
GU
connect®
POWERED BY COR2ED

INDIVIDUALISING TREATMENT STRATEGIES FOR nmCRPC

Dr. Ray A. Manneh Kopp, MD
Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia

NOVEMBER 2021

nmCRPC, non-metastatic castration-resistant prostate cancer

DISCLAIMER AND DISCLOSURES

Please note: The views expressed within this presentation are the personal opinions of the authors. They do not necessarily represent the views of the author's academic institution or the rest of the GU CONNECT group.

This content is supported by an independent educational grant from Bayer.

Dr. Ray A. Manneh Kopp has received financial support/sponsorship for research support, consultation or speaker fees from the following companies:

- Astellas, AstraZeneca, Bayer, BMS, Dr Reddy's, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Tecnofarma

INTRODUCTION

- Patients with nmCRPC progress to metastatic disease and are at risk of developing cancer-related symptoms and morbidity, eventually dying of their disease
- While patients with **nmCRPC are generally asymptomatic from their disease**, they are **often older and have chronic comorbidities that require long-term concomitant medication**. Therefore, careful consideration of the benefit–risk profile of potential treatments is required

CV, cardiovascular disease; nmCRPC, non-metastatic castration-resistant prostate cancer

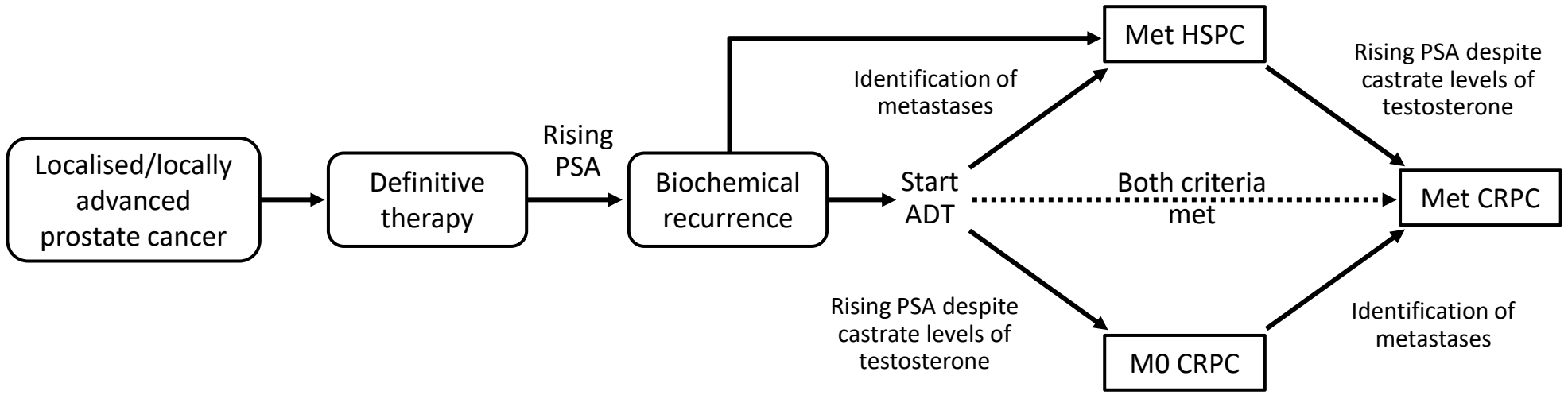
Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24(2):323-34; Morgans AK, et al. Urol Oncol. 2021;39(1):52-62

WHAT IS nmCRPC?

Testosterone in castration levels

Rising PSA levels

No evidence of disease w/ conventional imaging (CT, MRI, bone scan)



ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; CT, computed tomography; HSPC, hormone-sensitive prostate cancer; M0, non-metastatic; Met, metastatic; MRI, magnetic resonance imaging; PSA, prostate-specific antigen

Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24(2):323-34

SECOND-GENERATION ANDROGEN RECEPTOR INHIBITORS

- **Second-generation androgen receptor inhibitors** have demonstrated an **overall survival benefit in nmCRPC patients:**
  - Apalutamide
  - Enzalutamide
  - Darolutamide
- **It is important to balance the clinical benefit they offer with potential adverse events** and the consequential impact on quality of life, physical capacity, and cognitive function
- **Management strategies for patients with nmCRPC** also treated for comorbidities including CV disease **require appropriate selection of therapy**, diet, and exercise **to meet the needs of the individual patient profile**

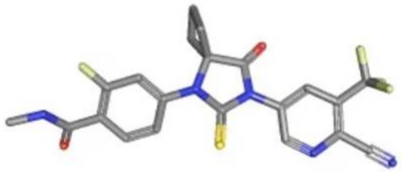
CV, cardiovascular disease; nmCRPC, non-metastatic castration-resistant prostate cancer

Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24(2):323-34; Morgans AK, et al. Urol Oncol. 2021;39(1):52-62

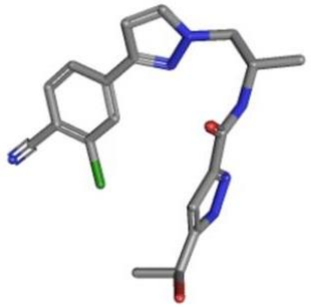
SECOND-GENERATION ANDROGEN RECEPTOR INHIBITORS

enzalutamide

apalutamide



darolutamide



- Darolutamide is structurally distinct from apalutamide and enzalutamide and is characterised by low blood–brain barrier penetration[1,2]
  - This could result in less CNS toxicity and improved tolerability

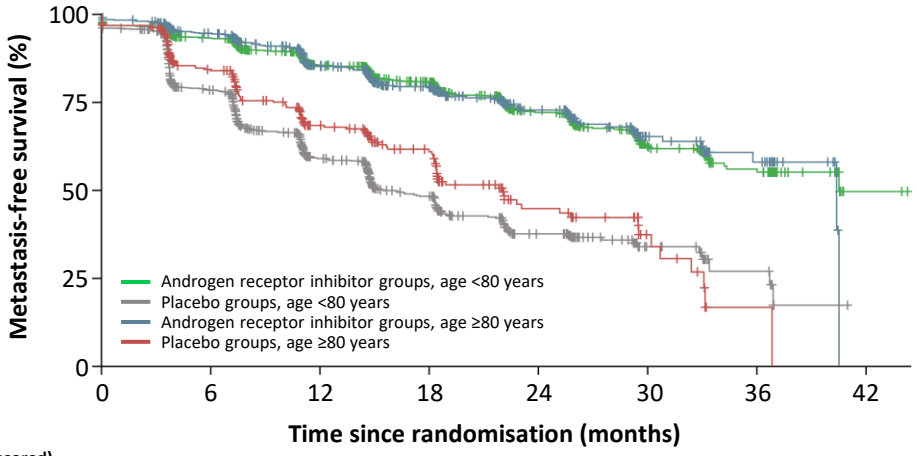
CNS, central nervous system

1. Zurth C, et al. J Clin Oncol. 2018;36 suppl 6:345; 2. Zurth C, et al. J Clin Oncol. 2019;37 suppl 7:156; Fizazi K, et al. J Clin Oncol. 2019;37 suppl 7:140; Images from PubChem database: https://pubchem.ncbi.nlm.nih.gov/; Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24(2):323-34

WHICH TREATMENT FOR WHICH PATIENT?

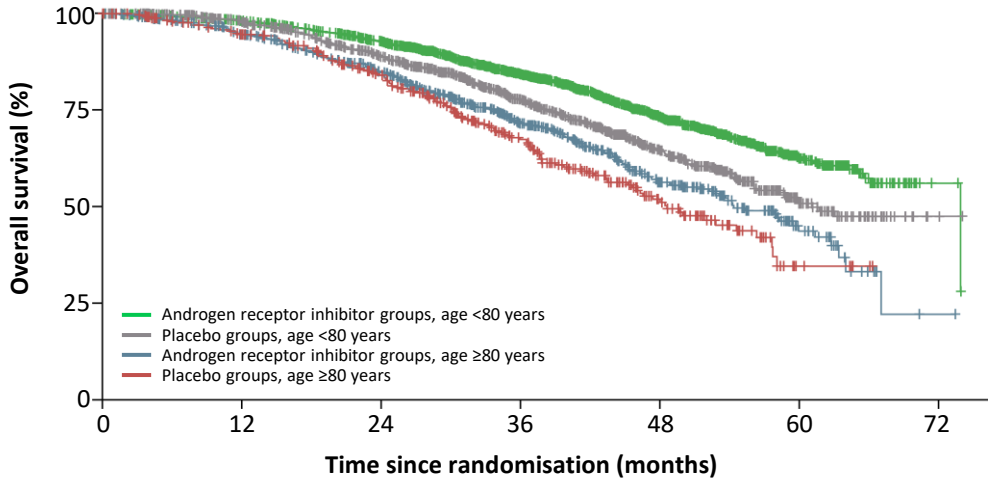
SURVIVAL OUTCOMES IN OLDER MEN WITH nmCRPC

METASTASIS-FREE SURVIVAL



Number at risk (number censored)								
Androgen receptor inhibitor groups, age <80 years	2,019 (0)	1,704 (183)	1,183 (580)	905 (798)	479 (1,149)	152 (1,434)	66 (1,510)	2 (1,572)
Placebo groups, age <80 years	1,075 (0)	694 (170)	342 (374)	204 (459)	94 (533)	23 (599)	8 (611)	0 (617)
Androgen receptor inhibitor groups, age ≥80 years	675 (0)	558 (83)	361 (233)	265 (307)	127 (429)	48 (498)	21 (521)	0 (540)
Placebo groups, age ≥80 years	348 (0)	238 (60)	141 (117)	90 (155)	36 (190)	11 (211)	1 (216)	0 (216)

OVERALL SURVIVAL



Number at risk (number censored)							
Androgen receptor inhibitor groups, age <80 years	2,019 (0)	1,916 (65)	1,707 (173)	1,187 (554)	630 (987)	157 (1,397)	3 (1,543)
Placebo groups, age <80 years	1,075 (0)	974 (79)	800 (167)	519 (362)	260 (550)	61 (712)	2 (768)
Androgen receptor inhibitor groups, age ≥80 years	675 (0)	602 (38)	486 (95)	307 (206)	144 (319)	32 (412)	1 (438)
Placebo groups, age ≥80 years	348 (0)	303 (27)	242 (56)	148 (107)	64 (163)	7 (208)	0 (215)

nmCRPC, non-metastatic castration-resistant prostate cancer

Fallah J, et al. Lancet Oncol. 2021:22:1230-39

CARDIOVASCULAR RISK

- **Prostate cancer and cardiovascular disease (CVD) share several risk factors**, with the incidence of both rising with increasing age
- ARIs are associated with an increased risk of hypertension and major adverse CV events
- It is important to **try to mitigate CV risk for nmCRPC patients where possible by considering drug–drug interactions** when prescribing ARIs, especially for men with CV comorbidities
- Apalutamide and enzalutamide are substrates of CYP2C8, CYP2C9, and CYP3A4, and this should be noted when prescribing vitamin K antagonists
- The potential for ARI interaction with statins or anti-hypertensives should be considered

THE ABCDE ALGORITHM FOR MANAGING CVD IN PATIENTS WITH PROSTATE CANCER

ARI, androgen receptor inhibitor; CV, cardiovascular; CVD, cardiovascular disease; CYP, cytochrome P450; nmCRPC, non-metastatic castration-resistant prostate cancer

Morgans AK, et al. Urol Oncol. 2021;39(1):52-62

COGNITIVE DYSFUNCTION

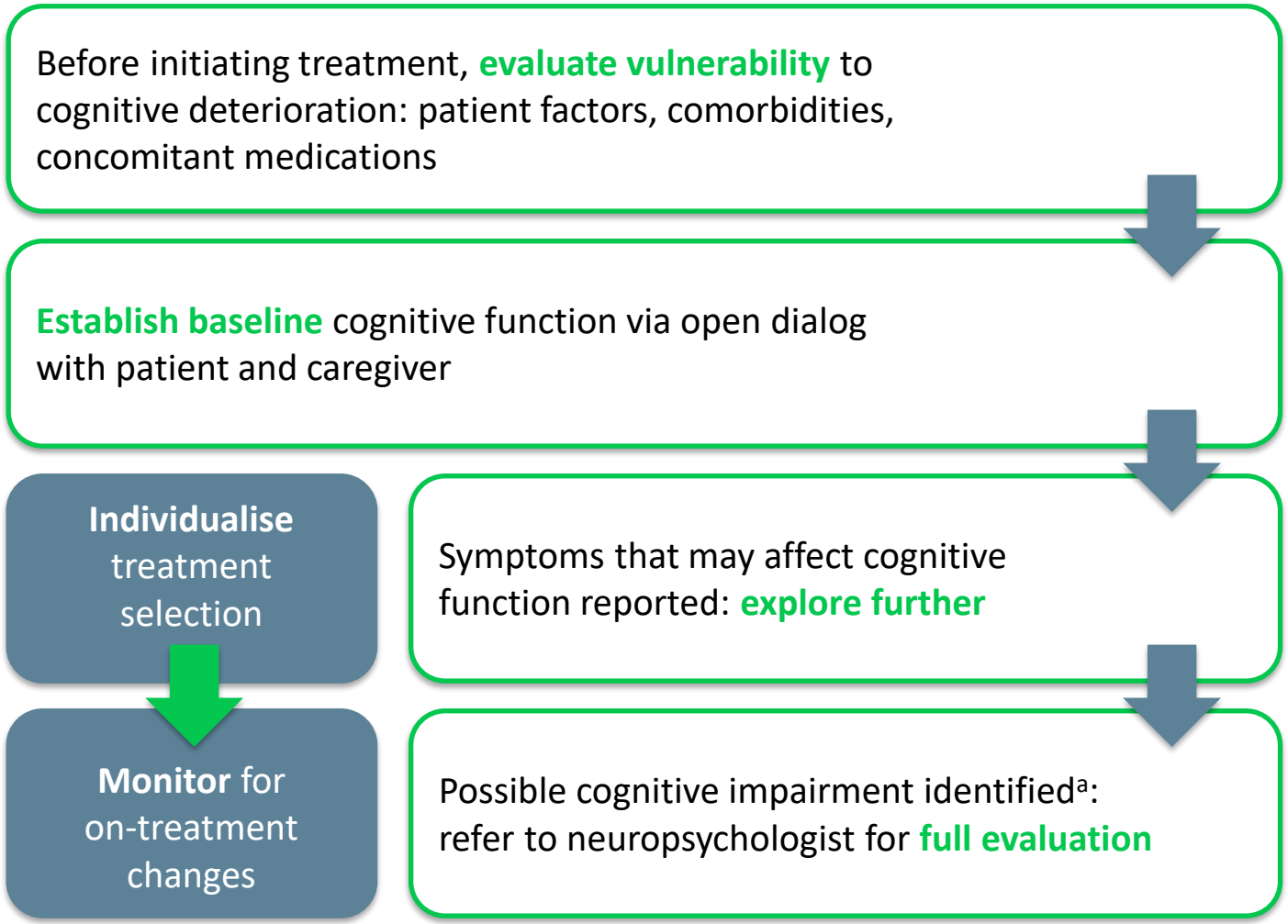
- **Prostate cancer is mainly a disease of older men**, with a median age of 66 years at diagnosis. The risk of neurocognitive decline generally increases over 60 years of age in people without cancer
- **Cognitive decline may further increase in prostate cancer patients due to exposure to androgen deprivation therapy and other hormonal therapies**
  - This is particularly an issue on CRPC patients as they receive continuous, long-term androgen deprivation therapy combined with a second-generation androgen receptor inhibitor
- **Second-generation anti-androgens** are well tolerated
- **Signs of cognitive decline should be proactively evaluated during treatment**
- The inclusion of specific questions for monitoring of cognitive function may be useful to enhance safety

CRPC, castration-resistant prostate cancer

Morgans AK, et al. Clin Genitourin Cancer. 2021;19(5):467.e1-467.e11; Manneh R, et al. Manuscript awaiting publication

ASSESSING ON-TREATMENT COGNITIVE FUNCTION IN PATIENTS WITH PROSTATE CANCER

GU connect® POWERED BY COR2ED



[a] In the absence of organic complications

Morgans AK, et al. Clin Genitourin Cancer. 2021;19(5):467.e1-467.e11

TOXICITY PROFILE

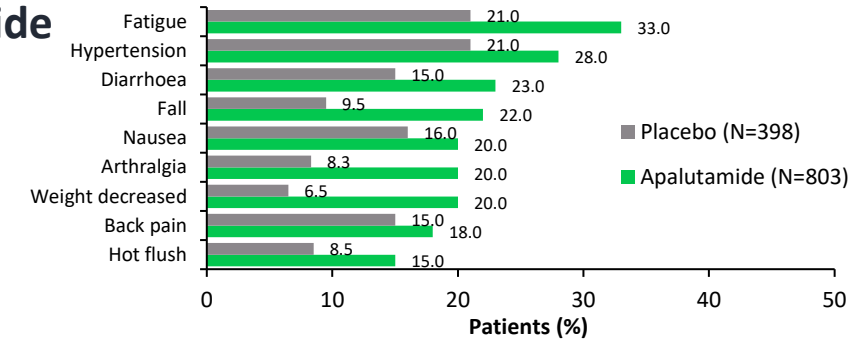
- There appears to be **increased grade 3–4 toxicity, serious adverse events, falls, and fractures in patients aged ≥ 80 years** compared with patients < 80 years, regardless of treatment with second generation ARIs or placebo
- Adverse events of special interest associated with ARI treatment, are:
  - Fatigue
  - Hypertension
  - Rash
  - Falls
  - Fractures
  - Mental impairment disorders
- **Enzalutamide, apalutamide and darolutamide have not been directly compared in a clinical trial**, therefore conclusions should not be drawn by comparing safety data across the trials due to differences in clinical trial design and populations
  - **the individual safety profiles should therefore be considered for each patient**

ARI, androgen receptor inhibitor; nmCRPC, non-metastatic castration-resistant prostate cancer

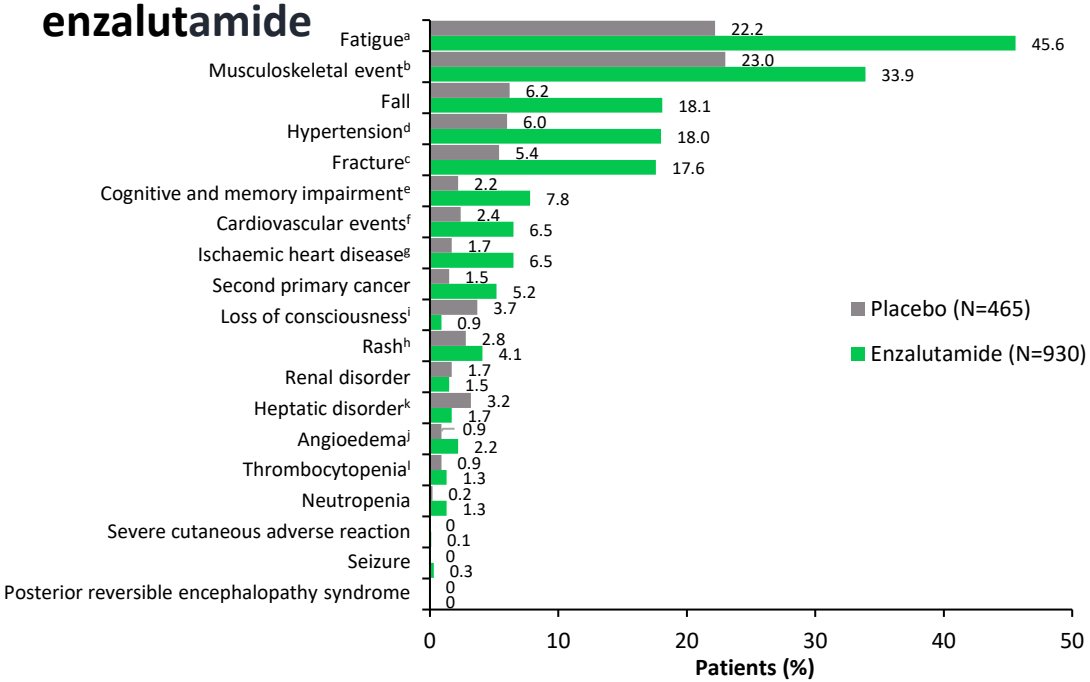
Fallah J, et al. Lancet Oncol. 2021:22:1230-39; Smith MR, et al. N Engl J Med. 2018;378:1408-18; Smith MR, et al. Eur Urol. 2021;79:150-8; Sternberg CN, et al. N Engl J Med. 2020;382:2197-206; Fizazi K, et al. N Engl J Med. 2020;383:1040-9

INCIDENCE OF ADVERSE EVENTS

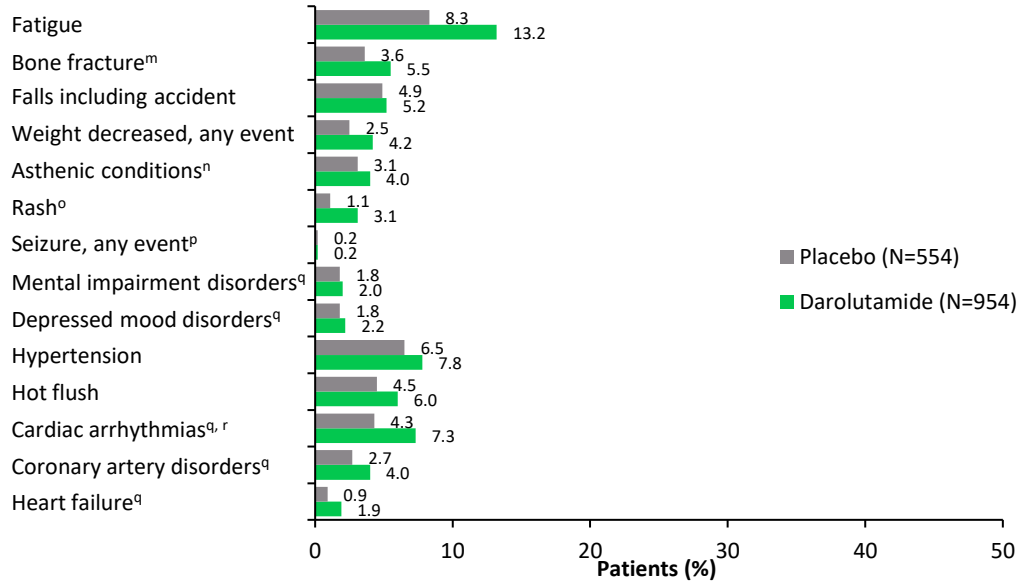
SPARTAN:[1,2] apalutamide



PROSPER:[3] enzalutamide



ARAMIS:[4] darolutamide



Incidence of adverse events 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]Fracture events included bone and joint injuries. [d]Hypertension events included hypertensive retinopathy, increased blood pressure, systolic hypertension, and hypertensive crisis. [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]Rash events included maculopapular rash, generalised rash, macular rash, papular rash, and pruritic rash. [i]Loss-of-consciousness events included syncope and presyncope. [j]Angio-oedema events included urticaria, eyelid oedema, periorbital oedema, swollen tongue, swollen lip, face oedema, laryngeal oedema, and pharyngeal oedema. [k]Hepatic disorders included hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions, and hepatitis and liver-related investigations, signs, and symptoms. [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.

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

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: Saad F, et al. Prostate Cancer Prostatic Dis. 2021;24(2):323-34

POTENTIAL DRUG–DRUG INTERACTIONS

- Polypharmacy for age-related comorbidities is common in patients with nmCRPC, and this increases the risk of drug–drug interactions
- Comorbidities and DDIs should therefore be considered when selecting treatment for nmCRPC patients

Apalutamide

- Concomitant use with medications that are sensitive substrates of **CYP3A4, CYP2C19, CYP2C9**, **UGT**, **P-gp**, **BCRP**, or **OATP 1B1** may result in loss of activity of these medications

Enzalutamide

- **CYP2C8** inhibitors may increase the plasma exposure of enzalutamide
- strong **CYP3A4** inducers may decrease the plasma exposure to enzalutamide
- **CYP3A4, CYP2C9 and CYP2C19** substrates may result in loss of activity of these medications

Darolutamide

- Avoid concomitant use with combined **P-gp** and strong or moderate **CYP3A inducers**
- Monitor patients for AEs with concomitant combined P-gp and strong **CYP3A inhibitors**
- Avoid concomitant use with drugs that are **BCRP** substrates where possible
- Concomitant use may increase the plasma concentrations of **OATP1B1 or OATP1B3** substrates

AEs, adverse events; BCRP, breast cancer resistance protein ; CYP, cytochrome; DDIs, drug–drug interactions; nmCRPC, non-metastatic castration-resistant prostate cancer; OATP, organic anion transporter peptide; P-gp, P-glycoprotein; UGT, uridine 50-diphosphoglucuronosyltransferase

apalutamide Prescribing Information (09/2021); enzalutamide Prescribing Information (07/2021); darolutamide Prescribing Information (01/2021)

POTENTIAL DRUG–DRUG INTERACTIONS

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		✗	✗
Anticonvulsants	Carbamazepine		✗	✗
Statins	Rosuvastatin	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; NICE, National Institute for Health and Care Excellence; PI, prescribing information; SGARIs, second-generation androgen receptor inhibitors; SPC, summary of product characteristics

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

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/SGARI	QoL Instrument	Median time to deterioration, Mo (95% CI)		P-value
		SGARI	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-NE)	25.86 (18.53-29.47)	<0.0001
	EORTC QLQ-PR25 Bowel	33.15 (29.50-HR)	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

ARIs, androgen receptor inhibitors; 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 (Cancer Subscale); 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 2021: doi: 10.1016/j.euf.2021.08.005; 2. Tombal B, et al. Lancet Oncol 2019; 20: 556-569; 3. Smith M, et al. European Journal of Cancer 2021; 154: 138-146

SUMMARY

- nmCRPC patients are generally asymptomatic and treatment should be carefully selected according the patient profile
- Risk–benefit analysis usually favours initiating treatment with second generation ARIs even in older patients
- Comorbidities and drug–drug interactions have to be considered
- Cognitive function should be evaluated prior to initiation of treatment as well as continuously monitored during treatment

ARIs, androgen receptor inhibitors; nmCRPC, non-metastatic castration-resistant prostate cancer

REACH GU CONNECT VIA TWITTER, LINKEDIN, VIMEO & EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.guconnect.info

Follow us on Twitter
@guconnectinfo

Follow the
GU CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
GU CONNECT

Email
sam.brightwell@cor2ed.com

GU connect®
POWERED BY COR2ED

GU CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

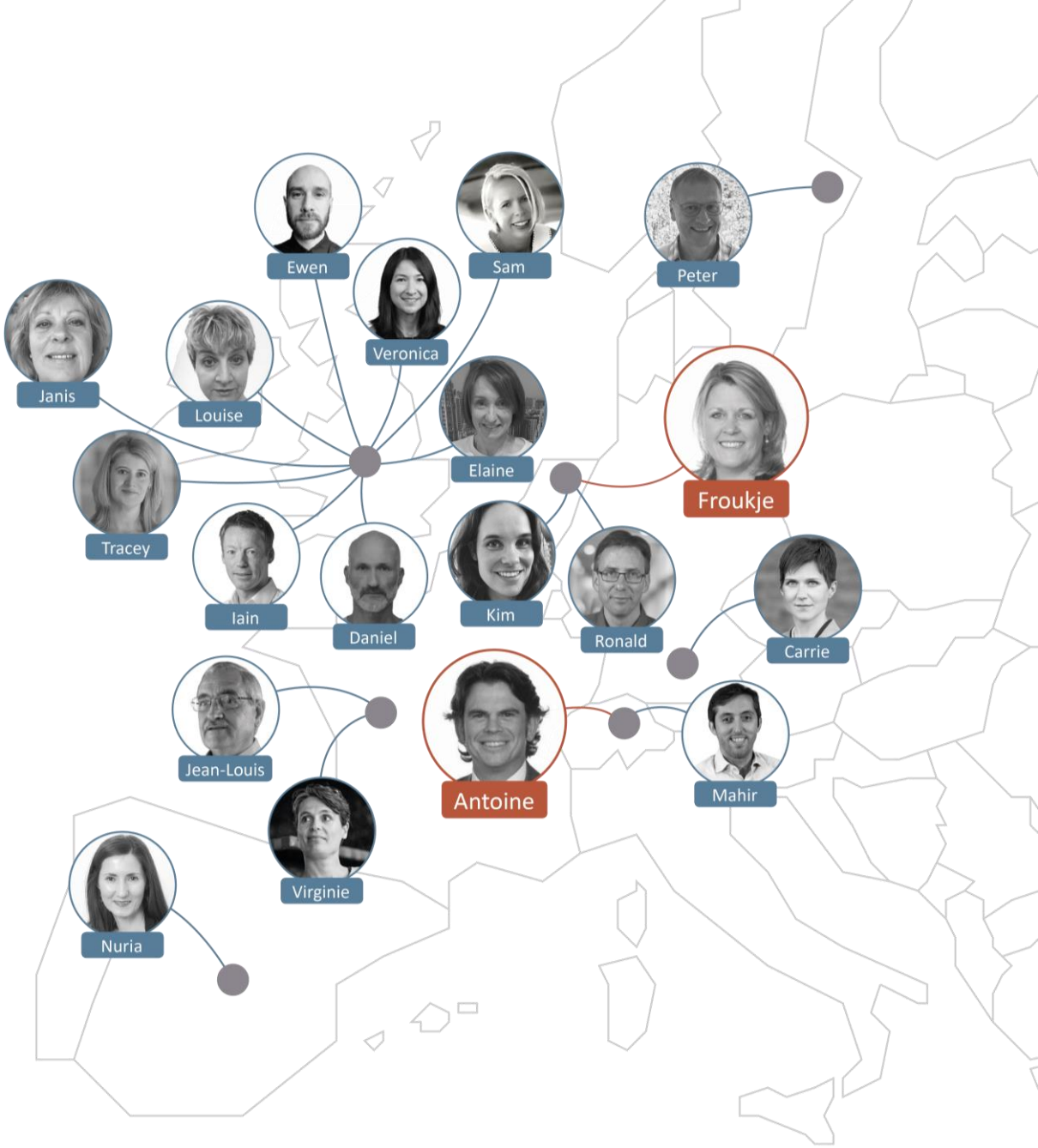
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @GU CONNECT

Watch on
Vimeo @GU CONNECT

Visit us at
guconnect.info

Follow us on
Twitter @guconnectinfo



Heading to the heart of Independent Medical Education Since 2012