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THE ROLE OF THE NURSE IN nmCRPC PATIENT MANAGEMENT

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EDUCATIONAL OBJECTIVES

1. To highlight the **considerations required for nmCRPC treatment selection** in clinical practice, and to educate nurses on the role of individualised treatment selection in mitigating possible adverse effects related to treatment

2. To assist nurses in the **education and support of patients with nmCRPC**, ensuring patients:

    a) Understand the risk of potential adverse effects of treatment

    b) Are aware of the role of individualised treatment selection in mitigating the possible adverse effects of treatment

nmCRPC, non-metastatic castration-resistant prostate cancer

CLINICAL TAKEAWAYS

- nmCRPC patients are generally asymptomatic and are often older with chronic comorbidities requiring long-term concomitant medication
- Risk–benefit analysis usually favours initiating treatment with second-generation ARIs, even in older patients
- Individualised treatment decision-making is important and should take into consideration comorbidities, potential drug–drug interactions, in addition to tolerability and safety profiles
- The nurse has a pivotal role in the management of nmCRPC patients

ARI, androgen receptor inhibitor; DDI, drug–drug interaction; nmCRPC, non-metastatic castration-resistant prostate cancer

WHAT IS nmCRPC?

- nmCRPC is defined as:
  - **Raised PSA concentration** (25% increase from nadir [starting PSA ≥1.0 ng/mL; minimum increase of 2 ng/mL]) after primary definitive therapy[a]
  - **Castrate levels of testosterone (≤50 ng/dL)** despite ongoing ADT[b] or surgical orchiectomy
  - **No detectable metastases** by conventional imaging
- Patients with **nmCRPC and a PSADT of ≤10 months** are at **significant risk for metastatic disease** and prostate cancer-specific mortality
- **Patients with nmCRPC are generally asymptomatic** for the disease; they are often older (age >65 years), with chronic comorbidities requiring long-term concomitant medication
- Therefore, **careful consideration of the benefit–risk profile of potential treatments** is required
  - Adverse events vs OS/PFS/MFS

[a] Primary therapy: prostatectomy, radiotherapy; [b] ADT: luteinising hormone-releasing hormone agonists or antagonists, first-generation non-steroidal antiandrogens or novel hormonal agents

ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time

Chung DY, et al. Biomedicines. 2021;9:661; Mateo J, et al. Eur Urol. 2019;75:285-93; Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58; Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24:323-34; Smith MR, et al. J Clin Oncol. 2013;31:3800-6

TREATMENT OPTIONS FOR nmCRPC

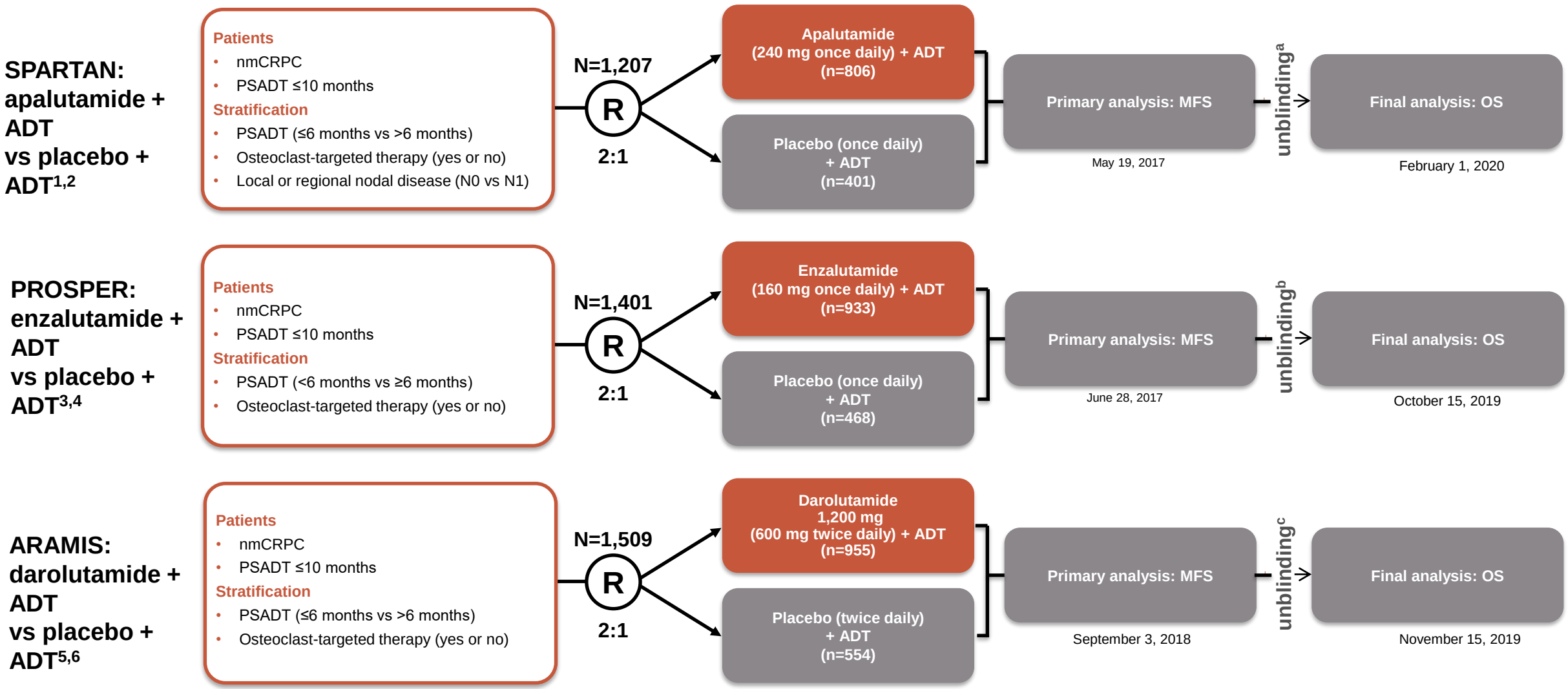
- The treatment landscape for nmCRPC has been transformed by the approval of three second-generation oral ARIs:[a]
  - **Apalutamide**
    - FDA approved for nmCRPC in 2018 based on the Phase 3 SPARTAN trial
  - **Enzalutamide**
    - FDA approved for nmCRPC in 2018 based on the Phase 3 PROSPER trial
  - **Darolutamide**
    - FDA approved for nmCRPC in 2019 based on the Phase 3 ARAMIS trial

[a] ADT should be given in conjunction with second-generation ARIs

ADT, androgen deprivation therapy; ARI, androgen receptor inhibitor; FDA, United States Food and Drug Administration; nmCRPC, non-metastatic castration resistant prostate cancer

Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

STUDY DESIGNS: SPARTAN, PROSPER, AND ARAMIS



[a] 76 patients randomised to placebo crossed over to apalutamide treatment after unblinding; [b] 87 patients randomised to placebo crossed over to enzalutamide treatment after unblinding; [c] 170 patients randomised to placebo crossed over to darolutamide treatment after unblinding[8]

ADT, androgen deprivation therapy; 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. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Smith MR, et al. Eur Urol 2021; 79: 150-158; 3. Hussain M, et al. N Engl J Med. 2018;378:2465-74; 4. Sternberg C, N Engl J Med 2020;382:2197-206; 5. Fizazi K, et al. N Engl J Med. 2019;380:1235-46; 6. Fizazi K, et al. N Engl J Med. 2020;383:1040-9

Figure adapted from: Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

EFFICACY RESULTS: PRIMARY ANALYSIS (MFS)

	SPARTAN (NCT01946204): Apalutamide + ADT (n=806) vs placebo + ADT (n=401)	PROSPER (NCT02003924): Enzalutamide + ADT (n=933) vs placebo + ADT (n=468)	ARAMIS (NCT02200614): Darolutamide + ADT (n=955) vs placebo + ADT (n=554)
Primary analysis			
Median follow-up	20.3 months	**Enzalutamide:** 18.5 months **Placebo:** 15.1 months	17.9 months
Primary endpoint	**Median MFS:** 40.5 vs 16.2 months; HR 0.28; 95% CI 0.23-0.35; p<0.001	**Median MFS:** 36.6 vs 14.7 months; HR 0.29; 95% CI 0.24-0.35; p<0.001	**Median MFS:** 40.4 vs 18.4 months; HR 0.41; 95% CI 0.34-0.50; p<0.001
Secondary endpoints	**Median PFS:** 40.5 vs 14.7 months; HR 0.29; 95% CI 0.24-0.36; p<0.001 **Median time to symptomatic progression:** NR vs NR; HR 0.45; 95% CI 0.32-0.63; p<0.001 **Median OS:** NR vs 39.0 months; HR 0.70; 95% CI 0.47-1.04; p=0.07 **Median time to first cytotoxic chemotherapy:** NR vs NR; HR 0.44; 95% CI 0.29-0.66	**Median time to PSA progression:** 37.2 vs 3.9 months; HR 0.07; 95% CI 0.05-0.08; p<0.001 **Median time to first use of new antineoplastic therapy:** 39.6 vs 17.7 months; HR 0.21; 95% CI 0.17-0.26; p<0.001 **Median OS:** NR vs NR; HR 0.80; 95% CI 0.58-1.09; p=0.15	**Median OS:** NR vs NR; HR 0.71; 95% CI 0.50-0.99; p=0.045 **Median time to pain progression:** 40.3 vs 25.4 months; HR 0.65; 95% CI 0.53-0.79; p<0.001 **Median time to first use of cytotoxic chemotherapy:** NR vs 38.2 months; HR 0.43; 95% CI 0.31-0.60; p<0.001 **Median time to first SSE**: NR vs NR; HR 0.43; 95% CI 0.22-0.84; p<0.01
Exploratory endpoints	**Second PFS:** NR vs 39.0 months; HR 0.49; 95% CI 0.36-0.66 **Median time to PSA progression**: NR vs 3.7 months; HR 0.06; 95% CI 0.05-0.08		**Median PFS:** 36.8 vs 14.8 months; HR 0.38; 95% CI 0.32-0.45; p<0.001 **Median time to PSA progression:** 33.2 vs 7.3 months; HR 0.13; 95% CI 0.11-0.16; p<0.001 **Median time to first prostate cancer-related invasive procedure:** NR vs NR; HR 0.39; 95% CI 0.25-0.61; p<0.001 **Median time to initiation of subsequent antineoplastic therapy:** NR vs NR; HR 0.33; 95% CI 0.23-0.47; p<0.001

Note: these data do not represent a head-to-head comparison of SPARTAN, PROPSER, and ARAMIS

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio, MFS, metastasis-free survival; NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; SSE, symptomatic skeletal event

Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

EFFICACY RESULTS: FINAL ANALYSIS (OS)

	SPARTAN (NCT01946204): Apalutamide + ADT (n=806) vs placebo + ADT (n=401)	PROSPER (NCT02003924): Enzalutamide + ADT (n=933) vs placebo + ADT (n=468)	ARAMIS (NCT02200614): Darolutamide + ADT (n=955) vs placebo + ADT (n=554)
Final analysis			
Median follow-up	52.0 months	48.0 months	29.1 months
Secondary endpoints	**Median OS:** 73.9 vs 59.9 months; HR 0.78; 95% CI 0.64-0.96; p=0.016 **Median time to cytotoxic chemotherapy**: NR vs NR; HR 0.63; 95% CI 0.49-0.81; p=0.0002 **Median time to symptomatic progression:** NR vs NR; HR 0.57; 95% CI 0.44-0.73; p<0.0001[a]	**Median OS:** 67.0 vs 56.3 months; HR 0.73; 95% CI 0.61-0.89; p=0.001 **Median time to use of cytotoxic chemotherapy:** NR vs NR; HR 0.54; 95% CI 0.44-0.67 **Median time to first use of new subsequent antineoplastic therapy:** 66.7 vs 19.1 months; HR 0.29; 95% CI 0.25-0.34 **Chemotherapy-free survival:** 58.3 vs 41.6 months; HR 0.62; 95% CI 0.52-0.72	**Median OS:** NR vs NR; HR 0.69; 95% CI 0.53-0.88; p=0.003 **Median time to first cytotoxic chemotherapy:** NR vs NR; HR 0.58; 95% CI 0.44-0.76; p<0.001 **Median time to pain progression:** 40.3 vs 25.4 months; HR 0.65; 95% CI 0.53-0.79; p<0.001 **Median time to first SSE:** NR vs NR; HR 0.48; 95% CI 0.29-0.82; p=0.005
Exploratory endpoints	**Median time to PSA progression:** 40.5 vs 3.7 months; HR 0.07; 95% CI 0.06-0.09; p<0.0001[a] **Median time to second PFS:** 55.6 vs 41.2 months; HR 0.55; 95% CI 0.46-0.66; p<0.0001[a]		

Note: these data do not represent a head-to-head comparison of SPARTAN, PROPSER, and ARAMIS

[a] Nominal p value

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio, MFS, metastasis-free survival; NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; SSE, symptomatic skeletal event

Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

MEDICAL TEAM INVOLVED IN nmCRPC TREATMENT

- A variety of disciplines are involved in the diagnosis, treatment selection, and surveillance and follow-up of patients with prostate cancer:[1]
  - Urologists
  - Nurses
  - Oncologists
  - Radiologists
  - Radiation oncologists
  - Psychologists
- The multidisciplinary approach guarantees a higher probability that the patient receives adequate information on their disease and on all possible therapeutic strategies, balancing advantages and related adverse effects
- The establishment of Prostate Cancer Units could provide financial savings, avoid inappropriate procedures, and improve outcomes, ultimately allowing for the delivery of higher-quality care to patients[1]

nmCRPC, non-metastatic castration-resistant prostate cancer

1. Sciarra A, et al. Am J Clin Exp Urol. 2013;1:12-7

THE NURSE ROLE

- Oncology nurses play a pivotal role in the management of patients with prostate cancer, educating them on disease state, risk and the likelihood of progression, therapeutic options, and TEAEs along their individualised treatment path[1]
- Nursing goals:
  - Discuss treatment options based on the latest research trials results
  - Identify and prevent adverse events
  - Ensure patient safety
  - Identify patient wishes
  - Facilitate communication between the medical team and the patient
  - Ensure the patient understands the information before, during, and after treatment

TEAE, treatment-emergent adverse event

1. Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

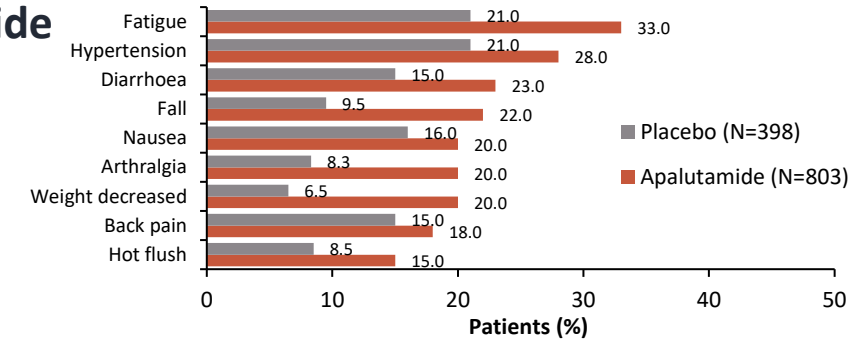
CHARACTERISTICS OF PATIENTS WITH nmCRPC

- Patients with nmCRPC are generally older (age >65 years), and with comorbidities such as CV disease, hyperlipidaemia, and hypertension
- Aging and comorbidities often lead to patients with nmCRPC being treated with long-term pharmacologic treatments, and frequently to polypharmacy, with the increased risk of DDI
- Patients with nmCRPC are generally asymptomatic for the disease, due to the lack of bone metastasis, which is one of the main issues in a metastatic prostate cancer patient.
- Patients with nmCRPC generally experience a good quality of life

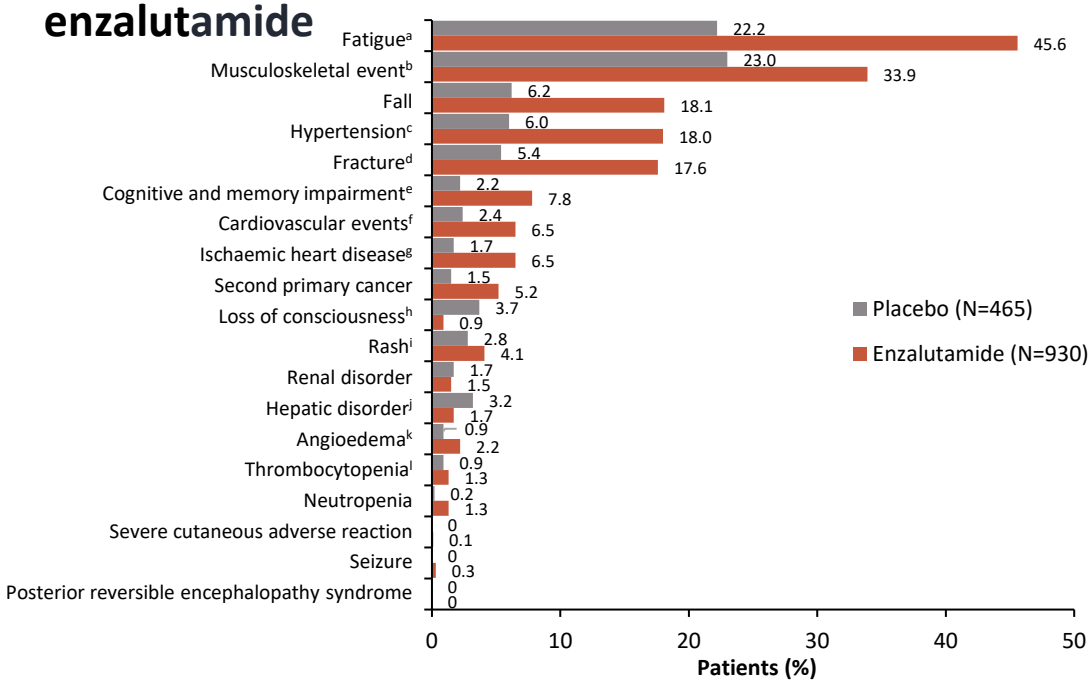
CV, cardiovascular; DDI, drug–drug interaction; nmCRPC, non-metastatic castration-resistant prostate cancer

SAFETY RESULTS: INCIDENCE OF AEs ASSOCIATED WITH ARIs

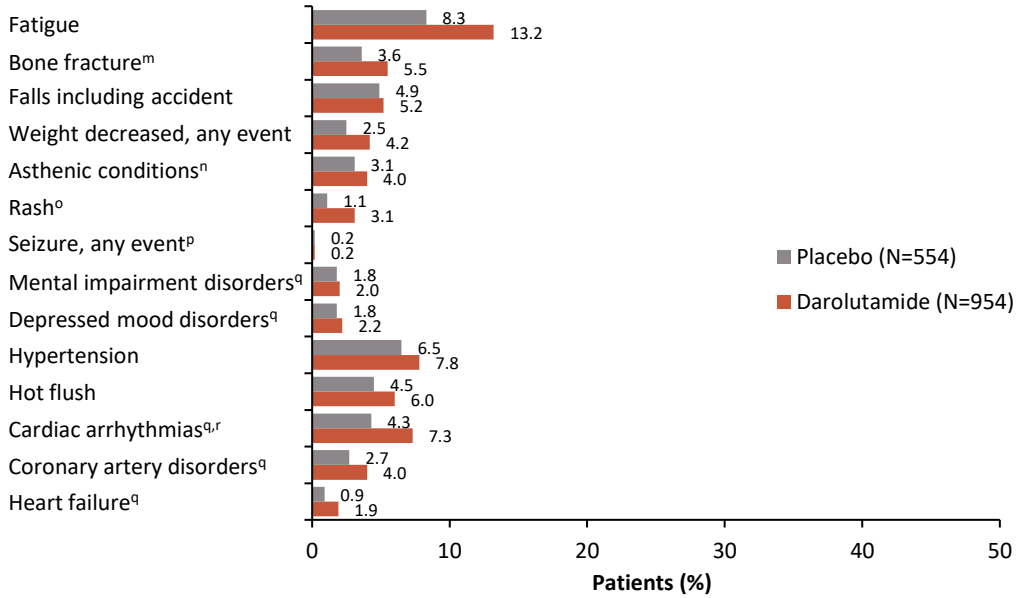
SPARTAN: apalutamide



PROSPER: enzalutamide



ARAMIS: darolutamide



Incidence of AEs associated with ARIs reported in the final analyses of the SPARTAN, PROSPER, and ARAMIS clinical trials

SPARTAN: at final analysis, median follow-up was 52.0 months; median treatment duration in apalutamide arm was 32.9 months and in the placebo arm was 11.5 months

PROSPER: at final analysis, median follow-up was 48.0 months; median treatment duration in enzalutamide arm was 33.9 months (95% CI 0.2-68.8) and in the placebo arm was 14.2 months (95% CI 0.1–51.3)

[a] Fatigue events included asthenia; [b] Musculoskeletal events included back pain, arthralgia, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal stiffness, muscular weakness, and muscle spasms; [c] Hypertension events included hypertensive retinopathy, increased blood pressure, systolic hypertension, and hypertensive crisis; [d] Fracture events included bone and joint injuries; [e] Events of cognitive and memory impairment included disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, dementia, senile dementia, mental impairment, and vascular dementia; [f] Cardiovascular events included haemorrhagic central nervous system vascular conditions, ischaemic central nervous system vascular conditions, and cardiac failure; [g] Events of ischaemic heart disease included myocardial infarction and other ischaemic heart disease; [h] Loss-of-consciousness events included syncope and presyncope; [i] Rash events included maculopapular rash, generalised rash, macular rash, papular rash, and pruritic rash; [j] Hepatic disorders included hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions, and hepatitis and liver-related investigations, signs, and symptoms; [k] Angioedema events included urticaria, eyelid oedema, periorbital oedema, swollen tongue, swollen lip, face oedema, laryngeal oedema, and pharyngeal oedema; [l] Thrombocytopenia events included decreases in platelet count

ARAMIS: at final analysis, median follow-up was 29.0 months; median exposure in darolutamide arm was 18.5 months and in the placebo arm was 11.6 months

[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, and thoracic cage fractures and dislocations; [n] Combined term comprising MedDRA terms of asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, and asthenia; [o] Combined term comprising MedDRA terms of rash, macular rash, maculopapular rash, papular rash, and pustular rash; [p] One additional incidence of seizure occurred in the darolutamide group during the open-label period, in a patient with a history of epilepsy; [q] MedDRA High Level Group term; [r] Although the incidence of cardiac arrhythmia was higher with darolutamide than with placebo, both a history of cardiac arrhythmia and electrocardiogram abnormalities were present to a greater extent in the darolutamide group at baseline, as observed at primary analysis.

AE, adverse event; ARI, androgen receptor inhibitor; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities

Figure adapted from: Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24:323-34

ADVERSE EVENT MANAGEMENT

- Effective and early management of AEs is likely to improve medication adherence and reduce discontinuation of therapy
  - Nurses can implement strategies to prevent and manage TEAEs along the patient's treatment path[1]
- Educate the patient to control blood pressure levels during treatment, recording levels to identify raises as soon as possible
- Explain rash reactions
  - Identify reactions and take pictures to evaluate progression
- Use QoL questionnaires to evaluate cognitive impairment
- Encourage patients to exercise regularly and eat a healthy diet
- Evaluate risk of bone fracture prior to initiation of any therapy, and evaluate ongoing risk during treatment

AE, adverse event; QoL, quality of life; TEAE, treatment-emergent adverse event

1. Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58

DRUG–DRUG INTERACTIONS

- Novel hormonal agents (NHAs) can modify the absorption, distribution, metabolism, and/or elimination of a concomitant drug taken by the patient for comorbidities
- Results from the studies (including pharmacokinetic results) can be used to guide treatment selection
- A close review of concomitant medications is essential before initiating therapy
  - Avoid enzalutamide and apalutamide in a patient with a history of CVD
  - Select the best therapy for pain control, when required, according to the different DDIs
  - Review and modify, when necessary, the medication in patients with high cholesterol levels
  - Evaluate concomitant medication in patients with a history of seizures taking anticonvulsants to prevent DDIs

CVD, cardiovascular disease; DDI, drug–drug interactions

POTENTIAL DRUG-DRUG INTERACTIONS OF NHA'S WITH COMMONLY USED PC MEDICATIONS

Interaction	**Substrate** AR inhibitor increases plasma level of comedication May increase risk of AEs associated with comedication	**Substrate** AR inhibitor decreases plasma level of comedication May lead to a decrease in activity of comedication	**Inducer** Comedication decreases plasma level of AR inhibitor May lead to a decrease in activity of AR inhibitor	**Inhibitor** Comedication increases plasma level of AR inhibitor May increase risk of AEs associated with AR inhibitor

Medicinal product		Apalutamide	Enzalutamide	Darolutamide
Antithrombotics	Clopidogrel		✗	
	Dabigatran	CAUTION	CAUTION	
	Rivaroxaban	✗	✗	
	Warfarin	✗	✗	
Calcium channel blockers	Amlodipine	CAUTION	CAUTION	
	Diltiazem		✓	✓
	Nifedipine, felodipine	✗	✗	
	Verapamil		CAUTION	✓
Cardiac glycosides	Digoxin	CAUTION	CAUTION	
Proton pump inhibitor	Omeprazole	✗	✗	
Analgesics	Fentanyl	CAUTION	✗	
Hypnotics	Diazepam	✗	✗	
	Midazolam	✗	✗	
Antipsychotics	Haloperidol	✗	✗	
Antibiotics	Clarithromycin	CAUTION		CAUTION
	Rifampicin		✗	CAUTION
Anticonvulsants	Carbamazepine		✗	CAUTION
Statins	Rosuvastatin	CAUTION		CAUTION

Note: Recommendations provided in the US PI, EMA SPC, and NICE BNF. ✓ Comedication can be combined with AR inhibitor. ✗ Avoidance or substitution of comedication is recommended. CAUTION indicates comedication should be administered with caution and/or dose adjustment based on efficacy/tolerability is recommended.

AE, adverse event; AR, androgen receptor; BNF, British National Formulary; EMA, European Medicines Agency; NHA, novel hormonal agent; NICE, National Institute for Health and Care Excellence; PC, prostate cancer; PI, prescribing information; SPC, summary of product characteristics

Adapted from: Olivier KM, et al. Int J Urol Nurs. 2021;15:47-58 in conjunction with US PI, EMA SPC, and NICE BNF

TREATMENT IS ASSOCIATED WITH MAINTENANCE OF HRQoL

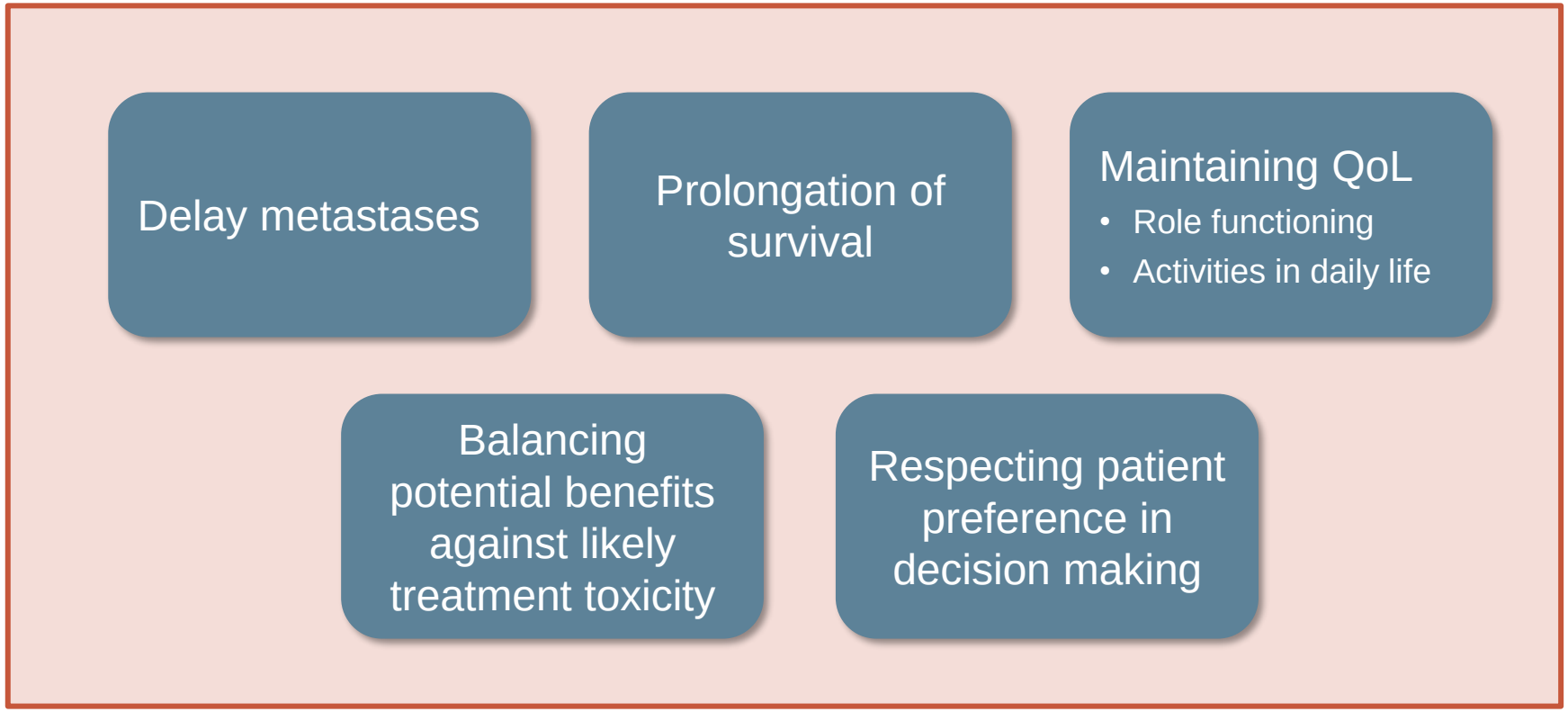
- **Second-generation ARIs prolonged survival while maintaining HRQoL**
- No treatment-induced deterioration in QoL occurred
- Improvement and delay in time to deterioration was also observed in some items evaluated

Study	QoL instrument	Median time to deterioration, months (95% CI)		p value
		Study drug	Placebo	
SPARTAN[1] (apalutamide)	FACT-P total score	6.6 (5.6-8.3)	8.4 (6.5-12.9)	0.60
	FACT-P PCS	3.8 (3.7-4.7)	3.8 (2.9-4.8)	0.60
PROSPER[2] (enzalutamide)	FACT-P total score	22.11 (18.63-25.86)	18.43 (14.85-19.35)	0.037
	FACT-P PCS	18.43 (14.85 -18.66)	14.69 (11.07-16.20)	0.0042
	EORTC QLQ-PR25 Urinary	36.86 (33.35-NR)	25.86 (18.53-29.47)	<0.0001
	EORTC QLQ-PR25 Bowel	33.15 (29.50-NR)	25.89 (18.43-29.67)	0.0018
ARAMIS[3] (darolutamide)	FACT-P PCS	11.07 (11.04-11.14)	7.88 (7.46-11.07)	0.0005
	EORTC QLQ-PR25 Urinary	25.8 (22.0-33.1)	14.8 (11.2-15.1)	<0.0001
	EORTC QLQ-PR25 Bowel	18.4 (14.8-18.5)	11.5 (11.1-14.8)	0.0027

ARI, androgen receptor inhibitor; CI, confidence interval; EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-P(CS), Functional Assessment of Cancer Therapy–Prostate; HRQoL, health-related quality of life; NR, not reached; PCS, prostate cancer subscale; QoL, quality of life

1. Oudard S, et al. Eur Urol Focus. 2022; 2022;8:958-67; 2. Tombal B, et al. Lancet Oncol. 2019;20:556-69; 3. Smith M, et al. Eur J Cancer. 2021;154:138-46

TREATMENT GOALS FOR nmCRPC



Be aware that the patient's goals and preferences may change over time as symptoms increase, side effects mount, or QoL declines

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

Lee VE, et al. J Cancer Sci Clin Ther. 2021;5:154-60

SUMMARY

- The recent approval of three second-generation oral ARIs for nmCRPC (apalutamide, enzalutamide and darolutamide) offers patients an expanded range of new and highly effective treatment options
- Individualised treatment selection is important; comorbidities and potential DDIs should be taken into consideration in addition to tolerability and safety profiles
- A multidisciplinary team with nurses taking a key role is essential for selecting the best therapy according to the patient's wishes, medical history, concomitant medication, and prognosis

ARI, androgen receptor inhibitor; DDI, drug–drug interactions

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