Non-Metastatic Castration-Resistant Landscape

5.00 pm – 5.20 pm	**Clinical Case and Evidence from Literature** E. Zanardi
5.20 pm – 5.50 pm	**Experts on stage** K. Fizazi – G. Procopio
5.50 pm – 6.30 pm	**Attendants in discussion** Drivers: N. Mottet - G. Pappagallo | Provokers: G. Facchini, L. Fratino, M. Maruzzo, R. Sabbatini
6.30 pm	*Closing remarks*

PRO STATE of the art 3rd ed.

24th, 25th January 2023

Teatro Sociale

Trento | Italy

SCIENTIFIC COMMITTEE

Orazio Caffo

Giovanni Pappagallo

Elisa Zanardi

UO Clinica di Oncologia Medica

IRCCS Policlinico San Martino – Genova

Disclosures

- Advisory Board/Honoraria: Janssen, Astellas, MSD, Ipsen, BMS

Clinical Case

S.R., 71y

Medical history: appendicectomy and tonsillectomy, anterior-posterior myocardial infarction (2000), hypercholesterolemia

Oncological history:

12/2010: radical prostatectomy + pelvic lymphadenectomy for adenocarcinoma of the prostate Gleason 3+5=8/10 pT3b pN0 (0/12) R1

PSA after surgery = 0.09 ng/ml

- 03/2011-04/2011: Adjuvant radiation therapy.

PSA nadir (08/2011)=0.07 ng/ml

- 11/2016: Biochemical recurrence and progression until PSA 2.31 ng/ml → Choline PET was performed, resulting negative; therefore, ADT (LHRHa agonist) was started.

Initial biochemical complete response and subsequent PSA increase, therefore patient was led to referral to our attention (Oncology Unit).

Clinical Case

- 12/2019: SR, 80y. Good general health conditions, ECOG PS 0.

Therapy: clopidogrel, metoprolol, ezetimib, triptorelin

Testosterone: 20 ng/dl
PSA (04/2019)=0.66 ng/ml
PSA (09/2019)=0.98 ng/ml
PSA (12/2019)=1.51 ng/ml

CT scan
Bone scan
PSA and testosterone

- CT scan (11/03/2020): neg
- Bone scan(15/03/2020): neg
- PSA (03/2020): 2.14 ng/ml (testosterone: 20 ng/dl)
- PSA DT: 5.3 months

Clinical Case

APALUTAMIDE GU Serie Generale n 289 del 10/12/2019

- Start Apalutamide (03/2020)

PSA (07/2020)=0.85 ng/ml
PSA (11/2020)=0.13 ng/ml
PSA (03/2021)=0.13 ng/ml
PSA (07/2021)=0.23 ng/ml
PSA (11/2021)=0.26 ng/ml
PSA (03/2022)=0.42 ng/ml
PSA (07/2022)=0.51 ng/ml
PSA (11/2022)=0.54 ng/ml

CT/bone scan: neg

Adverse Events

- Hypertension G2 → + perindopril and amlodipine

Supportive care

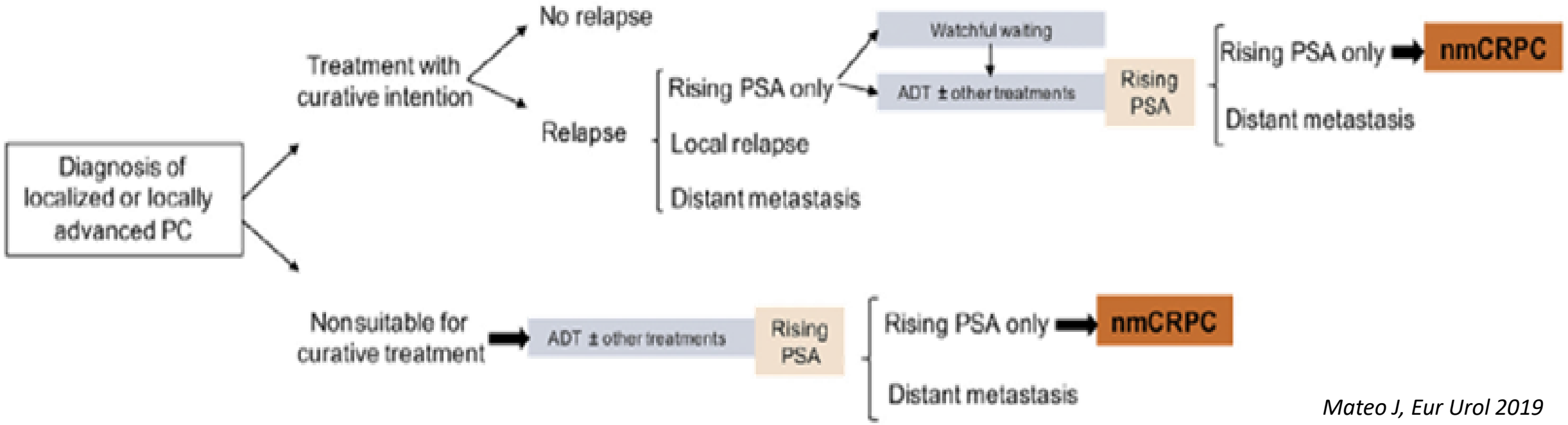
- Denosumab every six months

→ Apalutamide + LHRHa still ongoing

Evidence from Literature: Definition of nmCRPC

	No ADT	Progressed on ADT
No distant metastasis CT/BS	Localized or locally advanced PC	nmCRPC
Distant metastasis	mHNPC	mCRPC

non-metastatic CRPC (nmCRPC) prevalence has been estimated to 7% of prostate cancer in the EU



Mateo J, Eur Urol 2019
Cetin K, Urology 2013

Evidence from Literature: PSA DT

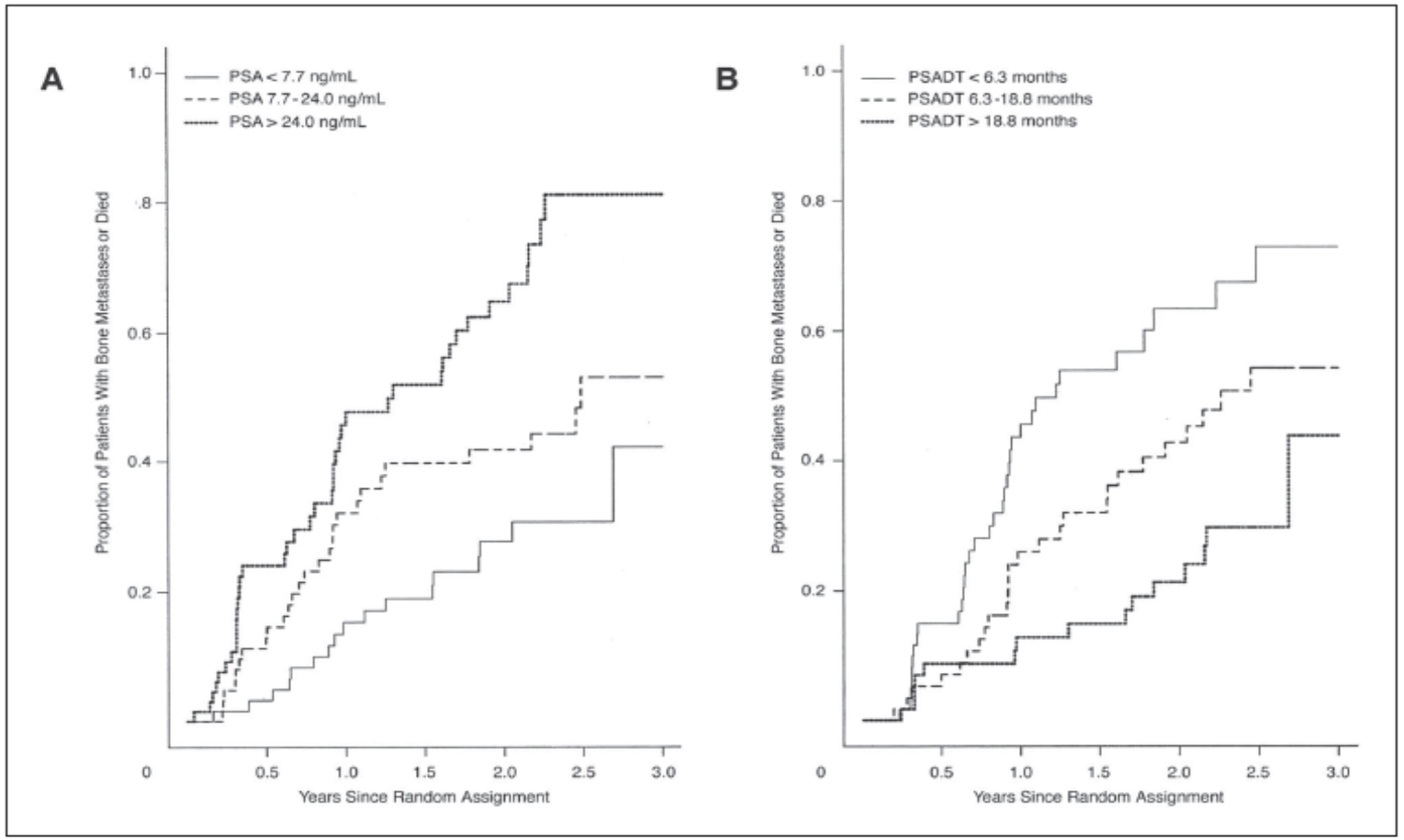
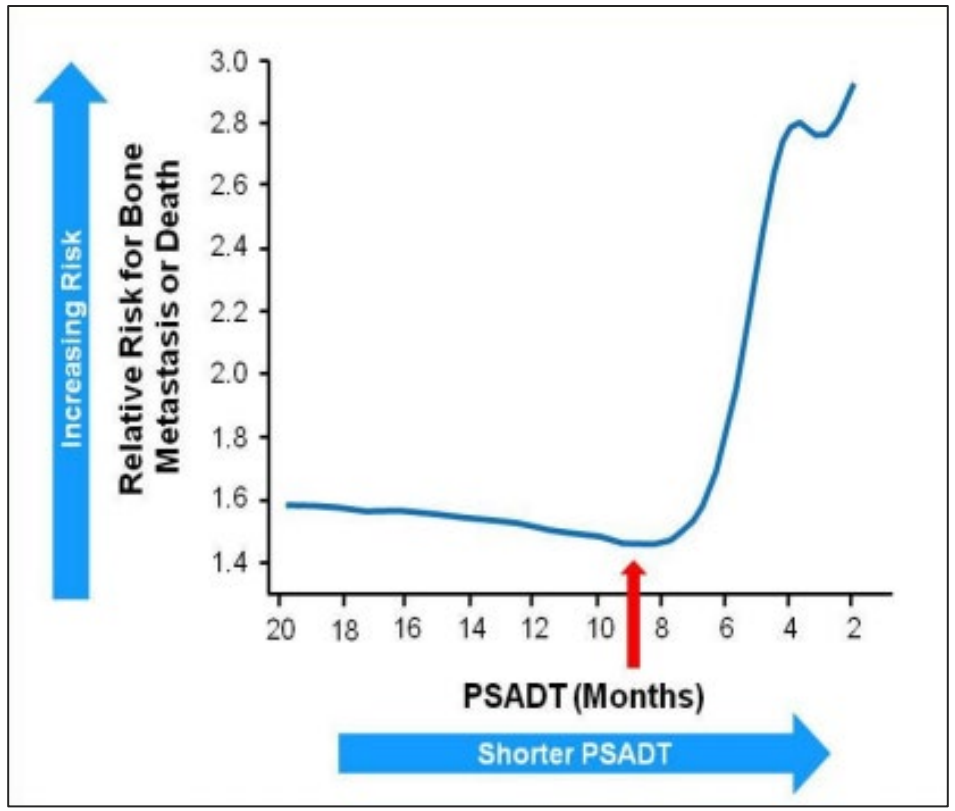


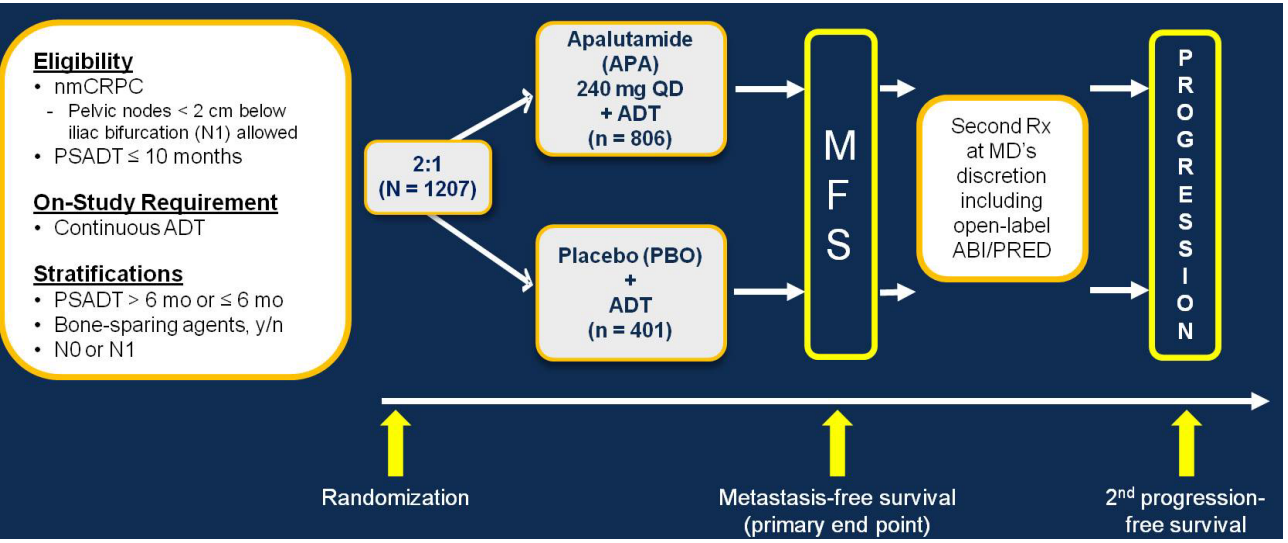
Fig 2. Kaplan-Meier time to bone metastasis or death according to tertiles of prostate-specific antigen (PSA) and PSA doubling time (PSADT).



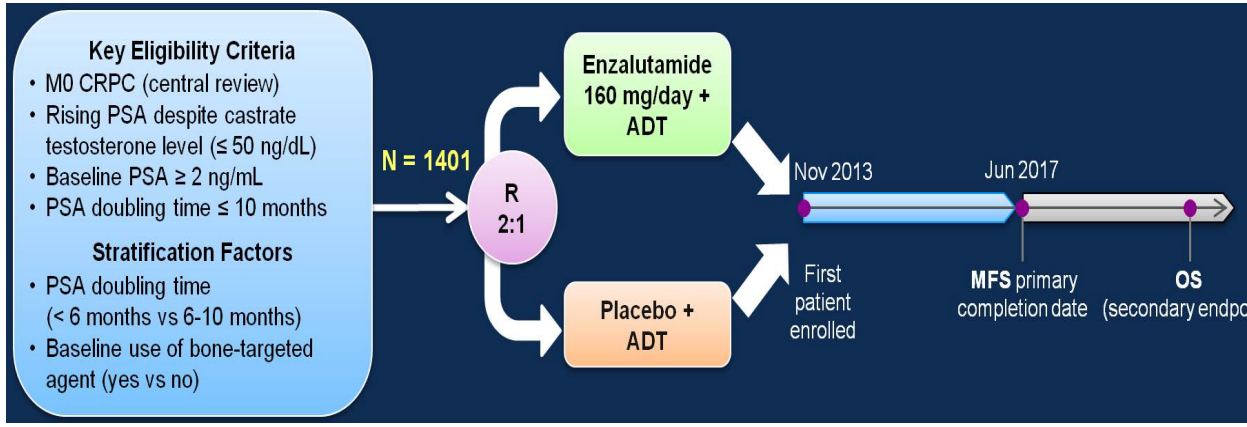
Smith MR, JCO 2005

Evidence from Literature: NHT in nmCRPC

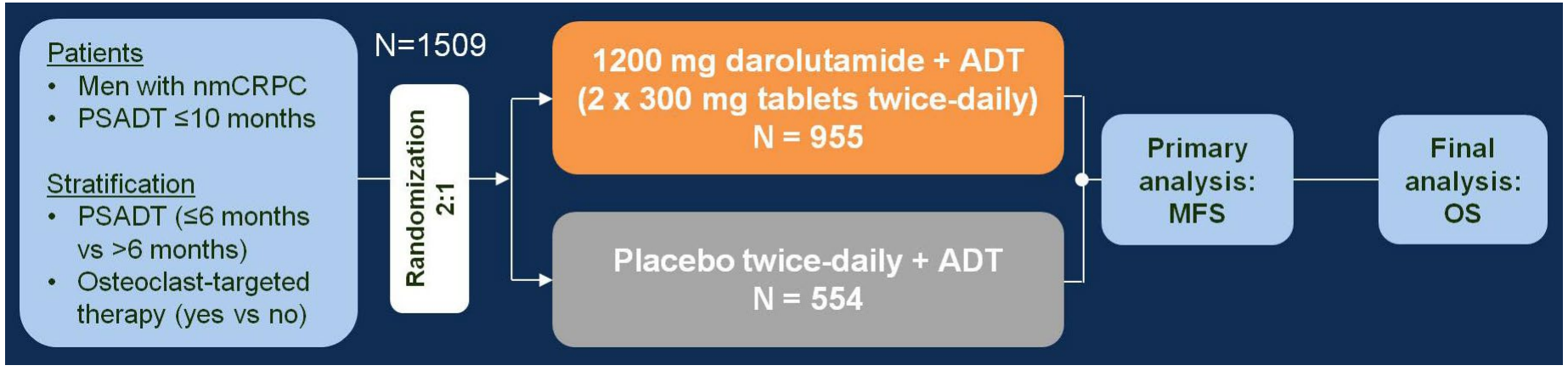
SPARTAN trial: Apalutamide



PROSPER trial: Enzalutamide

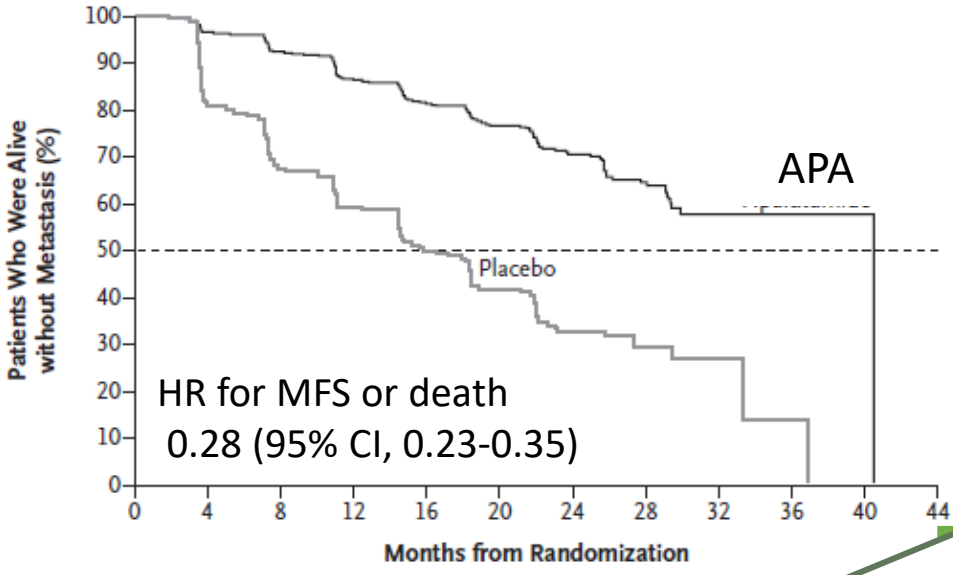


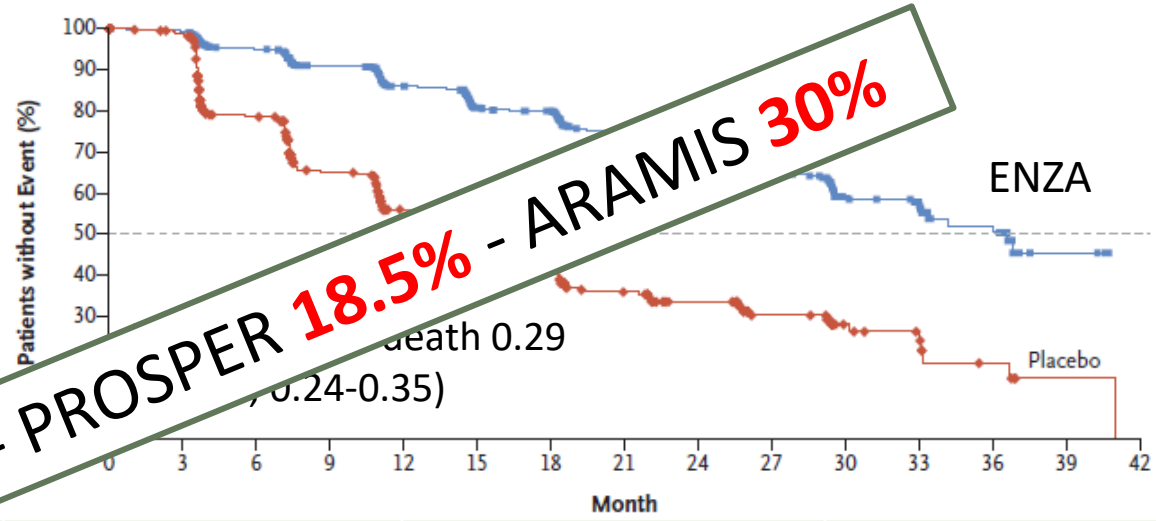
ARAMIS trial: Darolutamide



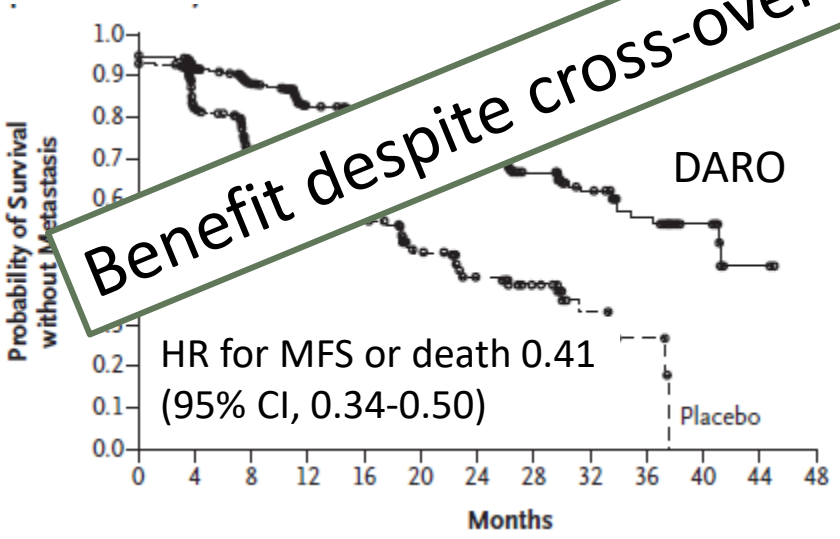
Smith MR, NEJM 2018
Hussain M, NEJM 2018
Fizazi K, NEJM 2019

Evidence from Literature: NHT in nmCRPC – MFS and OS





Benefit despite cross-over: SPARTAN **19%** - PROSPER **18.5%** - ARAMIS **30%**



	SPARTAN	PROSPER	ARAMIS
Overall Survival (OS)	*Smith, Eur Urol 2021*	*Stenberg, NEJM 2020*	*Fizazi, NEJM 2020*
Median, months (95% CI)	73.9 (61.2-NR) vs 59.9 (52.8-NR)	73.9 (61.2-NR) vs 59.9 (52.8-NR)	NR vs NR
HR (95% CI)	0.78 (0.64-0.96); P=.016	0.73 (0.61-0.89); P=.001	0.69 (0.53-0.88); P=.003
Treatment durantion, months	32.9 vs 11.5	33.9 vs 14.2	25.8 vs 11.6

Evidence from Literature: Adverse Events

	SPARTAN		PROSPER		ARAMIS	
AE (all grades, %)	APA (n=803)	PBO (n=398)	ENZA (n=930)	PBO (n=465)	DARO (n=954)	PBO (n=554)
Fatigue	30.4	21.1	33.0	14.0	12.1	8.7
Hypertension	24.8	19.8	12.0	5.0	6.6	5.2
Rash	23.8	5.5	NR	NR	2.9	0.9
Falls	15.6	9.0	11.0	4.0	4.2	4.7
Fractures	11.7	6.5	NR	NR	4.2	3.6
Mental impairment disorders	5.1	3.0	5.0	2.0	0.4	0.2
Hypotyroidism	8.1	2.0	NR	NR	0.2	0
Seizure	0.2	0	0.3	0	0.2	0.2
ANY SAE, %	**24.8**	**23.1**	**24**	**18**	**24.8**	**20.0**

Smith MR, NEJM 2018; Hussain M, NEJM 2018; Fizazi K, NEJM 2019

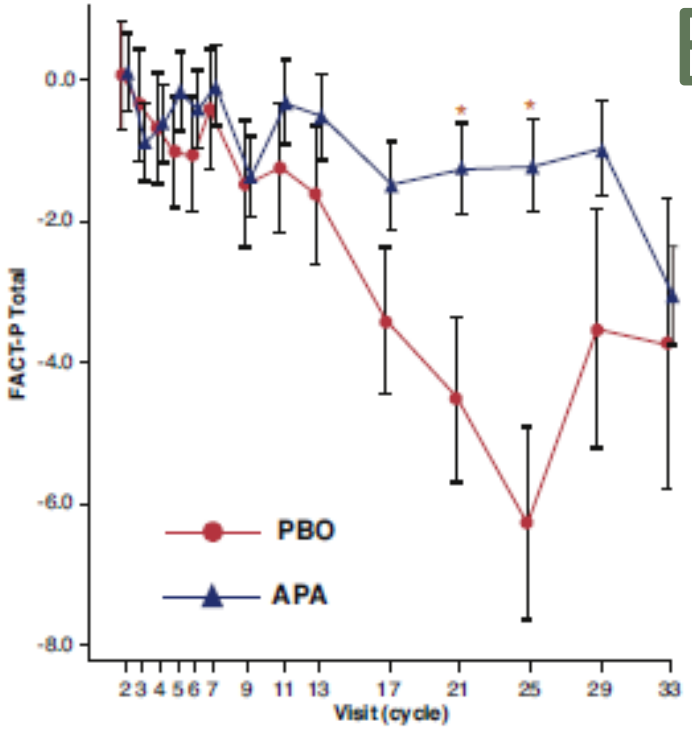
Evidence from Literature: Drug-Drug Interactions

Table 2. DDIs between ARIs and frequent treatments for common metabolic disorders in men with nmCRPC receiving ADT.

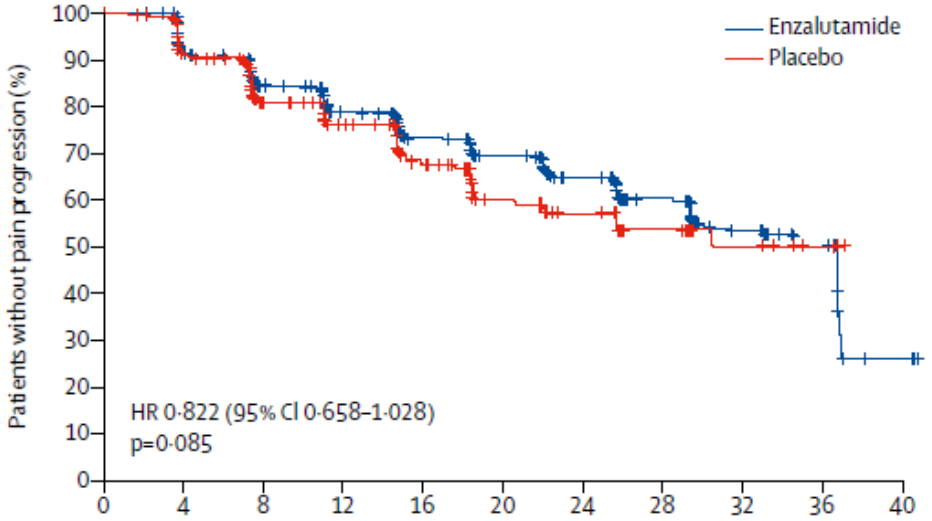
			Effect of ARIs on comedication exposure ('perpetrators')			Effect of comedications on ARI exposure ('victims')		
Condition	Drug class	Common treatments	Apalutamide	Enzalutamide	Darolutamide	Apalutamide	Enzalutamide	Darolutamide
Hypertension	Ca channel blocker	Diltiazem	↓↓/↓↓	↓↓/↓	-/-	-/-	-/-	-/-
		Nifedipine	↓↓/↓↓	↓↓/↓↓	-/-	-/-	-/-	-/-
		Verapamil	↓↓/↓↓	↓↓/-	-/-	-/-	-/↑	-/-
		Amlodipine	↓/↓↓	↓/↓↓	-/-	-/-	-/-	-/-
	ARB	Losartan	↓/↓	↓/↓	-/-	-/-	-/-	-/-
		Valsartan	-/↓	-/-	-/↑	-/-	-/-	-/-
	Beta-blocker	Atenolol	-/-	-/-	-/-	-/-	-/-	-/-
		Propranolol	-/↓	-/↓	-/-	-/-	-/-	-/-
		Bisoprolol	↓/-	↓/-	-/-	-/-	-/-	-/-
	ACE inhibitor	Enalapril	-/-	-/-	-/-	-/-	-/-	-/-
		Captopril	-/-	-/-	-/-	-/-	-/-	-/-
	Diuretics	Furosemide	-/-	-/-	-/-	-/-	-/-	-/-
		Hydrochlorothiazide	-/-	-/-	-/-	-/-	-/-	-/-
		Spironolactone	-/-	-/-	-/-	-/-	-/-	-/-
Dyslipidaemia	Statins	Rosuvastatin	↓/↓	-/-	↑↑/↑↑	-/-	-/-	-/-
		Atorvastatin	↓/↓	↓/↓	-/↑	-/-	-/-	-/-
		Simvastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-
		Fluvastatin	-/↓	↓/↓	-/↑	-/-	-/-	-/-
		Pravastatin	-/↓	-/-	-/↑	-/-	-/-	-/-
		Pitavastatin	-/↓	-/-	-/↑	-/-	-/-	-/-
		Lovastatin	-/↓	-/↓	-/↑	-/-	-/-	-/-
	Fibrates	Gemfibrozil	-/-	-/-	-/-	↑/↑	↑↑/↑	-/-
Diabetes mellitus	Biguanides	Metformin	-/-	-/-	-/-	-/-	-/-	-/-
	Sulfonylureas	Gliclazide	-/↓	↓/↓	-/-	-/-	-/-	-/-
		Glimepiride	-/↓	↓/↓	-/-	-/-	-/-	-/-
		Glyburide	-/↓	↓/↓	-/↑	-/-	-/-	-/-
	DPP-4 inhibitors	Linagliptin	↓↓/↓	↓↓/↓	-/-	-/-	-/-	-/-
		Saxagliptin	↓/↓	↓/↓	-/-	-/-	-/-	-/-
	Meglitinides	Repaglinide	↓/↓	↓/↓	-/↑	-/-	-/-	-/-
	Insulin	Insulin	-/-	-/-	-/-	-/-	-/-	-/-

Conde-Estevez D, Exp Opin Drug Metab Toxicol 2022

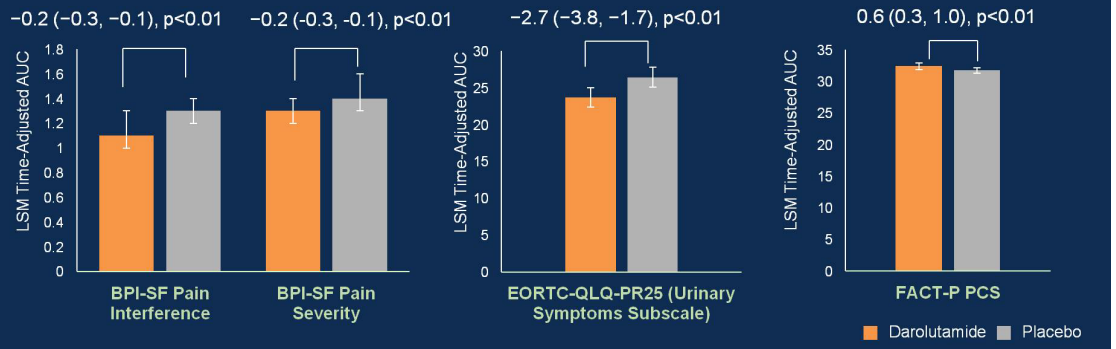
Evidence from Literature: QoL



Oudard S, Eur Urol Focus 2022



Health-related quality of life outcomes

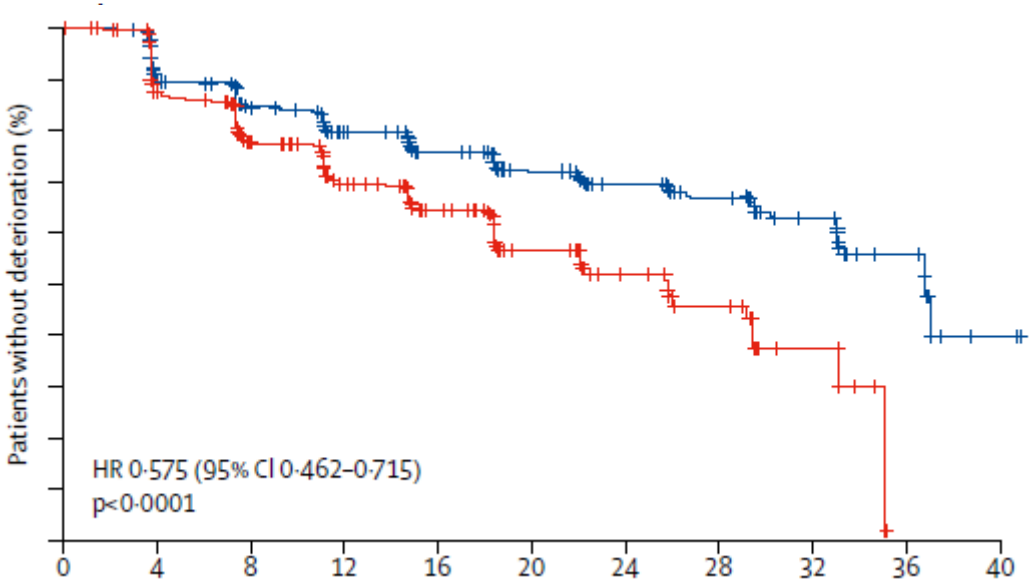


- Patient-reported scores tended to favor darolutamide for pain and urinary symptoms

AUC, area under the curve; BPI-SF, Brief Pain Inventory – Short Form; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer quality of life; FACT-P, Functional Assessment of Cancer Therapy-Prostate; LSM, least squares mean; PCS, prostate cancer subscale.

Presented by: Karim Fizazi

Fizazi K, ASCO GU 2019

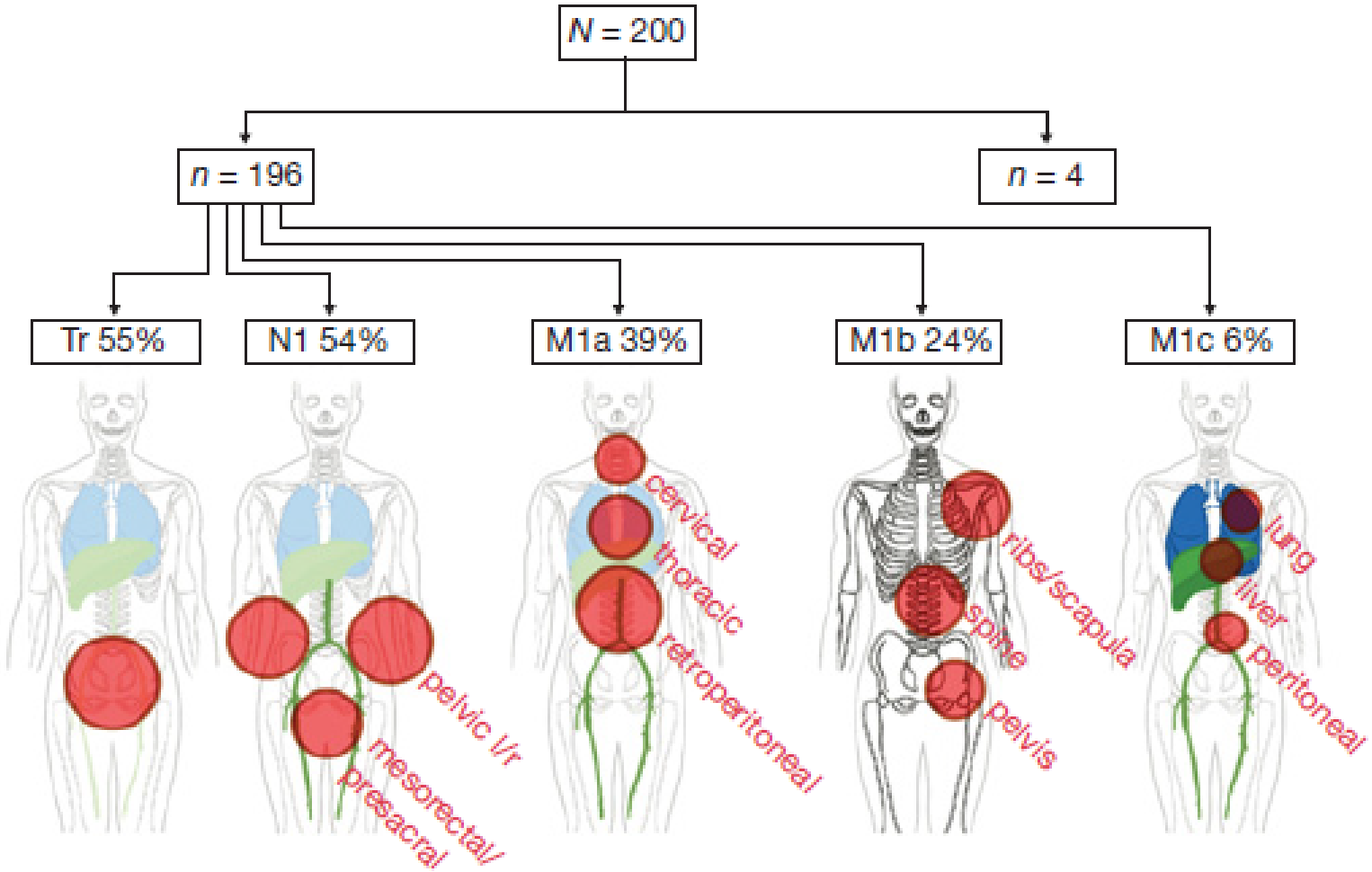


Tombal B, Lancet Oncol 2019

Evidence from Literature: Conventional Imaging (CIM) vs PSMA-PET/CT

44% local recurrence (24% on prostate bed)
55% M1
N/M disease extent in PSMA-PET:

- unifocal in 15%
- oligometastatic (2–3 metastases) in 14%
- multiple/disseminated 46%.

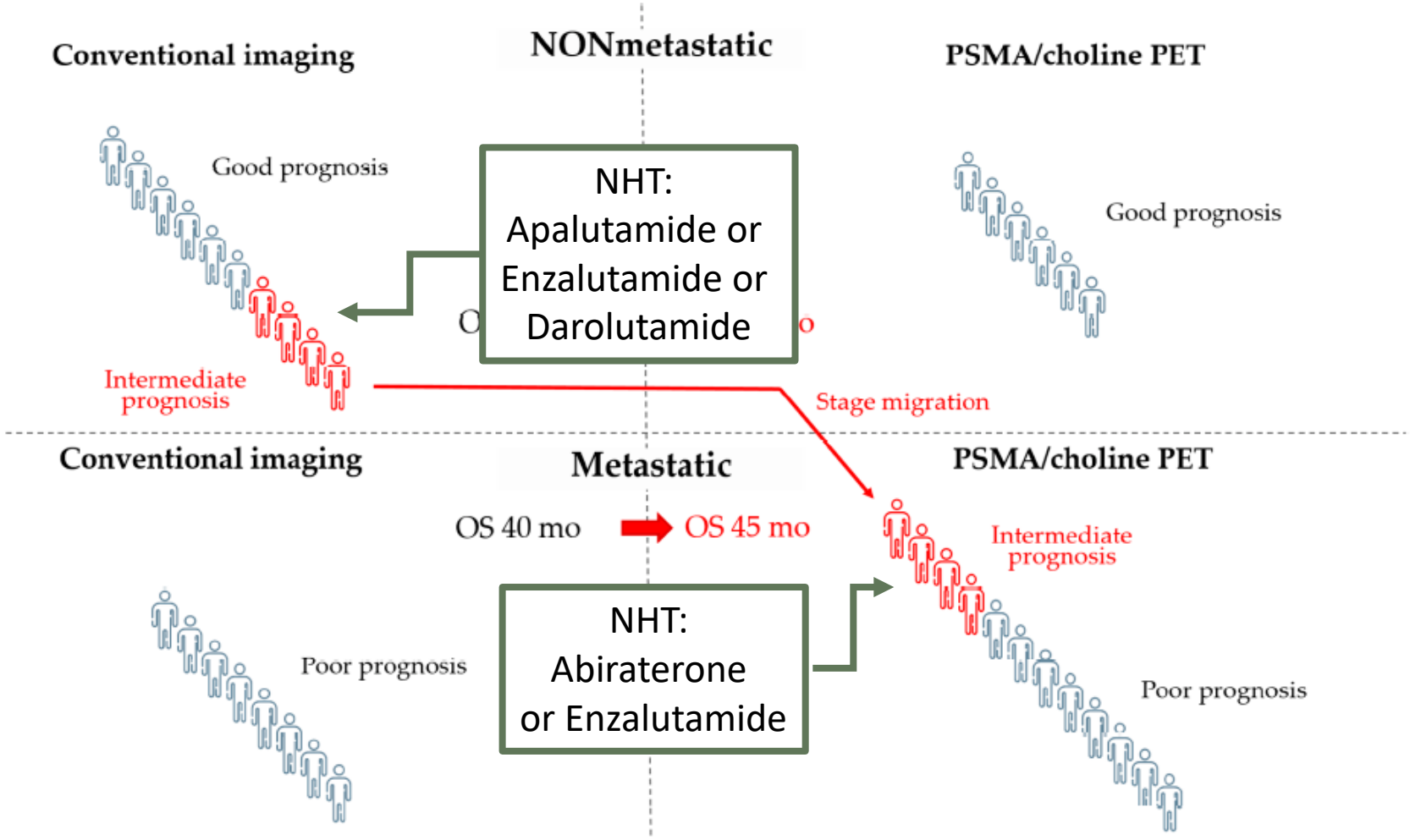


Fendler WP, Clin Cancer Res 2019

Evidence from Literature: Conventional Imaging (CIM) vs PSMA-PET/CT

Will Rogers phenomenon:

Use of PSMA PET/CT is associated with a stage migration that improve the prognosis of both groups, nmCRPC and mCRPC, without any change in individual outcomes.



Cattrini C, Cancers 2022

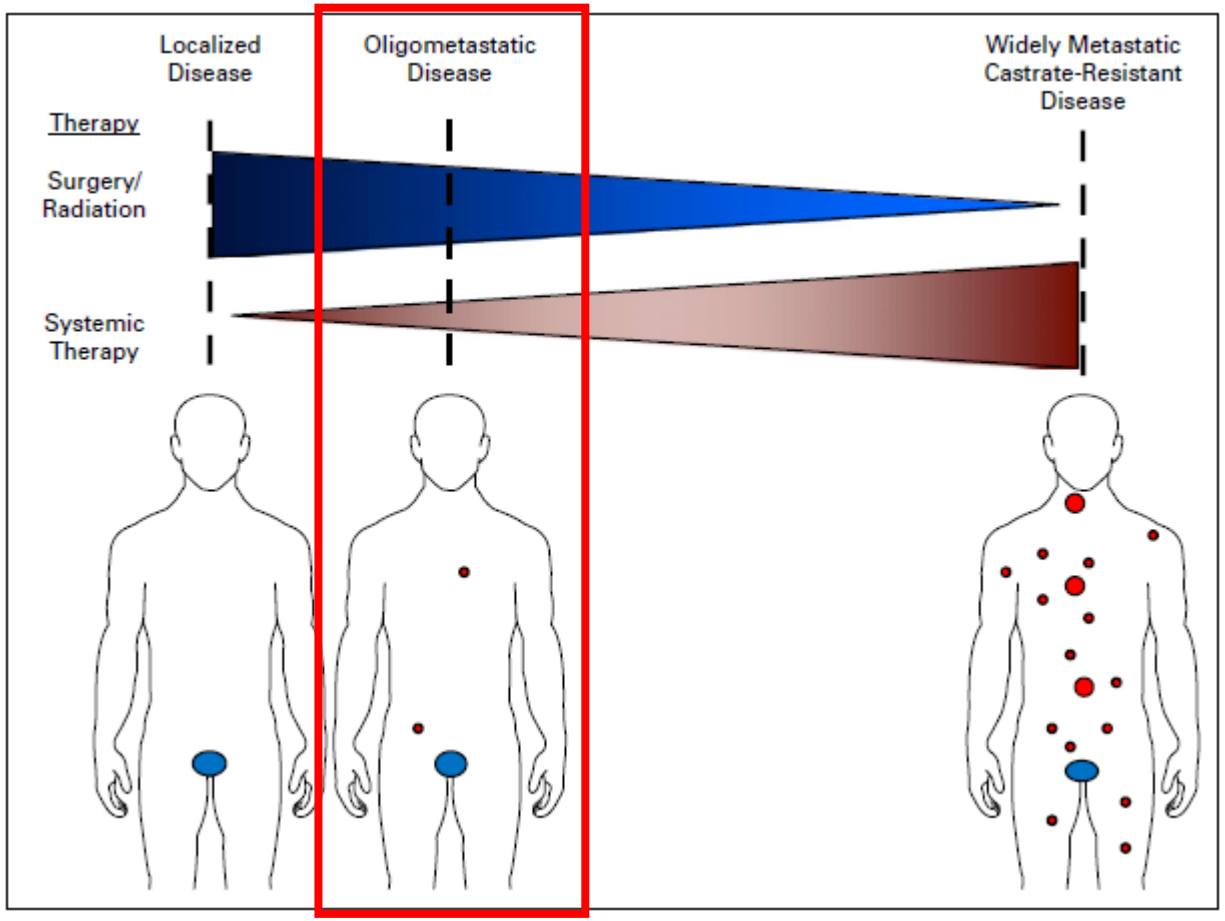
Evidence from Literature: Metastasis Directed Therapy

«For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs »

EDITORIAL

Oligometastases

«An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy»



MTD: metastasis directed therapy

Hellman S and Weichselbaum RR, JCO 1995

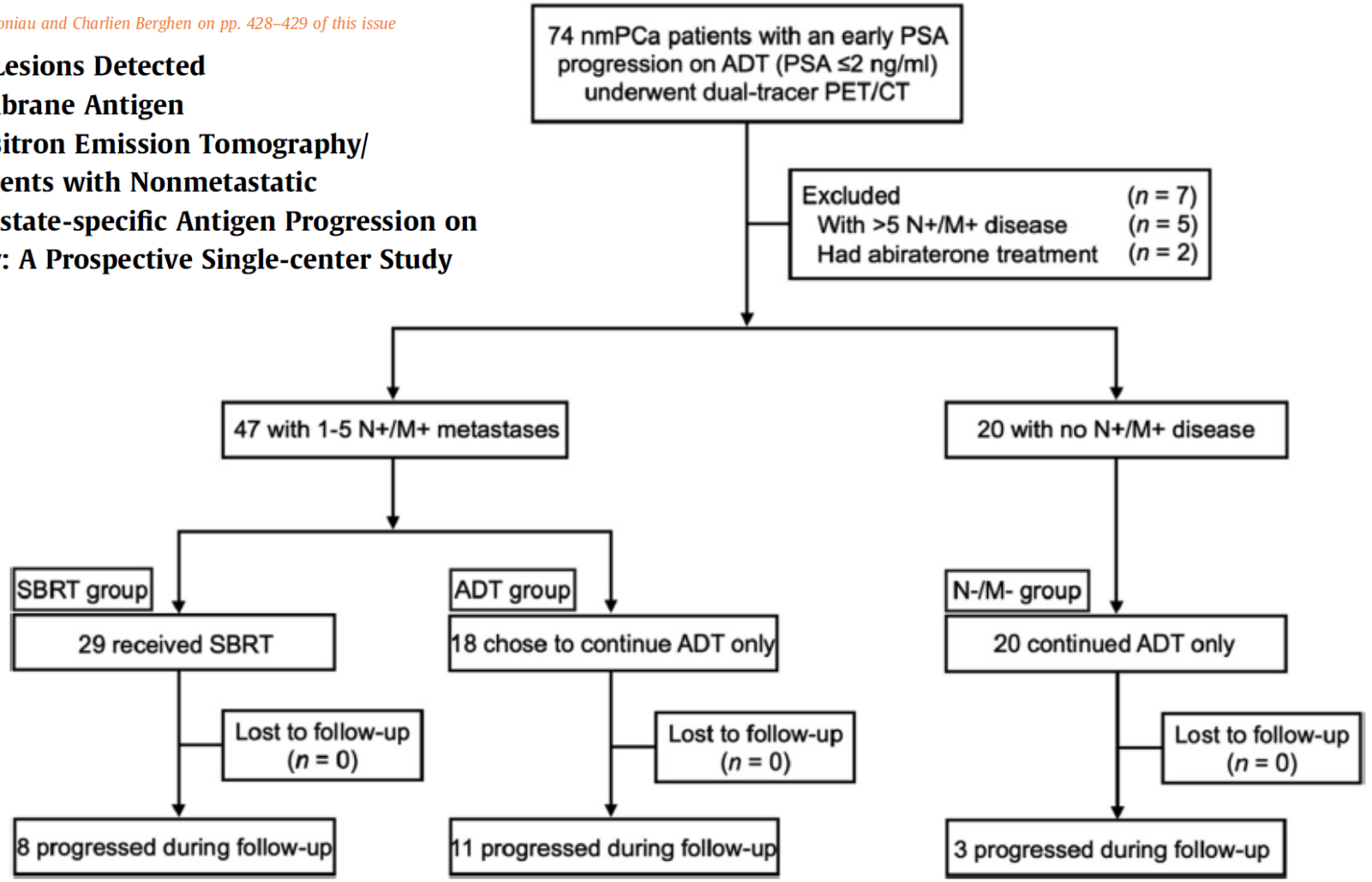
Evidence from Literature: Metastasis Directed Therapy

European Association of Urology

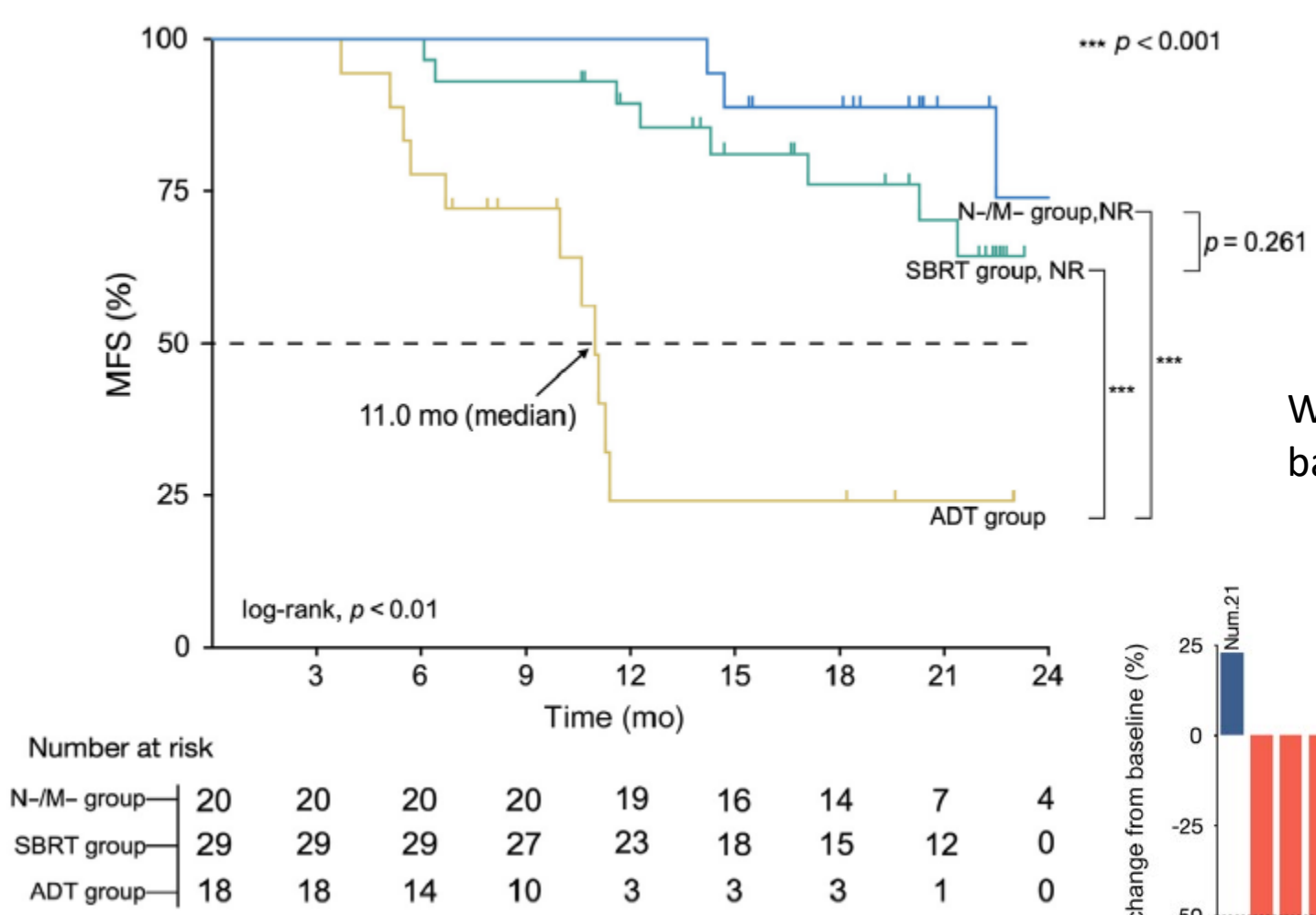
Priority Article

Editorial by Gert De Meerleer, Kato Rans, Steven Joniau and Charlien Berghen on pp. 428–429 of this issue

Stereotactic Radiotherapy for Lesions Detected via ^{68}Ga-Prostate-specific Membrane Antigen and ^{18}F-Fluorodexyglucose Positron Emission Tomography/ Computed Tomography in Patients with Nonmetastatic Prostate Cancer with Early Prostate-specific Antigen Progression on Androgen Deprivation Therapy: A Prospective Single-center Study

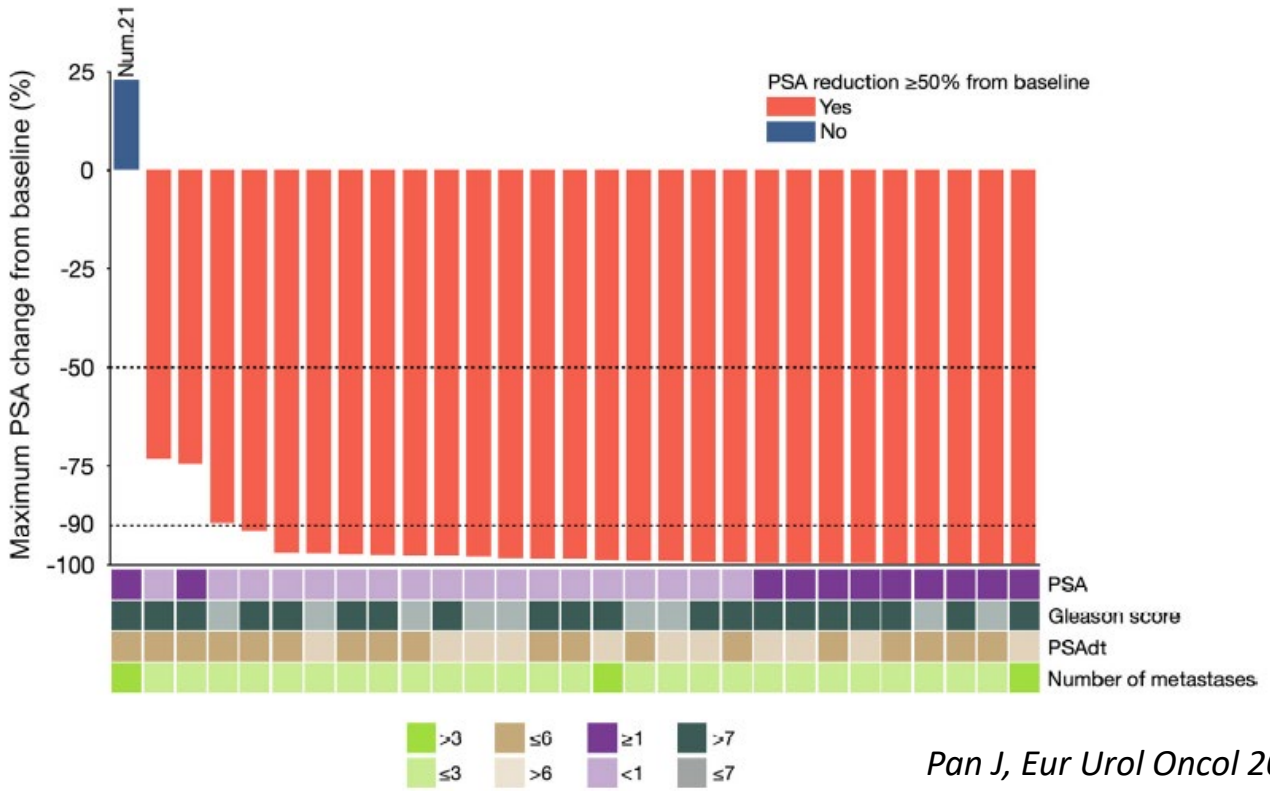


Pan J, Eur Urol Oncol 2022



Kaplan-Meier curves of median metastasis-free survival (MFS) for patients in the three subgroups.

Waterfall plot of the maximum change in PSA from baseline observed in the SBRT group.



Pan J, Eur Urol Oncol 2022

Evidence from Literature: Role of PSMA-PET/CT

EUO Priority Article

EAU-EANM Consensus Statements on the Role of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography in Patients with Prostate Cancer and with Respect to [^{177}Lu]Lu-PSMA Radioligand Therapy

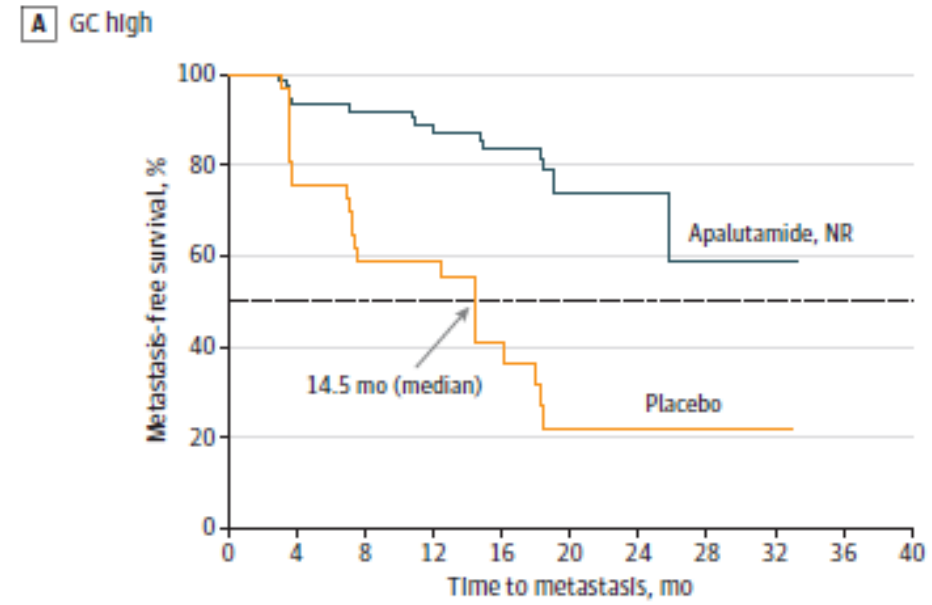
Table 1 – Proposed statements and Delphi voting results regarding the role of PSMA-based imaging and therapy in prostate cancer [a]

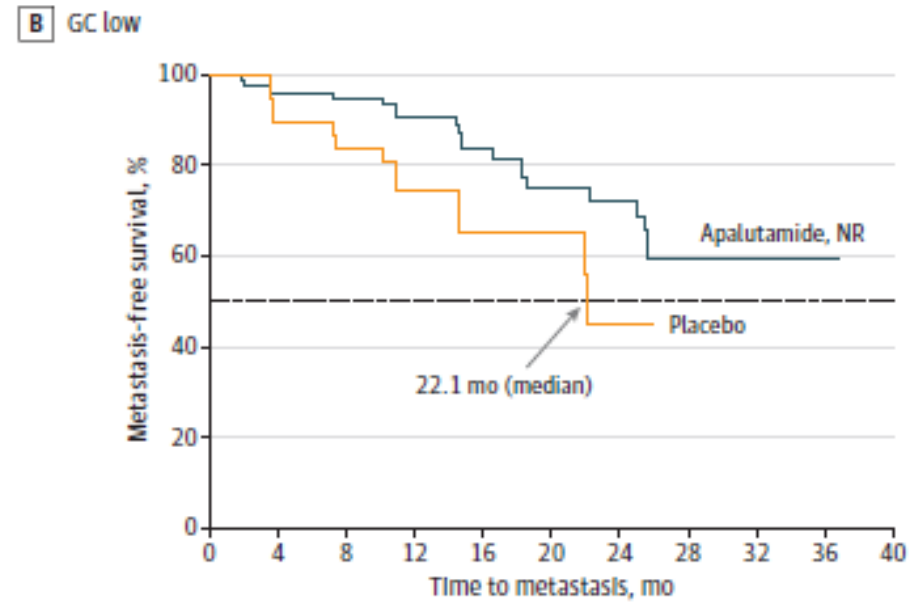
No.	Round 1 (original phrasing)	Round 1 (rephrased)	Round 1		Round 2	
			MS	CA	MS	CA
1	PSMA PET/CT should be performed in any high-risk PCa patient at staging		8	Yes		
2	PSMA PET/CT should be performed in some intermediate-risk PCa patients at staging	PSMA PET/CT should be considered in unfavourable intermediate-risk PCa patients at staging	7	Yes	8	Yes
3	PSMA PET/CT should be performed in any BCR patients	PSMA PET/CT should be performed in the majority of BCR patients	9	Yes	9	Yes
4	PSMA PET/CT should be performed in nmCRPC patients	PSMA PET/CT should be performed in the majority of nmCRPC patients	5.5	Yes	5	Yes
5	PSMA PET/CT should be performed in any mCRPC patient to evaluate disease progression	PSMA PET/CT should be performed in the majority of mCRPC patients to evaluate disease progression	3	No	3	Yes

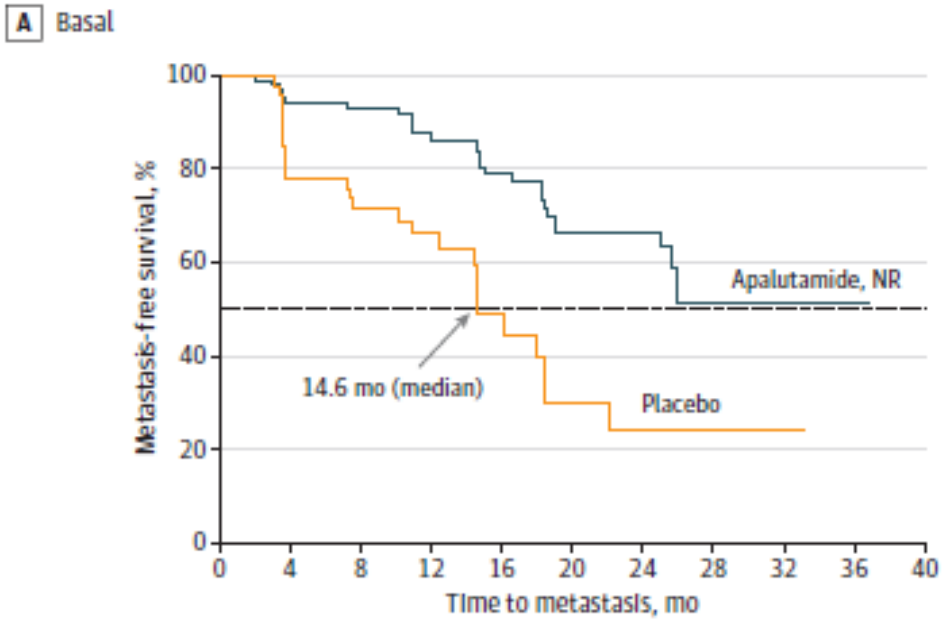
- Patient heterogeneity;
- Lack of long-term data regarding the benefit of metastasis directed therapy in CRPC (as a result of detecting distant lesions via PSMA PET/CT);
- Lack of data on appropriate sequencing of treatment.

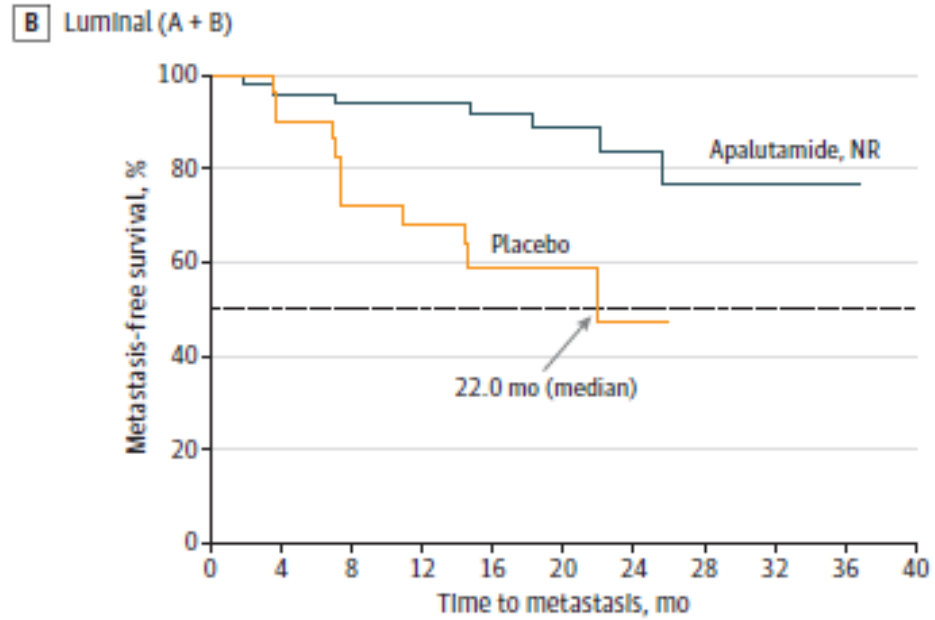
Fanti S, Eur Urol Oncol 2022

Evidence from Literature: Molecular Subtypes





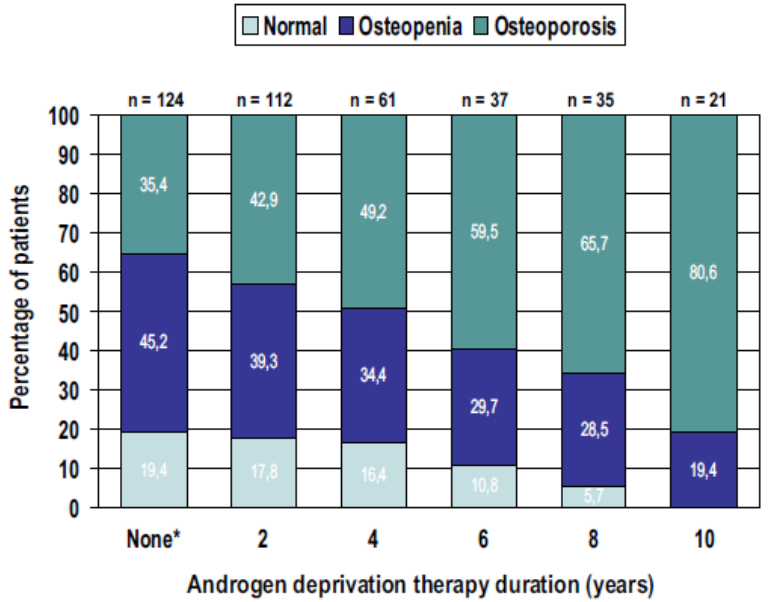




- Molecular profiling undertaken in archive tumor samples collected 6.7 y before nmCRPC status →estabilished at a much earlier clinical time
- High GC scores derived the greatest absolute benefit from APA+ADT
- Luminal tumors treated with APA+ADT had better outcomes

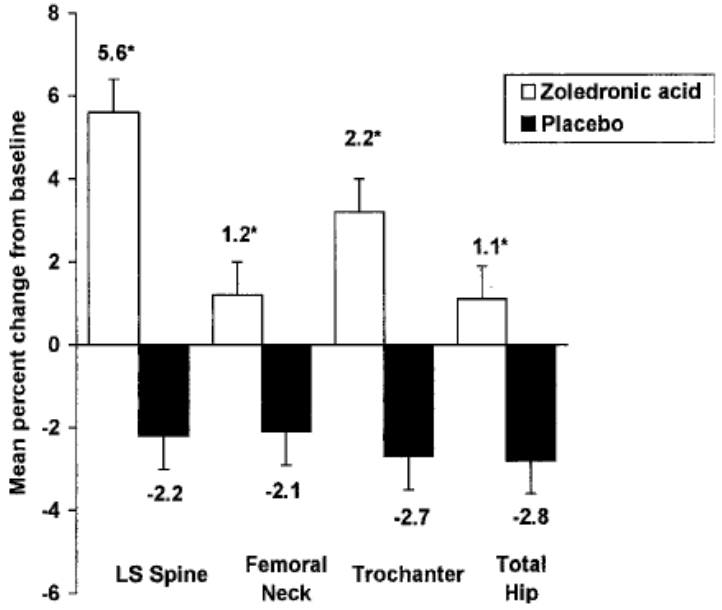
Feng FY, JAMA Oncol 2021

Evidence from Literature: Bone Protecting Agents



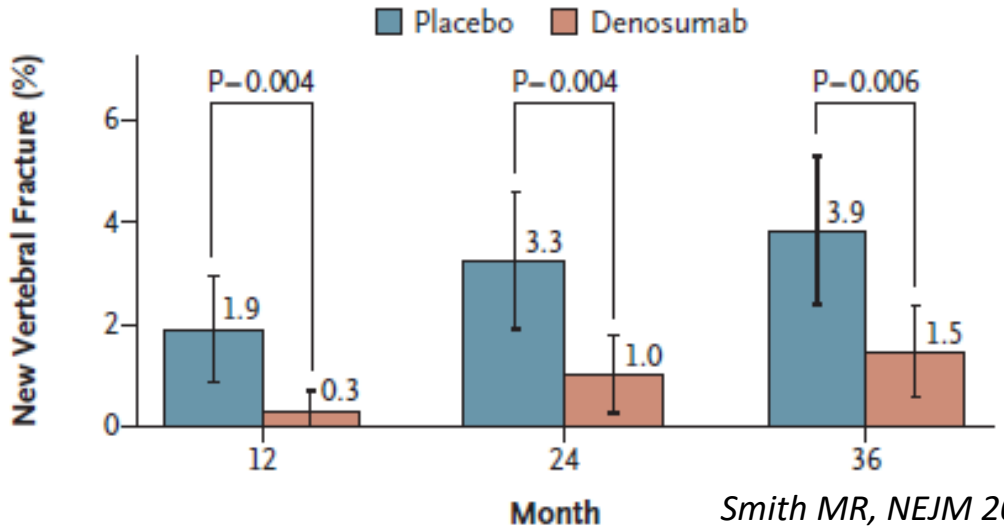
Morote, Urology 2007

RANDOMIZED CONTROLLED TRIAL OF ZOLEDRONIC ACID TO PREVENT BONE LOSS IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR NONMETASTATIC PROSTATE CANCER



Smith MR, J Urol 2003

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer



Smith MR, NEJM 2009

nmCRPC: Conclusions

- NHTs added to ADT prolongue MFS and OS
- The majority of AEs associated to NHTs are G1-G2 and easily manageable
- The different profile of pharmacological interactions allows to choose the most suitable molecule for each patient
- QoL was not worsened by adding NHT to ADT
- CIMs (TC and bone scan) should be used to select patients with PSA rise during ADT and with PSA DT ≤ 10 months
- Prospective Randomized Clinical trials ongoing to identify the role of NGI and of MDT in management of nmCRPC
- Genomic biomarkers could help us to identify patients with higher benefit from addition of NHT to ADT
- Remember the importance of Bone Protecting Agents in these patients that are exposed from long time to ADT