INTEGRATING PATIENT PREFERENCE INTO TREATMENT DECISIONS FOR ADVANCED PROSTATE CANCER

Dr. Alicia K. Morgans, MD, MPH
Dana-Faber Cancer Institute, Boston, MA, USA

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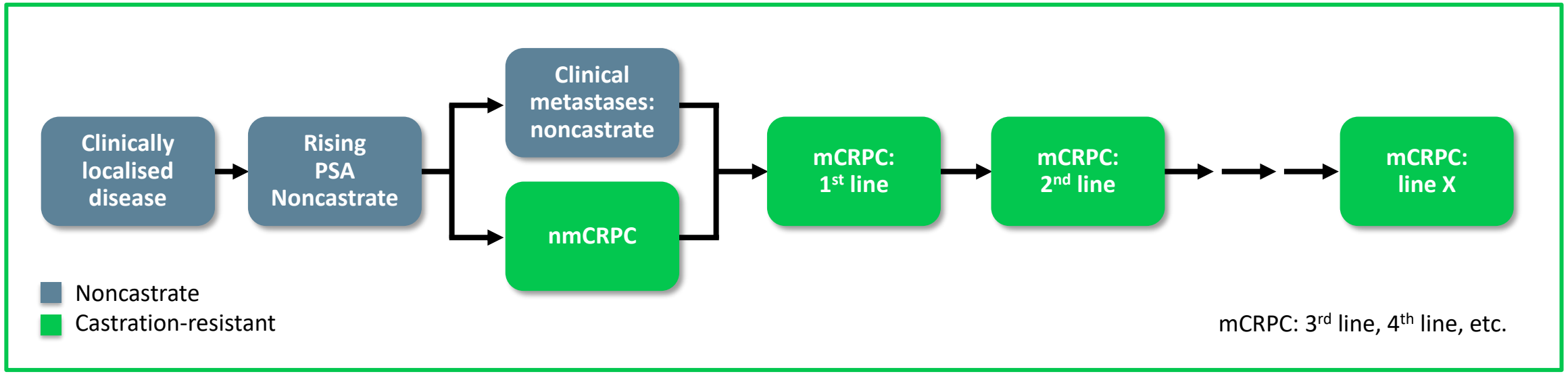
CLINICAL DISEASE-STATES MODEL OF PROSTATE CANCER

What is advanced prostate cancer?

- Castration-resistant prostate cancer (CRPC) is a form of advanced prostate cancer. CRPC means the prostate cancer is growing or spreading even though testosterone levels are low from hormone therapy

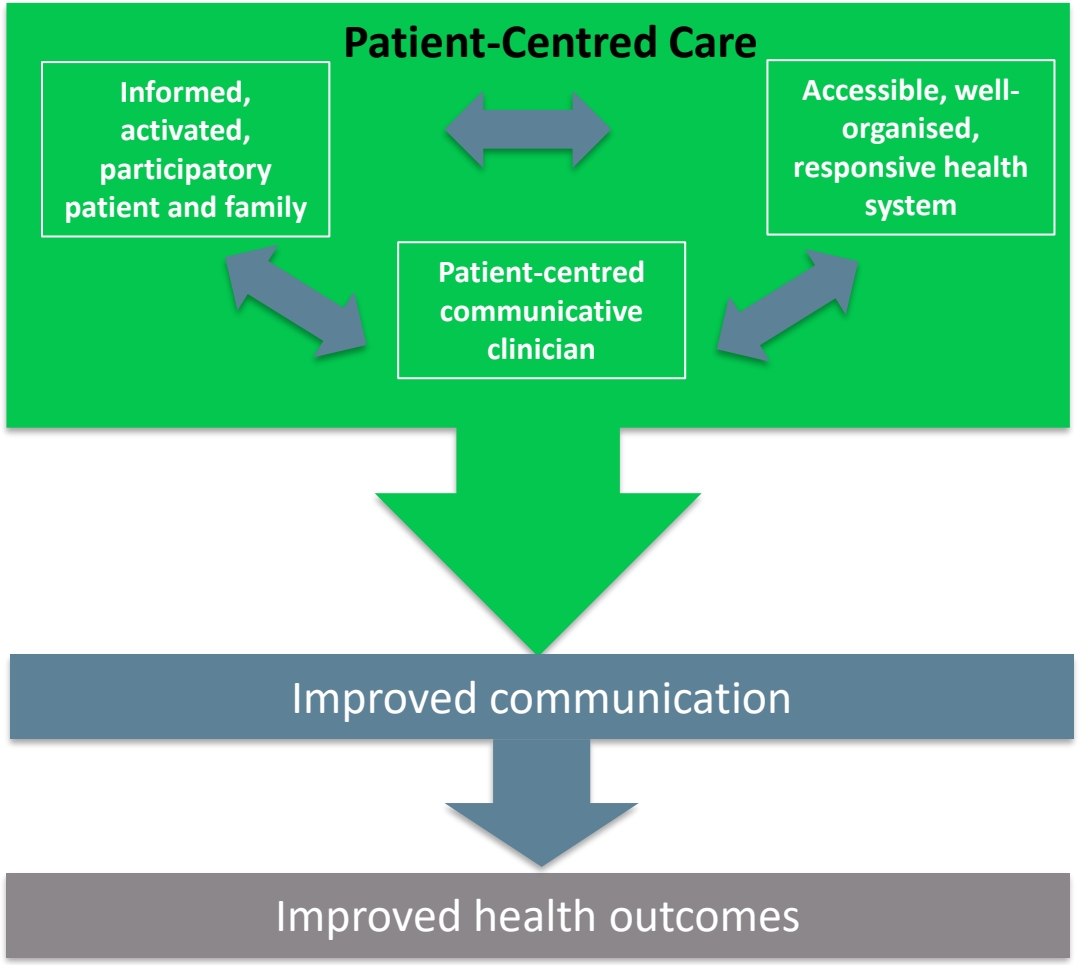


(n)mCRPC, (non)metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen

Scher HI, et al. J Clin Oncol. 2016;34:1402-18

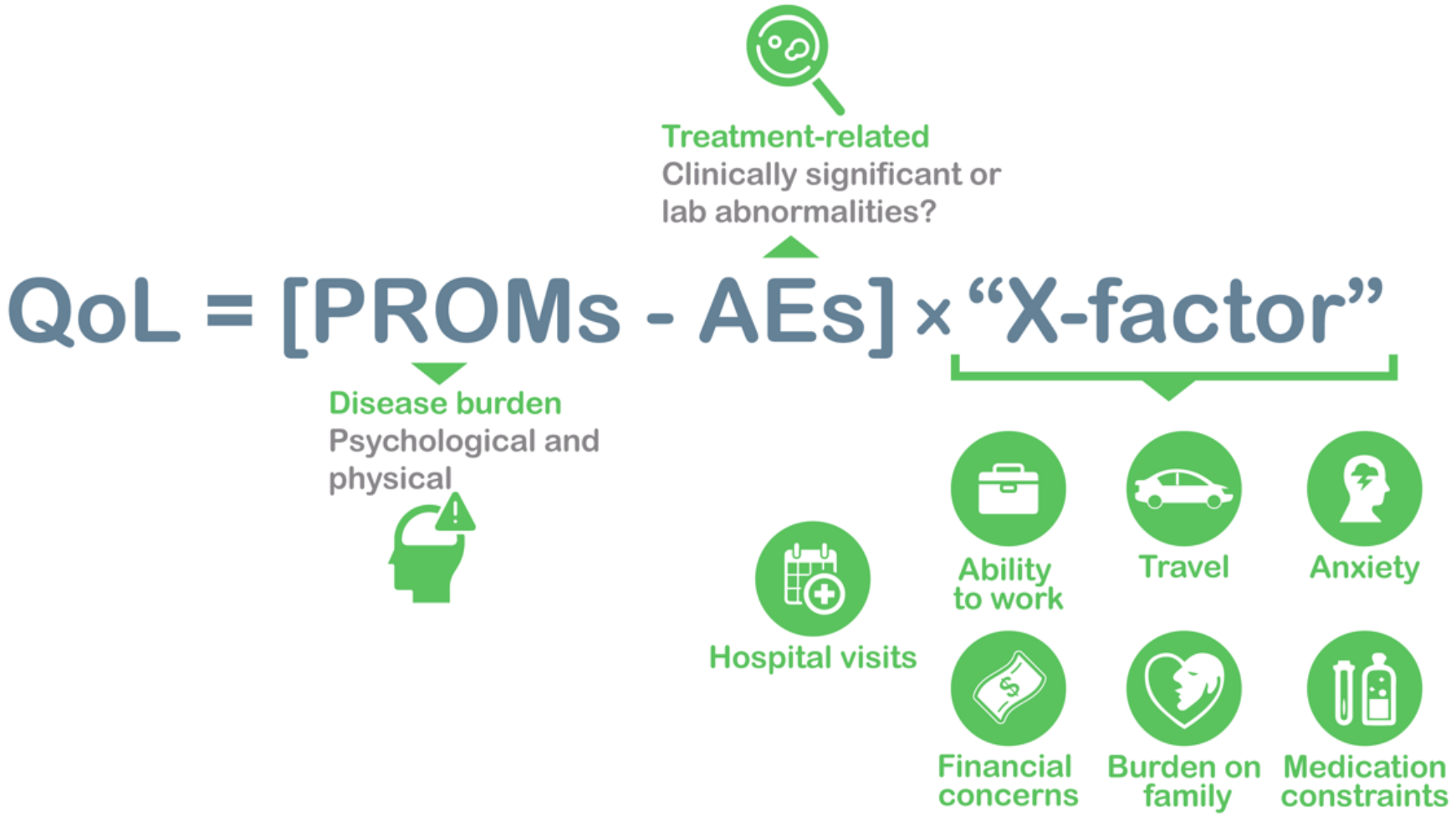
PATIENT-CENTRED CARE CAN IMPROVE OUTCOMES

- Patient satisfaction
- Adherence to treatment plans
- Clinical outcomes
  - Pain
  - Psychological distress
  - Quality of life
  - Disease-specific outcomes



Schmittdiel J, et al. J Gen Intern Med. 2008;23:77-80; Epstein RM, et al. National Cancer Institute, NIH Publication No. 07-6225. Bethesda, MD, 2007; Meterko M, et al. Health Serv Res. 2010;45:1188-204; Glasgow RE, et al. Diabetes Care. 2005;28:2655-61; Kehl KL, et al. JAMA Oncol. 2015;1:50-8

WHAT CONTRIBUTES TO QoL?



AE, adverse event; PROM, patient-reported outcome measure; QoL, quality of life

TREATMENT IS ASSOCIATED WITH MAINTENANCE OF HRQoL

- **SGARIs prolonged survival while maintaining HRQoL.** No treatment-induced deterioration in overall QoL as measured by FACT-P total score
- 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-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

CI, confidence interval; EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HRQoL, health-related quality of life; Mo, month; NR, not reached; PCS, Prostate Cancer Subscale; QoL, quality of life; SGARIs, second-generation androgen receptor inhibitors

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;20:556-69; 3. Smith MR, et al. Eur J Cancer. 2021;154:138-46

ADVERSE EVENTS IN nmCRPC

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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 (17.0)	41 (9.0)	85 (8.9)	48 (8.7)
AE leading to death, n (%)	24 (3.0)	2 (0.5)	51 (5.0)	3 (1.0)	38 (4.0)[c]	19 (3.4)[c]
AE (all grades), %						
Fatigue	33	21	37	16	13.2	8.3
Hypertension	28	21	18	6	7.8	6.5
Rash	26	6.3	4	3	3.1	1.1
Falls	22	9.5	18	5	5.2	4.9
Fractures	18	7.5	18	6	5.5	3.6
Mental impairment disorder[a]	5.1[b]	3.0[b]	8	2	2.0	1.8

[a] SPARTAN: disturbance in attention, memory impairment, cognitive disorder and amnesia; PROSPER: disturbance in attention, cognitive disorders, amnesia, alzheimer's disease, mental impairment, dementia, vascular dementia and senile dementia; ARAMIS trial: MedRA High Level Group Term; [b] Data taken from first interim analysis as not reported in final analysis[1]; [c] reported as grade 5 adverse event

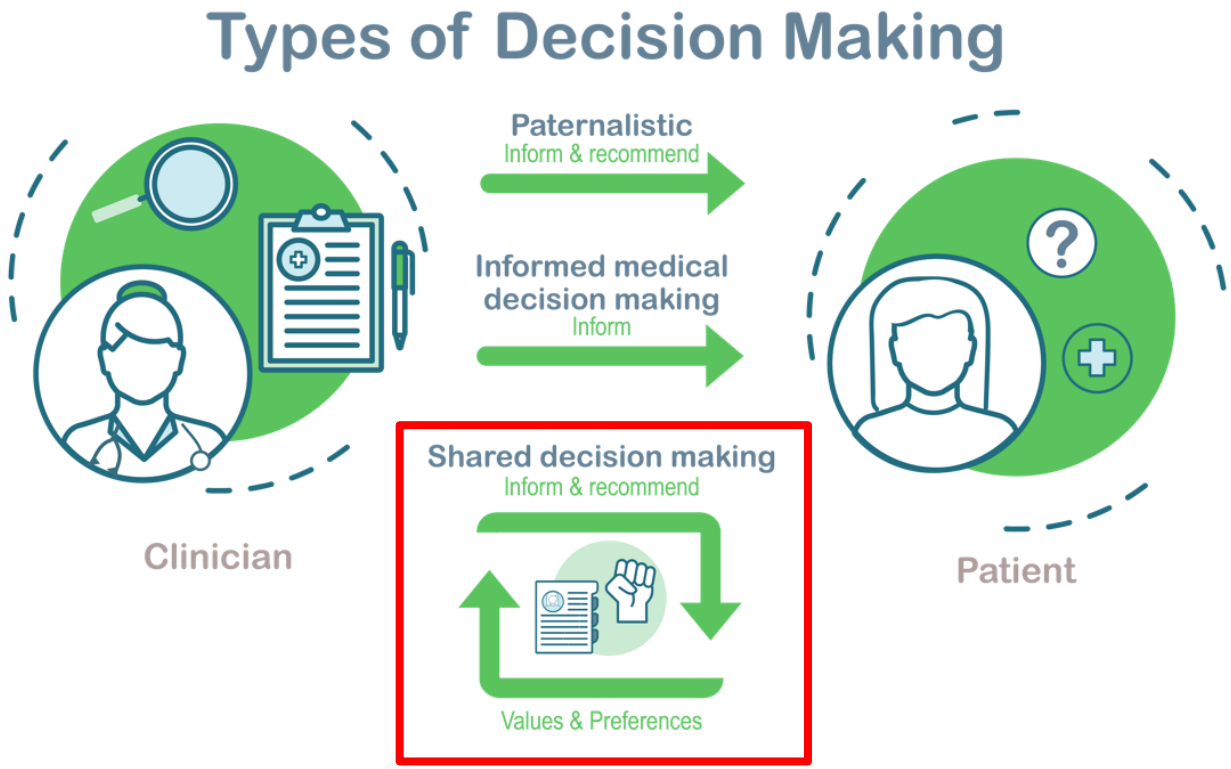
Presented for information, safety comparisons across trials should not be made

AE, adverse event; APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide; nmCRPC, nonmetastatic castration-resistant prostate cancer; 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

OTHER PATIENT FACTORS MUST ALSO GUIDE TREATMENT CHOICE

- Patient preferences critical, especially in settings of multiple treatment options
- Preferences may relate to obligations at home or work, past experiences, fears, cost of care, and others
- Pain and other symptoms that could prompt palliative radiation or other specialty care should also be discussed



Van Stam M-A, et al. The Journal of Urology 2018; 200: 582-589;https://www.therapeuticassociates.com/shared-decision-making/

DRUGS FOR CV INDICATIONS AND THEIR METABOLIC PATHWAYS

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Drug Class	Drugs	Indications	Metabolic Pathway	Management of Interaction
Anti-coagulant	rivaroxaban	Stroke; embolism prophylaxis; DVT	CYP3A4 and P-gp substrate	Avoid apalutamide; reduced rivaroxaban exposure
	dabigatran	Stroke; embolism prophylaxis; DVT	P-gp substrate	Avoid apalutamide; reduced dabigatran exposure
	apixaban	Stroke; embolism prophylaxis; DVT	CYP3A4 and P-gp substrate	Avoid apalutamide; reduced apixaban exposure; increased risk of stroke
	heparin	DVT; arterial thromboembolism	RES	NA
	warfarin	Prophylaxis of thromboembolism	CYP2C9 and CYP3A4	Strong potential for apalutamide and enzalutamide to reduce warfarin exposure
Anti-platelet agent	clopidogrel	Arterial thromboembolism prophylaxis; MI; unstable angina; TIA	CYP2C8 inhibitor, CYP2C19	Monitor for increased apalutamide-related AEs; avoid coadministration with enzalutamide due to increased prasugrel exposure
	prasugrel	Arterial thromboembolism prophylaxis; MI; unstable angina	CYP3A4 and CYP2B6 substrate	None noted
	ticagrelor	Arterial thromboembolism prophylaxis in patients with ACS	CYP3A4 substrate	Avoid apalutamide or enzalutamide coadministration due to decreased ticagrelor exposure
ACE inhibitor	captopril	HTN; heart failure	Hepatic, renal, P-gp inhibitor	NA
	enalapril	HTN	Renal	NA
	lisinopril	HTN; heart failure	Renal	NA
	perindopril	HTN	Hepatic, renal	NA
Angiotensin receptor blocker	candesartan	HTN; heart failure	Renal, fecal	NA
	losartan	HTN; stroke prophylaxis in patients with LVH; heart failure	CYP2C9, CYP3A4 substrate	NA
	valsartan	HTN; heart failure; reduction of mortality in patients with LVD or LVH following MI	CYP2C9 substrate	NA
Beta-blocker	atenolol	HTN; angina; acute MI	Renal, faecal	NA
	propranolol	HTN; angina; heart rate control	CYP2C19, CYP2D6, CYP1A2, P-gp substrate	Monitor for reduced effect if apalutamide or enzalutamide coadministered
	sotalol	Maintenance of normal sinus rhythm; ventricular arrhythmias; AF prophylaxis	Renal	NA
	metoprolol	Angina; HTN; heart failure; MI; heart rate control	CYP2D6 substrate	NA
	carvedilol	HTN; heart failure; reduction of mortality in patients with LVD following MI, angina, heart rate control	CYP2D6 substrate; CYP2C9, CYP3A4, CYP2C19, CYP1A2, CYP2E1, P-gp substrate and inhibitor	Monitor for decreased efficacy if apalutamide coadministered

ACS, acute coronary syndrome; AEs, adverse events; AF, atrial fibrillation; CV, cardiovascular; CYP, cytochrome; DVT, deep vein thrombosis; HTN, hypertension; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, not applicable; P-gp, P-glycoprotein; RES, reticuloendothelial system; TIA, transient ischaemic attack

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

KEY PHASE 3/4 TRIALS IN mCRPC

OVERALL SURVIVAL RESULTS

Study	Treatments	N	Population	HR	95% CI; p value
TAX 327[1]	Docetaxel[a]/prednisone vs mitoxantrone/prednisone	1,006	mCRPC	0.76	0.62-0.94; p=0.009
TROPIC[2]	Cabazitaxel/prednisone vs mitoxantrone/prednisone	755	mCRPC (post docetaxel)	0.70	0.59-0.83; p<0.0001
COU-AA-301[3]	Abiraterone/prednisone vs placebo/prednisone	1,195	mCRPC (post docetaxel)	0.74	0.64-0.86; p<0.0001
COU-AA-302[4]	Abiraterone/prednisone vs placebo/prednisone	1,088	mCRPC (chemotherapy naive)	0.81	0.70-0.93; p=0.0033
PREVAIL[5]	Enzalutamide vs placebo	1,717	mCRPC (pre chemotherapy)	0.71	0.60-0.84; p<0.001
AFFIRM[6]	Enzalutamide vs placebo	1,199	mCRPC (post docetaxel)	0.63	0.53-0.75; p<0.001
ALSYMPCA[7]	Radium-223 vs placebo	921	mCRPC	0.70	0.58-0.83; p<0.001
IMPACT[8]	Sipuleucel-T vs placebo	512	mCRPC (pre chemotherapy[b])	0.78	0.61-0.98; p=0.03
CARD[9]	Cabazitaxel/prednisone vs ASTI[c]	255	mCRPC (post docetaxel and post abiraterone or enzalutamide)	0.64	0.46-0.89; p=0.008
PROfound[10]	Olaparib vs ASTI[c]	387	mCRPC with HRR mutations (post abiraterone or enzalutamide or both. Previous taxane chemotherapy[d] was allowed))	0.69[e]	0.50-0.97; p=0.02
VISION[11]	^{177}Lu-PSMA-617 + SOC vs SOC[f]	831	PSMA-positive mCRPC previously treated with next-generation androgen receptor signaling inhibition and 1–2 taxane regimens	0.62	0.52-0.74; p<0.001

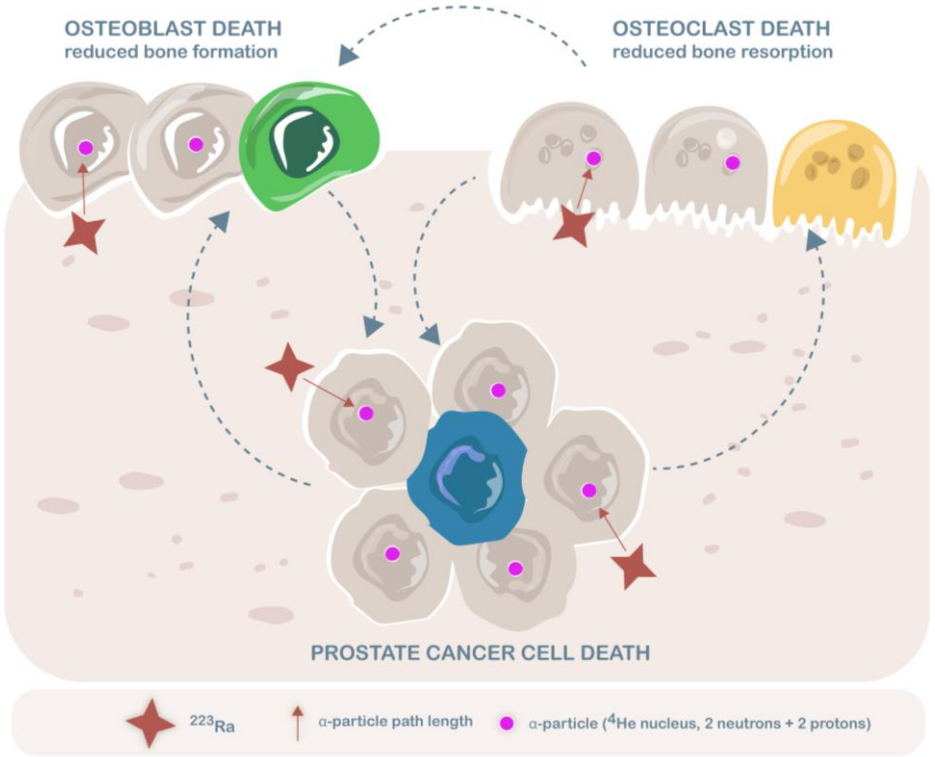
[a] 3-weekly docetaxel cycle; [b] 18.2% had received previous treatment with chemotherapy; [c] enzalutamide or abiraterone plus prednisone; [d] approximately 65% of patients had previously received taxanes; [e] Results for cohort A of study: patients with alterations in *BRCA1, BRCA2, ATM;* [f] SOC was investigator determined but excluded cytotoxic chemotherapy and radium-223

ASTI, androgen signaling targeted inhibitor; ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer 1/2; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; SOC, standard of care

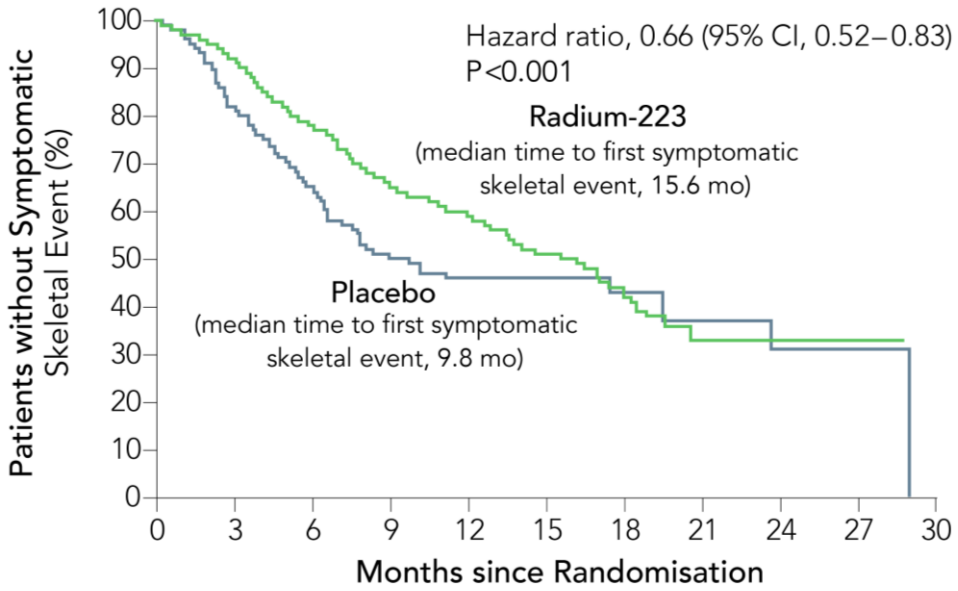
1. Tannock IF, et al. N Engl J Med. 2004;351:1502-12; 2. de Bono JS, et al. Lancet. 2010;376:1147-54; 3. Fizazi K, et al. Lancet Oncol. 2012;13;983-92; 4. Ryan CJ, et al. Lancet Oncol. 2015;16:152-60; 5. Beer TM, et al. N Engl J Med. 2014;371:424-33; 6. Scher HI, et al. N Engl J Med. 2012;367:1187-97; 7. Parker C, et al. N Engl J Med. 2013;369:213-23; 8. Kantoff PW, et al. N Engl J Med. 2010;363:411-22; 9. de Wit R, et al. N Engl J Med. 2019;381:2506-18; 10. Hussain M, et al. N Engl J Med. 2020;383:2345-57; 11. Morris MJ, et al. J Clin Oncol. 2021;39 suppl 18:LBA4

SYMPTOM MANAGEMENT: FOCUS ON PAIN

MECHANISM OF ACTION OF RADIUM-223



TIME TO FIRST SKELETAL EVENT



No. at Risk

Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

^{4}He, helium-4; ^{223}Ra, radium-223; CI, confidence interval; mo, months

Morris MJ, et al. Nat Rev Urol. 2019;16:745-56; Parker C, et al. N Engl J Med. 2013;369:213-23

CONCLUSIONS

- Involving patients in shared decision making for treatment of advanced prostate cancer is critical
- Patient preferences for quality-of-life outcomes and medication-related factors must be considered
- Optimise comorbidity management via engagement with specialists and primary care teams, and remember drug-drug interactions
- Pain is a top priority for patients and should be addressed via treatment of the cancer or use of other strategies (pain medications, palliative radiation, etc)

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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

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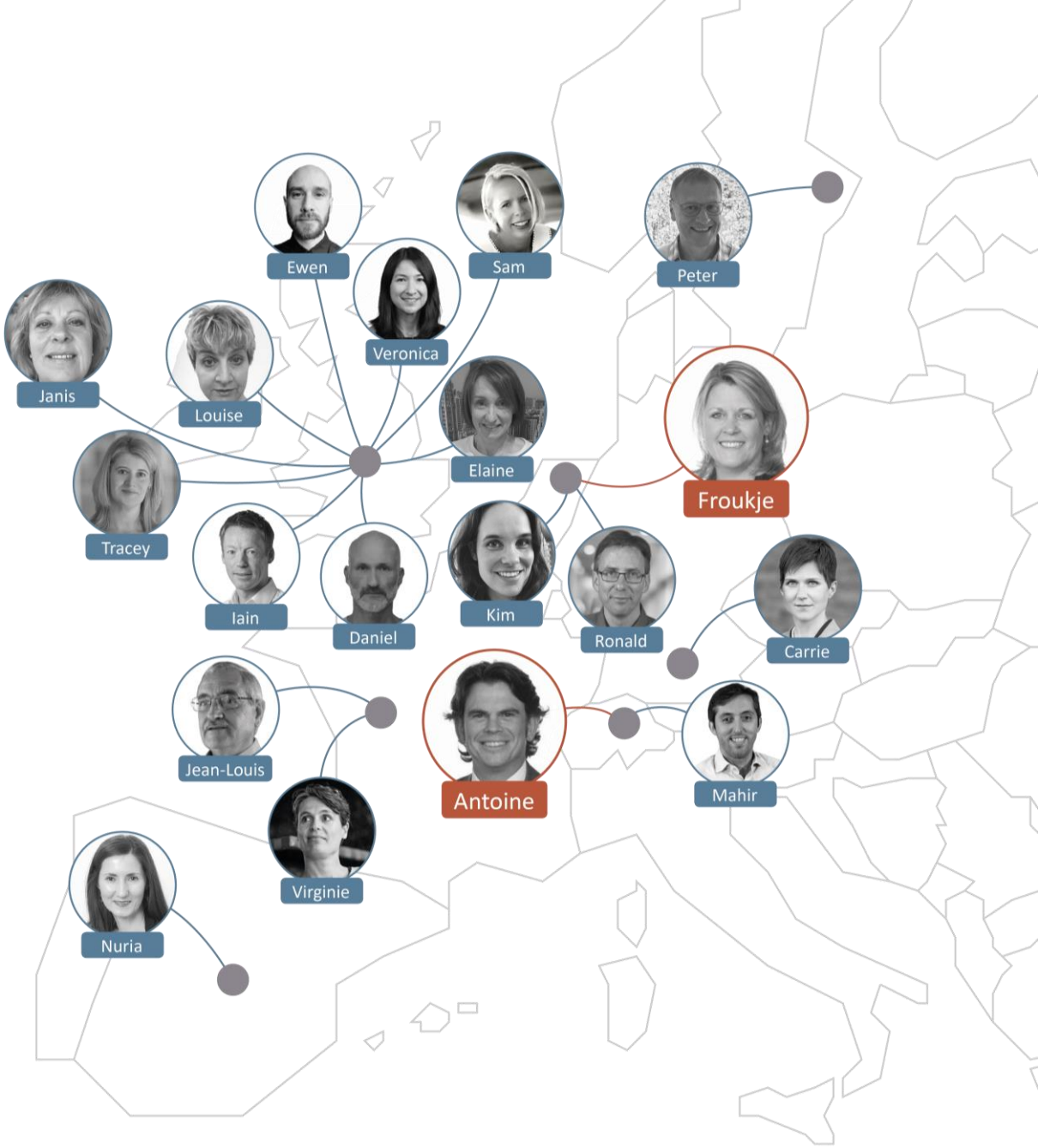

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