d., twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; N, node; OS, overall survival; PSADT, prostate-specific antigen doubling time; R, randomisation

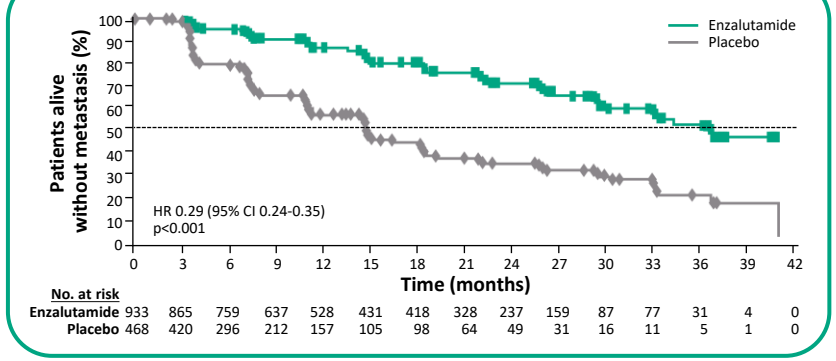
1. Small EJ, et al. J Clin Oncol. 2018;36(6_suppl):161; 2. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 3. Hussain M, et al. J Clin Oncol. 2018;36(6_suppl):3; 4. Hussain M, et al. N Engl J Med. 2018;378:2465-74; 5. Fizazi K, et al. J Clin Oncol. 2019;37(7_suppl):140; 6. Fizazi K, et al. N Engl J Med. 2019;380:1235-46; 7. Fizazi K, et al. N Engl J Med. 2020;383:1040-9; 8. Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

PRIMARY ENDPOINT: METASTASIS-FREE SURVIVAL

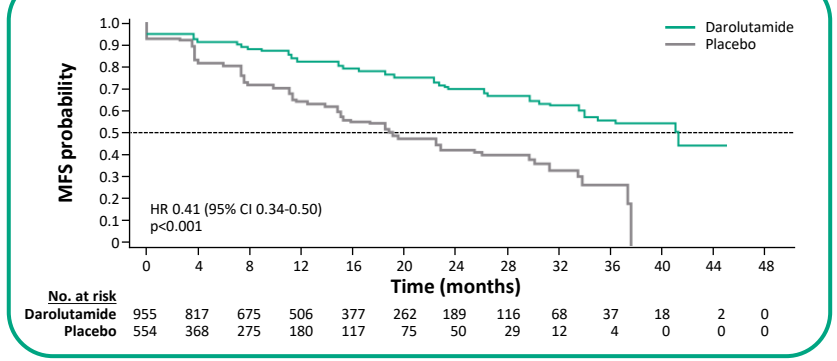
SPARTAN:[1] Apalutamide



PROSPER:[2] Enzalutamide



ARAMIS:[3] Darolutamide



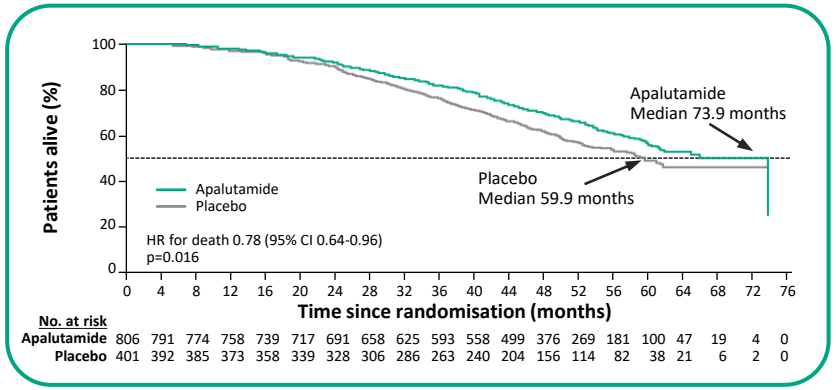
	SPARTAN		PROSPER		ARAMIS	
	APA (n=806)	PBO (n=401)	ENZA (n=933)	PBO (n=468)	DARO (n=955)	PBO (n=554)
Median follow-up	20.3 months		18.5 months	15.1 months	17.9 months	
Median MFS, months	40.5	16.2	36.6	14.7	40.4	18.4
HR (95% CI)	0.28 (0.23-0.35)		0.29 (0.24-0.35)		0.41 (0.34-0.50)	
p value	<0.001		<0.001		<0.001	

APA, apalutamide; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; MFS, metastasis-free survival; No., number; PBO, placebo

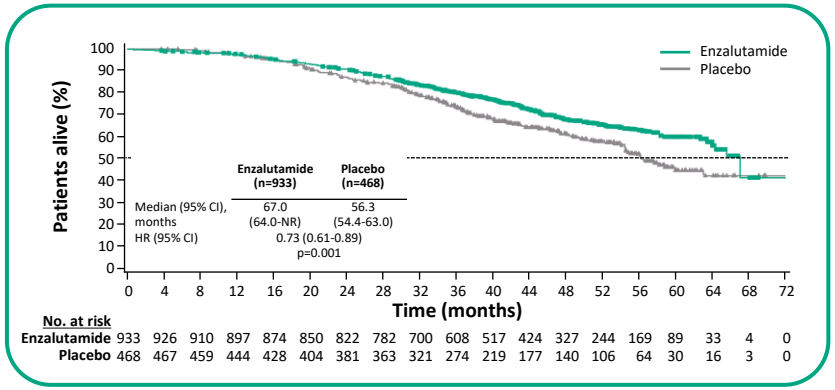
1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Hussain M, et al. N Engl J Med. 2018;378:2465-74; 3. Fizazi K, et al. N Engl J Med. 2019;380:1235-46

SECONDARY ENDPOINT: FINAL OVERALL SURVIVAL

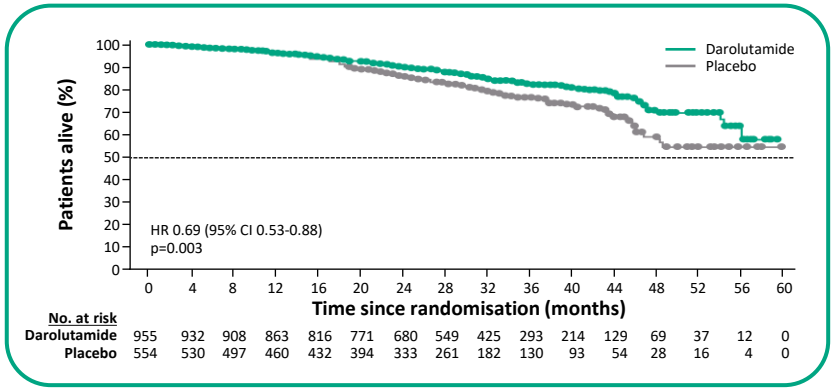
SPARTAN:[1] Apalutamide



PROSPER:[2] Enzalutamide



ARAMIS:[3] Darolutamide



	SPARTAN		PROSPER		ARAMIS	
	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 OS, months	73.9	59.9	67.0	56.3	NR	NR
HR (95% CI)	0.78 (0.64-0.96)		0.73 (0.61-0.89)		0.69 (0.53-0.88)	
p value	0.016		0.001		0.003	

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

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

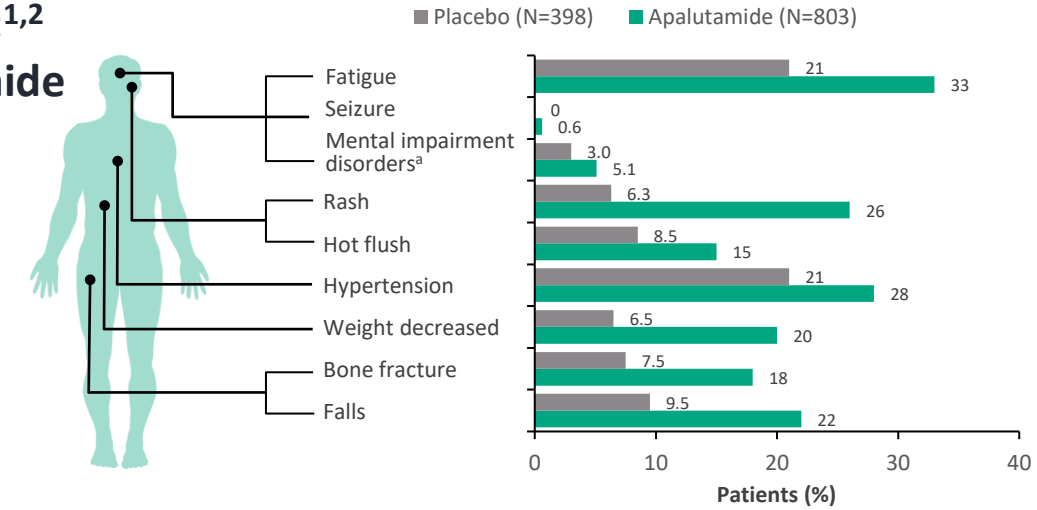
ROLE OF THE NURSE IN MANAGING ADVERSE EVENTS

- With the availability of new AR-targeted options for nmCRPC, **oncology nurses play a crucial role in the decision-making process**, educating and supporting patients in managing their prostate cancer, and ensuring that they receive the most appropriate treatment
- Since **nmCRPC patients are largely asymptomatic** from their disease, maintaining **QoL becomes a major objective**
- Oncology nurses educate patients on potential treatment-emergent adverse events (TEAEs) and their management, and serve as advocates to ensure that patients receive optimal care based on their individual therapeutic requirements

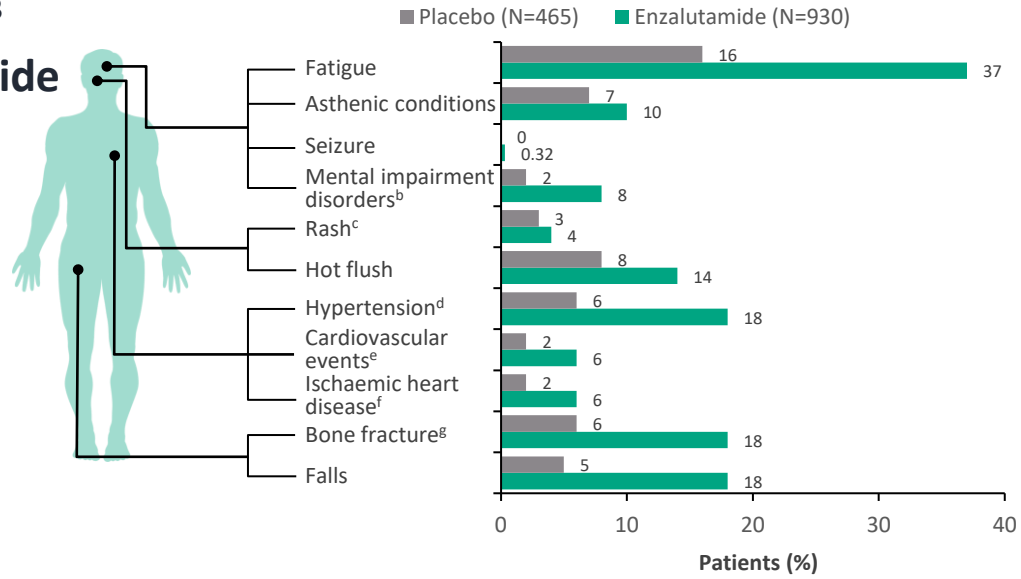
AR, androgen receptor; nmCRPC, non-metastatic castration resistant-prostate cancer; QoL, quality of life

Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

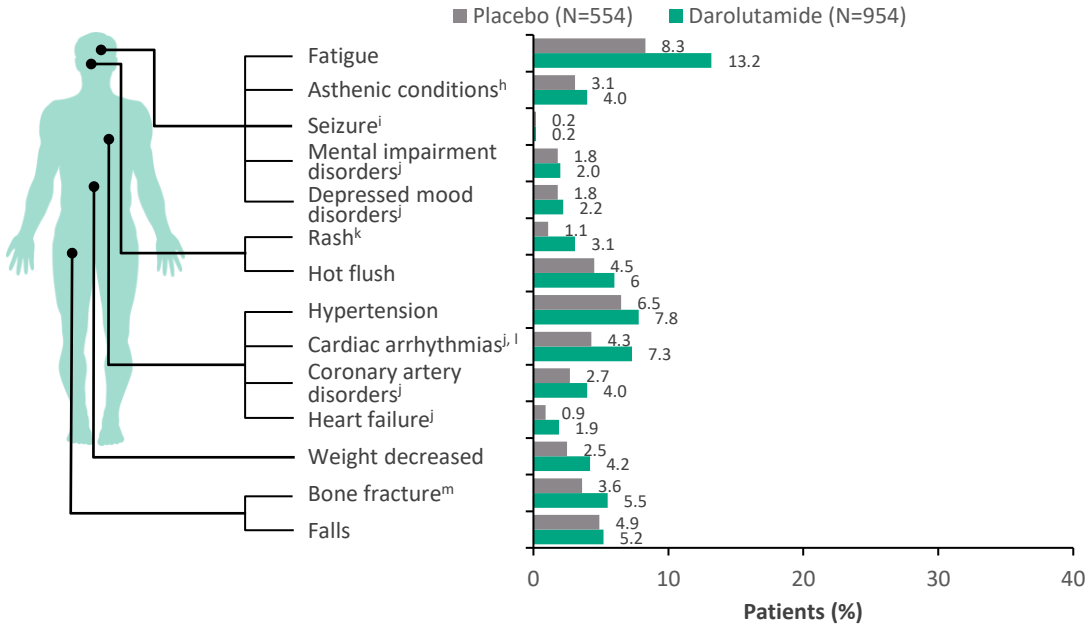
SPARTAN:[1,2] Apalutamide



PROSPER:[3] Enzalutamide



ARAMIS:[4] Darolutamide



Note: these data do not represent a head-to-head comparison of SPARTAN, PROSPER, and ARAMIS.
[a] Data not reported in final analysis; [b] Includes disturbances in attention, cognitive disorders, amnesia, Alzheimer's disease, dementia, senile dementia, mental impairment, vascular dementia; [c] Includes maculopapular rash, generalised rash, macular rash, papular rash, pruritic rash; [d] Includes hypertensive retinopathy, increased blood pressure, systolic hypertension, hypertensive crisis; [e] Includes haemorrhagic CNS vascular conditions, ischaemic CNS vascular conditions, cardiac failure; [f] Includes myocardial infarction, other ischaemic heart disease; [g] Includes bone and joint injuries; [h] Combined term comprising of MedDRA terms of asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, and asthenia; [i] One additional incidence of seizure occurred in the darolutamide group during the open-label period, in a patient with a history of epilepsy; [j] MedDRA High Level Group term; [k] MedDRA labelling grouping, including preferred terms of rash, rash macular, rash maculopapular, rash papular, rash pustular; [l] Although the incidence of the AE of cardiac arrhythmias was higher with darolutamide than with placebo, medical history of cardiac arrhythmia and electrocardiogram abnormalities were both present to a greater extent in the darolutamide group at baseline, as observed at primary analysis; [m] Combined term comprising MedDRA terms of any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, thoracic cage fractures and dislocations

AE, adverse event; CNS, central nervous system; MedDRA, Medical Dictionary for Regulatory Activities, version 20.0; MI, myocardial infarction

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.

Figure adapted from: Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

MANAGING TREATMENT-EMERGENT ADVERSE EVENTS

- **Fatigue**
  - Nurses should encourage regular exercise and eating a healthy diet
  - If severe or unmanageable, nurses should encourage prescribers to modify treatment strategy, including dose interruptions or reductions

- **Bone health**
  - Evaluate bone health and fracture risk prior to ADT and throughout treatment (dual energy X-ray absorptiometry [DEXA], FRAX® Fracture Risk Assessment Tool)
  - Vitamin D and calcium supplementation and, where applicable, bisphosphonate or denosumab
  - Nurses should encourage weight-bearing exercise and implementation of lifestyle changes to prevent falls

ADT, androgen deprivation therapy

Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

MANAGING TREATMENT-EMERGENT ADVERSE EVENTS

- **Cognitive impairment**
  - Screen for cognitive function at baseline and periodically throughout treatment
  - Nurses should elicit observations of cognitive changes from caregivers or responsible family members

- **Rash**
  - Nurses should educate patients on the risk of developing rash
  - If rash is detected on physical examination, nurses should encourage prescribers to consider management with oral antihistamines and/or systemic corticosteroids (for Grade 3 or 4 rash) in addition to topical corticosteroids or dose interruption
  - Early intervention may lessen severity and recurrence of rash, and may prevent dose interruptions

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MANAGING TREATMENT-EMERGENT ADVERSE EVENTS

- **Metabolic changes**
  - Monitor fasting glucose and liver function at baseline and throughout treatment
  - Nurses should educate patients on regular exercise and dietary modifications

- **Cardiovascular AEs**
  - Monitor at baseline and throughout treatment
  - Nurses should educate patients on a heart-healthy diet
  - Nurses should educate patients on how to recognise, control, and prevent hypertension, deep vein thrombosis (DVT), and pulmonary embolism

AE, adverse event

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MANAGING TREATMENT-EMERGENT ADVERSE EVENTS

- **Hot flushes**
  - Consider venlafaxine, gabapentin, or medroxyprogesterone acetate

- **Sexual health**
  - Nurses can foster open communication between patients and their partners, and provide counselling on pharmacological and non-pharmacological options to reduce the burden of erectile dysfunction

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IN SUMMARY

- The treatment landscape in nmCRPC is evolving rapidly given the recent approvals of the **three next-generation AR inhibitors**
- While **no head-to-head comparisons of apalutamide, enzalutamide, and darolutamide have been conducted** to date, **all three have demonstrated comparable efficacy and maintained QoL** in the SPARTAN, PROSPER, and ARAMIS trials, **with differing AE profiles**
- **Balancing treatment efficacy against the potential risk of TEAEs is an important clinical consideration** in nmCRPC, since the incidence of cancer-related symptoms is low and pretreatment QoL scores are relatively high in this patient population
- **Oncology nurses can make a major contribution** to successful therapeutic outcomes by educating patients with nmCRPC on their disease and available therapeutic options, recognising and managing specific TEAEs, and modifying treatment decisions accordingly

AE, adverse event; AR, androgen receptor; nmCRPC, non-metastatic castration resistant-prostate cancer; TEAE, treatment emergent adverse event; QoL, quality of life

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; 4. Olivier KM, et al. Int J Urol Nurs. 2021. DOI: 10.1111/ijun.12263

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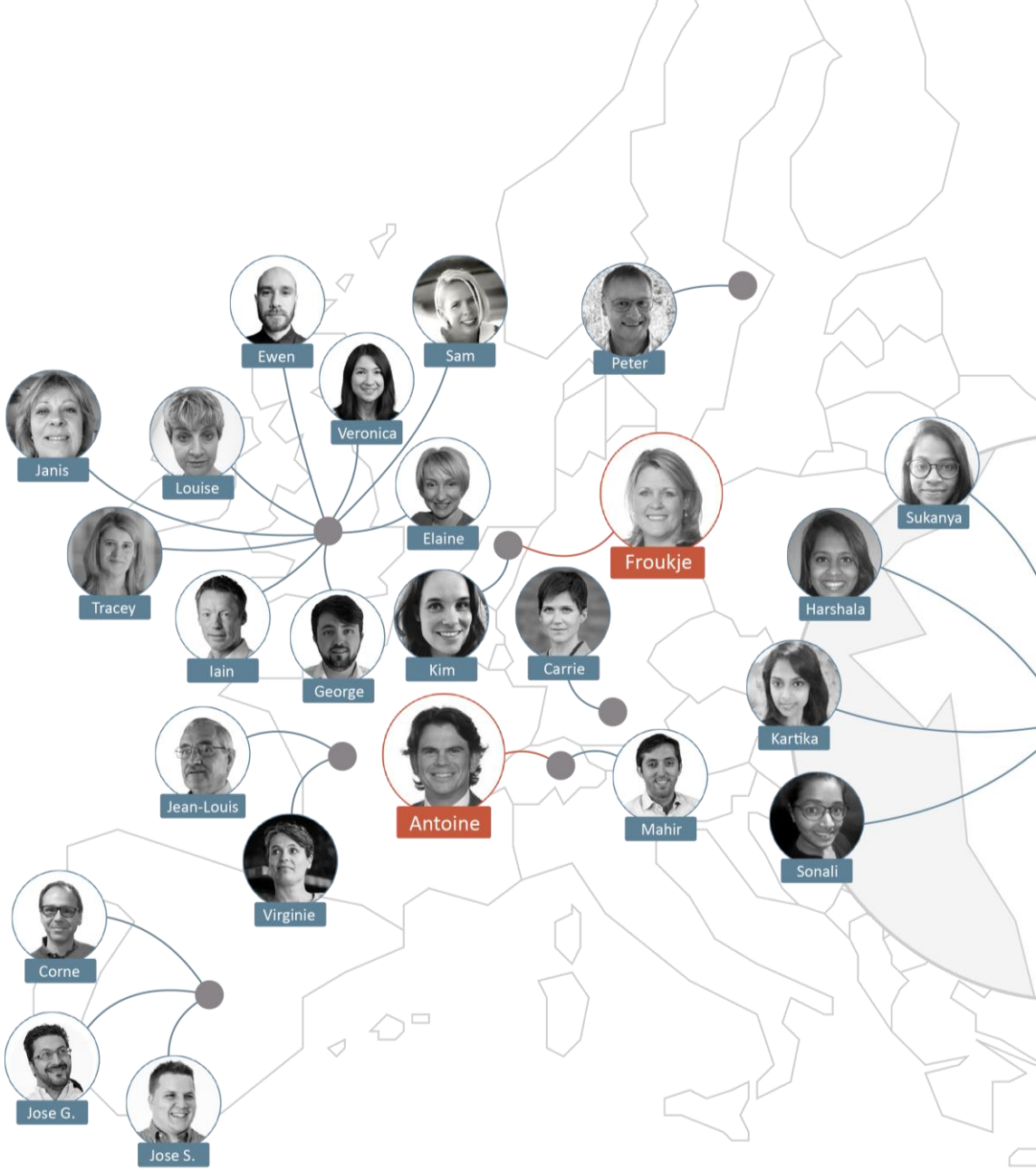

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