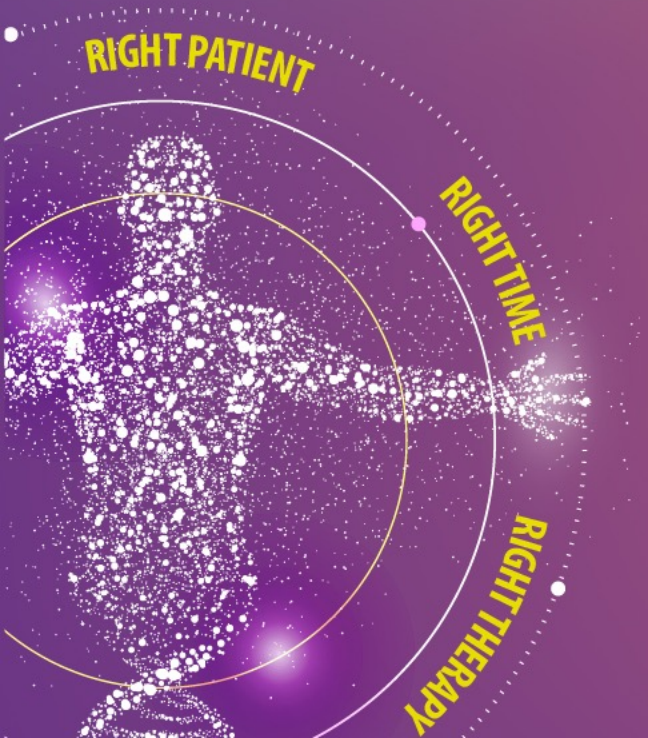
TERZA EDIZIONE

PersonMed

PATIENT CENTRIC APPROACH ON ADVANCED PROSTATE CANCER

› IL VALORE DEL TEMPO ‹



16-17 GIUGNO 2022

NAPOLI

Renaissance Naples Hotel Mediterraneo
Via Ponte di Tappia, 25

70 anni (1945) , scuola di ballo

Diabetico, iperteso
(ipoglicemizzante orale, calcioantagonista)

PSA 10 ng/ml Bx: CaP Gleason 4+4 cT2
RM prostata: sospetta patologia localizzata, PIRADS 5 (apice dx 18 mm)
Scintigrafia e TAC negative

RARP nel 2015: CaP Gleason 4+4, pT3a N1 (1/22 linf) M0 R1 (10 mm apice dx)

PSA dopo 6 settimane 0,01 ng/ml

Continente, D.E.

TMD (Urologo, Oncologo medico, Radioterapista Oncologo, Radiologo, Medico Nucleare, Anatomo Patologo)

RT adiuvante
(loggia prostatica 66 Gy in 30 fx + pelvi 52,5 Gy)

+

ADT adiuvante
(consigliata per 24-36 mesi)

Aprile 2017 PSA 0.3 ng/ml Testosterone tot 20 ng/dl
Settembre 2017 PSA 0.6 ng/ml
Gennaio 2018 PSA 0,8 ng/ml
Aprile 2018 PSA 1,1 ng/ml

Asintomatico

Quale decisione clinica?

- Ristadiazione con tecniche di radiologia tradizionale
- Proseguire ADT
- Manipolazione ormonale (es. aggiunta bicalutamide)
- Ristadiazione con nuove tecniche di imaging

Decisione TMD: proseguire ADT

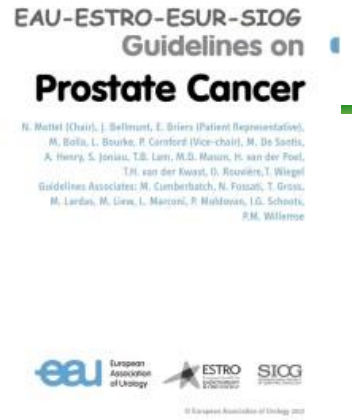
Aprile 2017 PSA 0.3 ng/ml Testosterone tot 20 ng/dl
Settembre 2017 PSA 0,6 ng/ml
Gennaio 2018 PSA 0,8 ng/ml
Aprile 2018 PSA 1,1 ng/ml
Settembre 2018 PSA 1,5 ng/ml
Dicembre 2018 PSA 2,3 ng/ml

PSADT 8 mesi

Asintomatico

Present

CRPC: definition



3 main criteria:

Castrate serum testosterone

< 50 ng/dl or 1.7 nmol/L

+ either

Biochemical progression

3 consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL

OR

Radiological progression

Appearance of ≥ 2 lesions (bone scan) or

soft tissue lesion enlargement RECIST

Symptomatic progression alone to be questioned and not sufficient to define mCRPC

CRPC, castration-resistant prostate cancer; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria In Solid Tumours.

- Dicembre 2018 PSA 2,1
- PSADT 8 mesi Asintomatico

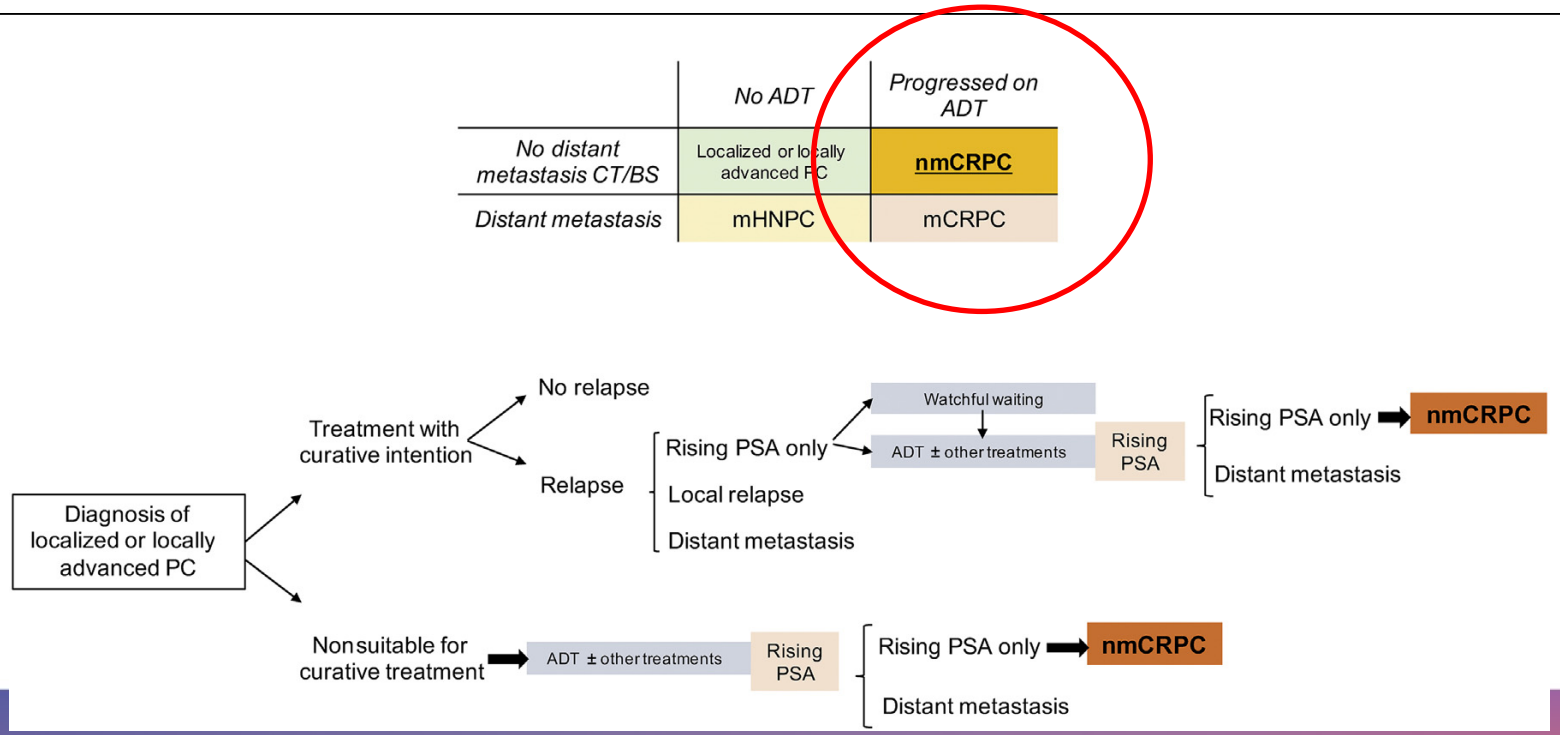


Fig. 1 – Schematic representation of disease evolution patterns to the clinical states of nonmetastatic castration-resistant prostate cancer (nmCRPC). ADT = androgen deprivation therapy; BS = bone scintigraphy; CT = computerised tomography; HNPC = hormone-naïve prostate cancer; CRPC = castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PC = prostate cancer; PSA = prostate specific antigen.

Quale tecniche di imaging utilizzereste per la ristadiazione?

1. TAC e Scintigrafia ossea
2. PET-TC Colina
3. PET-TC PSMA
4. Whole-Body RM

6.5.4 Non-metastatic CRPC

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

N. Mottet (Chair), P. Cornford (Vice-chair), R.C.N. van den Bergh, E. Briers, Expert Patient Advocate (European Prostate Cancer Coalition/Europa UOMO), M. De Santis, S. Gillessen, J. Grummet, A.M. Henry, T.H. van der Kwast, T.B. Lam, M.D. Mason, S. O'Hanlon, D.E. Oprea-Lager, G. Ploussard, H.G. van der Poel, O. Rouvière, I.G. Schoots. D. Tilki, T. Wiegel
Guidelines Associates: T. Van den Broeck, M. Cumberbatch, A. Farolfi, N. Fossati, G. Gandaglia, N. Grivas, M. Lardas, M. Liew, E. Linares Espinós, L. Moris, P-P.M. Willemse

- One-third will develop bone metastases within two years, detected by conventional imaging [207].
- In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis- free survival and OS [207, 1200].
- A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1201].
- Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1202]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Ability of CT and BS to detect metastasis

- CT has limited sensitivity for the detection of metastatic lymph Nodes: **42%** [95% CI 26–56%]

Mateo J et al, Eur Urol, doi:10.1016/j.eururo.2018.07.035

- Bone scan positivity according to PSA and PSA-DT in nmCRPC

	PSA (ng/ml)			
	<5	5–14.9	15–49.9	≥50
PSADT (months)				
≥15	6 (4–8)	11 (9–14)	22 (18–28)	47 (40–54)
9–14.9	6 (4–10)	12 (10–14)	24 (22–26)	49 (46–52)
3–8.9	8 (5–14)	16 (13–18)	30 (27–33)	57 (53–60)
<3	12 (8–19)	22 (19–25)	40 (37–42)	67 (64–69)

CI: confidence interval; PSA: prostate-specific antigen; PSADT: PSA level doubling time.

Moreira DM et al Prostate Cancer Prostatic Dis, doi: 10.1038/pcan.2015.25

Review Article

0022-5347/19/2014-0682/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2018.05.164
Vol. 201, 682-692, April 2019
Printed in U.S.A.

A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (RADAR III)

E. David Crawford,*† Phillip J. Koo,‡ Neal Shore,§ Susan F. Slovin,¶ Raoul S. Concepcion,‖ Stephen J. Freedland,** Leonard G. Gomella,†† Lawrence Karsh,‡‡ Thomas E. Keane,§§ Paul Maroni, David Penson,¶¶ Daniel P. Petrylak,‖‖ Ashley Ross,*** Vlad Mouraviev,††† Robert E. Reiter, Chaitanya Divgi and Evan Y. Yu‡‡‡ for the RADAR III Group

Abbreviations and Acronyms
^{18}F-DCFBC = (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine
^{18}F-FACBC = ^{18}F-fluciclovine

	Newly Diagnosed Patients	Biochemical Recurrent Patients	M0 Castrate-Resistant Patients	M1 Castrate-Resistant Patients*
RADAR I Conventional Scan Recommendations	Conventional scan high- and intermediate-risk patient with at least 2 of the following criteria positive: • PSA level >10 ng/ml • Gleason score ≥7 • Palpable disease (≥T2b)	1st conventional scan when PSA level between 5 and 10 ng/ml Imaging frequency if negative for previous conventional scan: 2nd scanning when PSA=20 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	1st conventional scan when PSA level ≥2 ng/ml Imaging frequency if negative for previous conventional scan: 2nd conventional scan when PSA=5 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	Utilize conventional scans, and consider NGI only if conventional scans are negative and the clinican still suspects disease progression NGI based on at least one of the following: • With every doubling of PSA since the previous image • Every 6-9 months in the absence of PSA rise • Change in symptomatology • Change in performance status
RADAR III NGI Recommendations	If conventional imaging is equivocal or negative with continued high suspicion for metastatic disease, consider NGI	Consider NGI for PSA ≥0.5 PSA <0.5 can be considered based on specific performance of various NGI techniques	Only consider NGI in the setting of PSADT <6 months, when M1 therapies would be appropriate	

Challenging Dogma: New Evidence to Guide Practice in Urologic Oncology

Special Collection

Therapeutic Advances in Medical Oncology

Review

Guiding management of therapy in prostate cancer: time to switch from conventional imaging to PSMA PET?

Ther Adv Med Oncol

2019, Vol. 11: 1–14

DOI: 10.1177/1758835919876828

Ramin Alipour, Arun Azad and Michael S. Hofman

STRENGTHS OF CONVENTIONAL IMAGING

- The major strength of conventional imaging is its wide availability.
- Thanks to decades of exposure and experience with CT, MRI and bone scan, both reporting physicians and the referring clinicians are confident with interpreting their results despite their limitations.
- Another major advantage of these tests is their standardization and incorporation into clinical trial designs and guidelines such as RECIST and PCWG.
- Last but not least, these scans, unlike PSMA PET/CT, are funded by healthcare providers for both staging and restaging prostate cancer

5.3.4 Summary of evidence and practical considerations on initial N/M staging

The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT…….

……..The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases detectable only with PET/CT or whole-body MRI should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [468].

Results from RCTs evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, PSMA PET/CT and MRI are awaited before a decision can be made to treat patients based on the results of these tests [469].

EUROPEAN UROLOGY 75 (2019) 285–293

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer – Editor's Choice

Managing Nonmetastatic Castration-resistant Prostate Cancer

Joaquin Mateo[a], Karim Fizazi[b], Silke Gillessen[c], Axel Heidenreich[d], Raquel Perez-Lopez[a], Wim J.G. Oyen[e], Neal Shore[f], Matthew Smith[g], Christopher Sweeney[h], Bertrand Tombal[i], Scott A. Tomlins[j], Johann S. de Bono[e,]*

[a] *Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain;* [b] *Institut Gustave Roussy and University of Paris Sud, Villejuif, France;* [c] *Department of Oncology and Hematology, Kantonsspital St. Gallen, Switzerland;* [d] *University Hospital Aachen, Cologne, Germany;* [e] *The Royal Marsden Hospital and The Institute of Cancer Research, London, UK;* [f] *Carolina Urologic Research Center and Atlantic Urology Clinics, Myrtle Beach, SC, USA;* [g] *Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA;* [h] *Dana Farber Cancer Institute and Harvard Medical School, Boston, MA, USA;* [i] *Cliniques Universitaires Saint Luc, Brussels, Belgium;* [j] *Michigan Center for Translational Pathology, Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, MI, USA*

Prior to direct extrapolation of data to the nmCRPC space, we need to better understand how AR signalling, ADT, and the development of castration resistance modulate PSMA expression, with studies of PSMA-PET/CT in nmCRPC.

Only 24% of these patients had previously received ADT.

EURURO-9101; No. of Pages 20
ARTICLE IN PRESS
EUROPEAN UROLOGY XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer

Philip Cornford [a,], Roderick C.N. van den Bergh [b], Erik Briers [c], Thomas Van den Broeck [d], Marcus G. Cumberbatch [e], Maria De Santis [f,g], Stefano Fanti [h], Nicola Fossati [i], Giorgio Gandaglia [i], Silke Gillessen [j,k,l,m], Nikolaos Grivas [n], Jeremy Grummet [o], Ann M. Henry [p], Theodorus H. van der Kwast [q], Thomas B. Lam [r,s], Michael Lardas [t], Matthew Liew [u], Malcolm D. Mason [v], Lisa Moris [d,w], Daniela E. Oprea-Lager [x], Henk G. van der Poel [n], Olivier Rouvière [y,z], Ivo G. Schoots [aa,bb], Derya Tilki [cc,dd], Thomas Wiegel [ee], Peter-Paul M. Willemse [ff], Nicolas Mottet [gg]*

4. Castration-resistant PCa

4.2.2.4. Follow-up during treatment.

- Baseline examinations should include a medical history, clinical examination, as well as baseline blood tests (PSA, testosterone, full blood count, renal function, liver function tests, and ALP), **bone scan, and CT of the chest, abdomen, and pelvis.**

- The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely **not as beneficial as for patients with BCR**. Flares, PSMA upregulation, and discordant results compared with PSA response or progression on ARTAs have been described

ASCO special articles

Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

Edouard J. Trabulsi, MD[1]; R. Bryan Rumble, MSc[2]; Hossein Jadvar, MD, PhD[3]; Thomas Hope, MD[4]; Martin Pomper, MD, PhD[5]; Baris Turkbey, MD[6]; Andrew B. Rosenkrantz, MD[7]; Sadhna Verma, MD[8]; Daniel J. Margolis, MD[9]; Adam Froemming, MD[10]; Aytekin Oto, MD[11]; Andrei Purysko, MD[12]; Matthew I. Milowsky, MD[13]; Heinz-Peter Schlemmer, MD[14]; Matthias Eiber, MD[15]; Michael J. Morris, MD[16]; Peter L. Choyke, MD[6]; Anwar Padhani, MD[17]; Jorge Oldan, MD[13]; Stefano Fanti, MD[18]; Suneil Jain, NMD[19]; Peter A. Pinto, MD[6]; Kirk A. Keegan, MD[20]; Christopher R. Porter, MD[21]; Jonathan A. Coleman, MD[16]; Glenn S. Bauman, MD[22]; Ashesh B. Jani, MD[23]; Jeffrey M. Kamradt, MD[24]; Westley Sholes, MPA; and H. Alberto Vargas, MD[16]

Recommendation 4.8. Nonmetastatic CRPC

For ***men with nonmetastatic CRPC***, NGI can be offered only if a change in the clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on detection capabilities of NGI in this setting and impact on management are limited

(Type: consensus, benefits/harms ratio uncertain;
Evidence quality: weak;
Strength of recommendation: moderate).

LIMITATIONS OF PSMA PET

- **No standardized reporting system or criteria**. In the context of clinical trial design, this is a major disadvantage.

- International collaborative work promoted by the European Association of Nuclear Medicine, which provides a valuable framework for standardized reporting.[30] published on a PSMA-RADS system for reporting PSMA PET scans.[31]

- **Molecular imaging TNM (miTNM) staging** on PSMA PET/CT 'Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) has been published through an international collaborative work.[32] None of the above has yet been incorporated into the daily clinical practice.

- Currently, any degree of PSMA uptake (above the adjacent background uptake) in a region without physiological PSMA expression is considered abnormal and would be suggestive of 'recurrent' or 'metastatic' disease and interpreted as such in the absence of a clear alternative explanation.[30]

- **PSMA expression**, however, has been shown and reported in the literature in multiple extraprostatic, benign and nonprostatic, malignant lesions, although this is usually characterized by a lower- intensity uptake.[33,34]

This emphasizes the high degree of vigilance and careful interpretation required by reporting physicians when unexpected PSMA expression is observed in lesions out of context with the patient's PSA, Gleason score or clinical presentation.

So what for NGI?

EDITORIAL

Prostate Cancer CRPC Stage M0 and M1: Do We Need Stage M0.5?

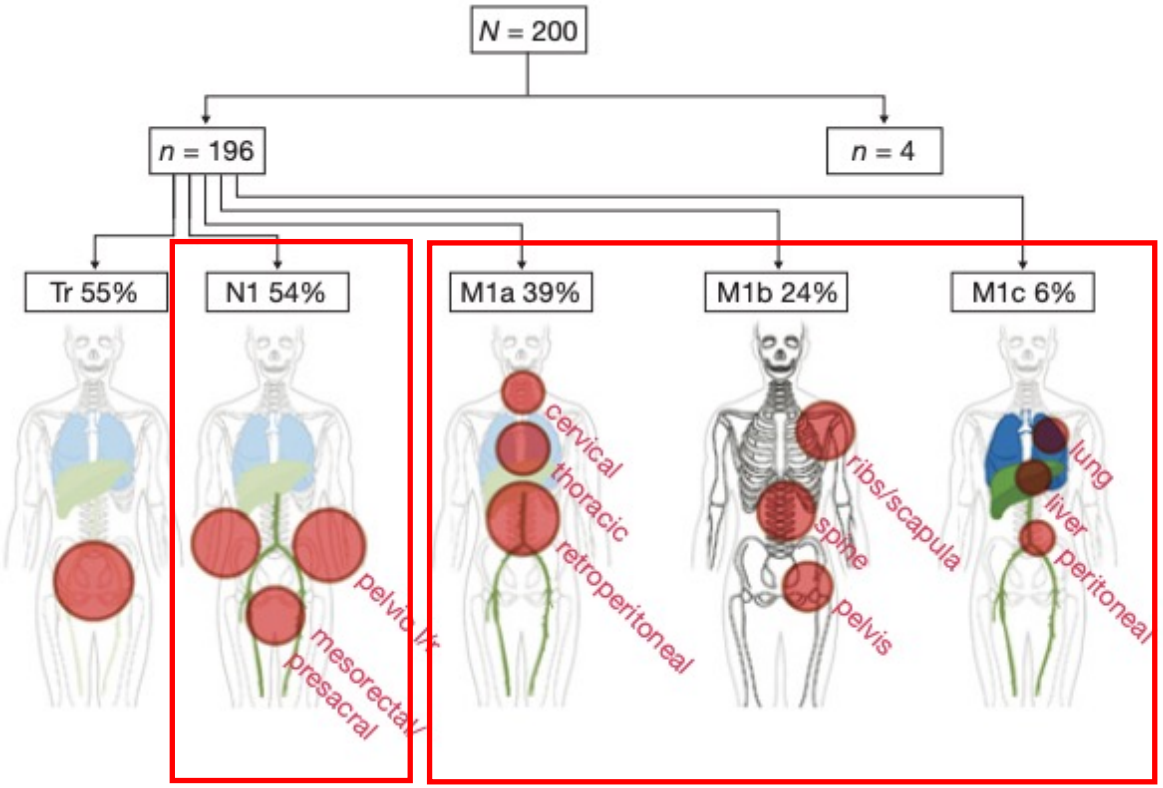
How do we address this paradigm shift of earlier identification of metastatic disease through these new PET scans? Should we define M1 CRPC based solely on traditional imaging or should we consider a new classification based on a PET based schema: M1 with traditional imaging and M0.5 to denote PET scan detected metastasis before traditional imaging?

Gomella LG, The Canadian Journal of Urology; 25(2); April 2018

Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer

200 M0 CRPC
Conventional Imaging

98%
PSMA-PET Positive



54% N1

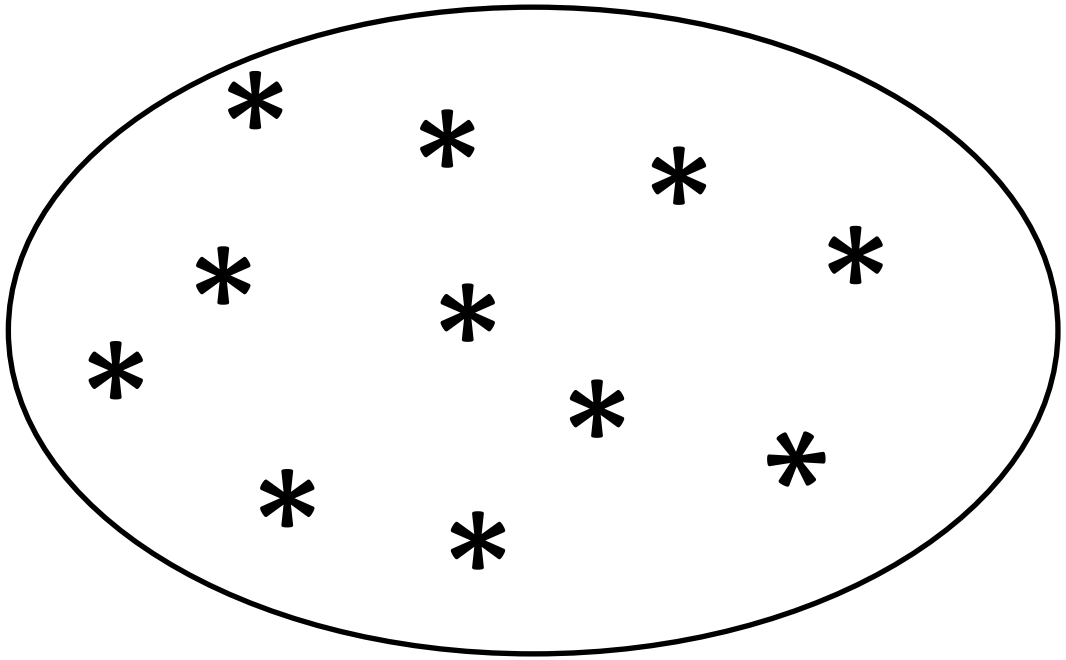
55% M1

Impact of stage migration on management and prognosis is unknown

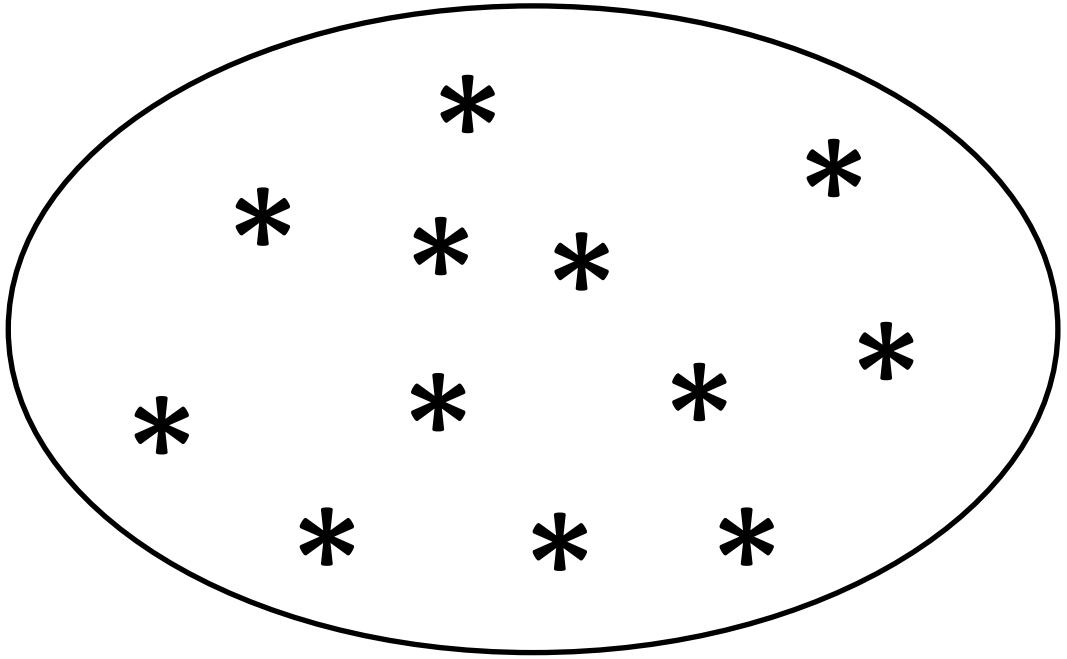
Fendler, Clin Canc Res 2019

NGI and stage migration in nmCRPC

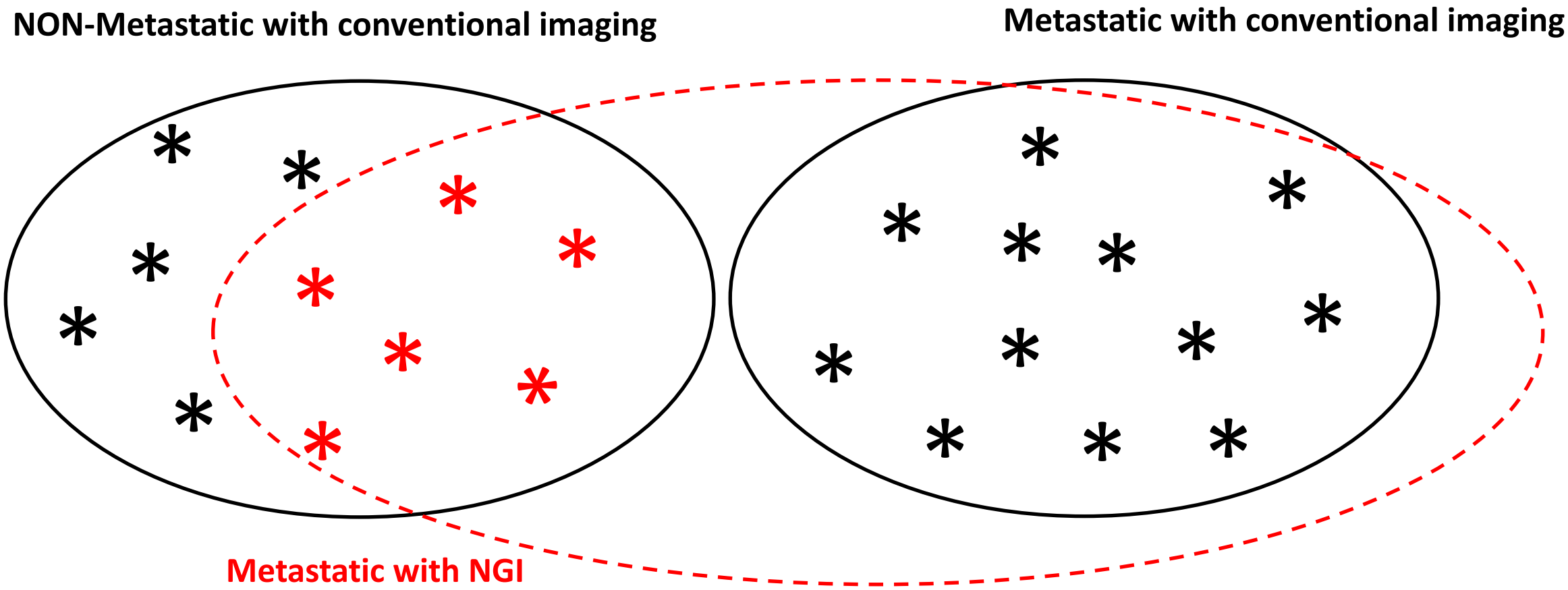
NON-Metastatic with conventional imaging



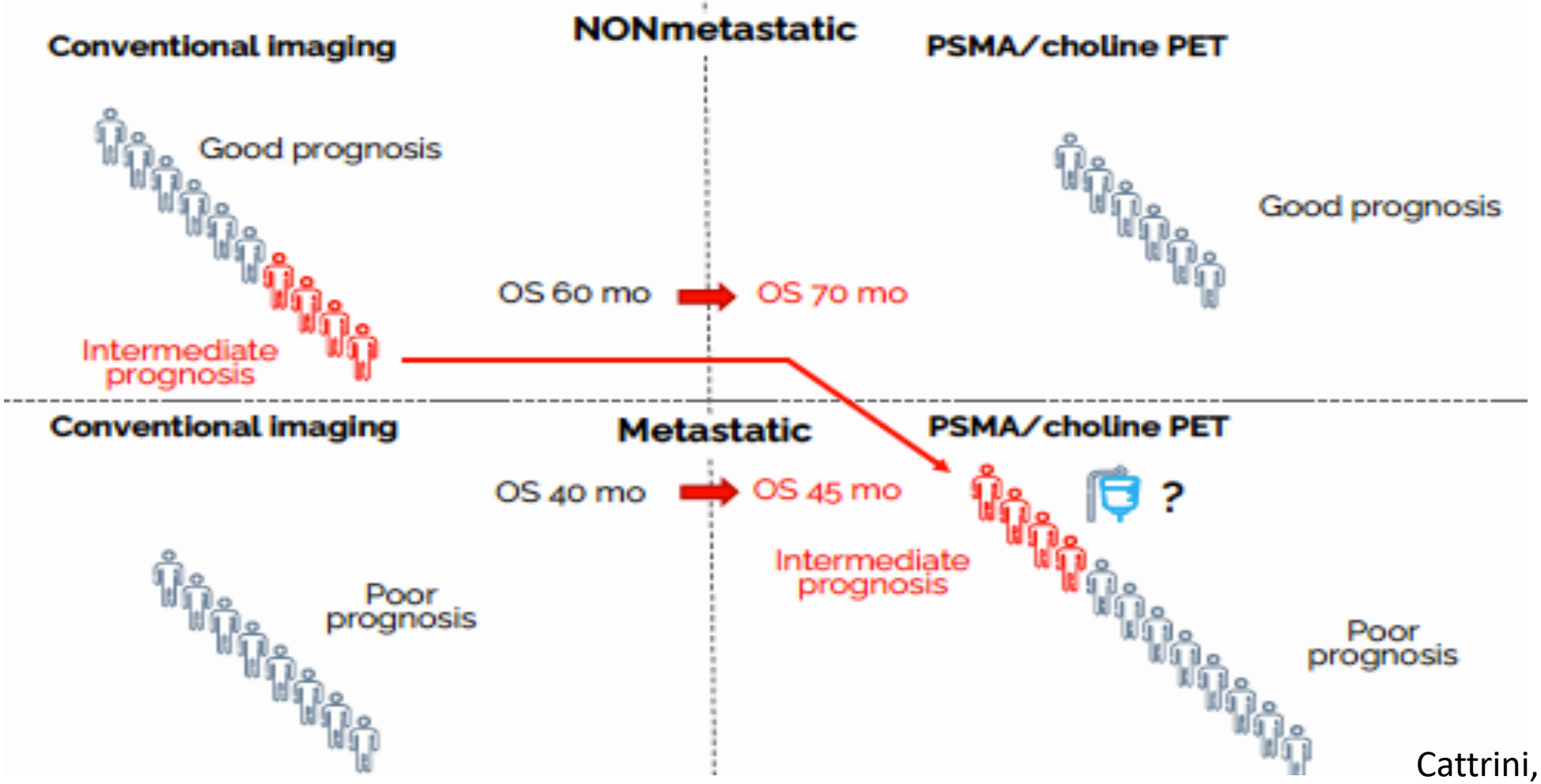
Metastatic with conventional imaging



NGI and stage migration in nmCRPC



Will Rogers phenomenon



Cattrini, Cancers 2022

Stage migration: Not all glitters is gold

Conventional imaging M0 → 10.7% → PSMA PET low/high volume M1 — Pienta et al. J Urol 2021 (OSPREY)

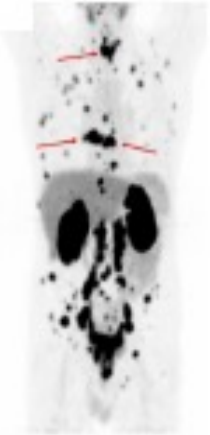
Treatment options:
RP
RT+/ADT

Treatment options:
ADT + RT (low volume only)
ADT + ARPI
ADT + Docetaxel

Risk of *undertreatment*?

Conventional imaging low volume M1 → 19% → PSMA PET high volume M1 — Barbato et al. J Nucl Med 2021

Treatment options:
ADT + RT
ADT + ARPI
ADT + Docetaxel



Treatment options:
ADT + ARPI
ADT + Docetaxel

Risk of *overtreatment*?

Zacho et al. EJNMMI Res 2020; Pienta KJ J Urol 2021; Durack et al. ASCO 2021; Barbato et al. J Nucl Med 2021 Sundahl et al. Eur Urol 2021

Stage migration in nmCRPC

The standard of care for both nmCRPC and mCRPC is virtually the same, but you lose apalutamide and darolutamide with upstaging

There are no data to suggest that patients with a positive PSMA result should not be treated with enza/apa/daro, even if they have M1 disease on PSMA

There are no data showing that PSMA-PET imaging is valuable for treatment Guidance and clinically relevant ouctomes

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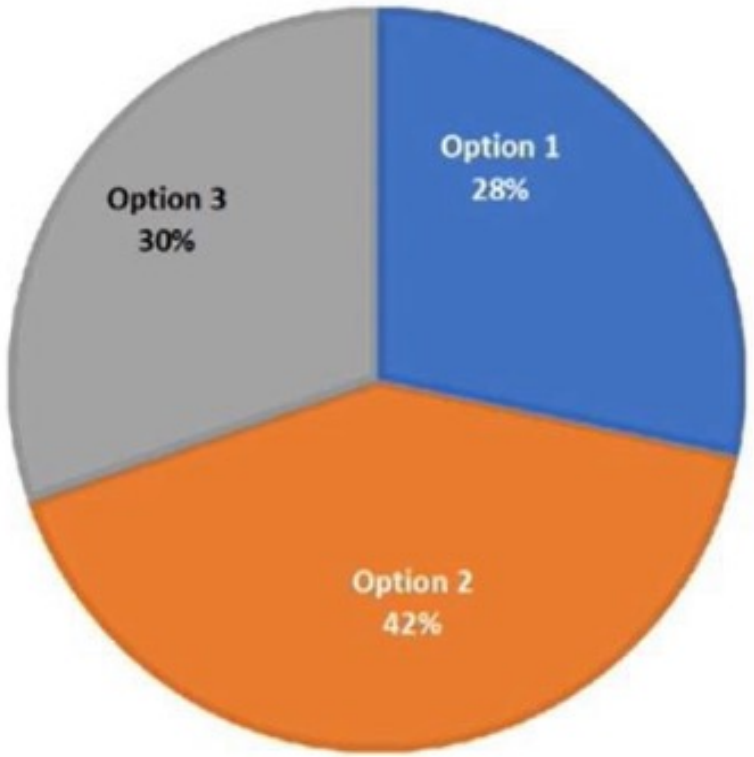
113 and 114 For the majority of patients with nmCRPC on conventional imaging do you recommend a PSMA PET prior to starting apalutamide, darolutamide, or enzalutamide?

1. Yes
2. Yes, but only for patients who are candidates for radiation therapy (for local relapse and/or oligometastatic disease)
3. No
4. Abstain/unqualified to answer

PSA DT ≤10 months



Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

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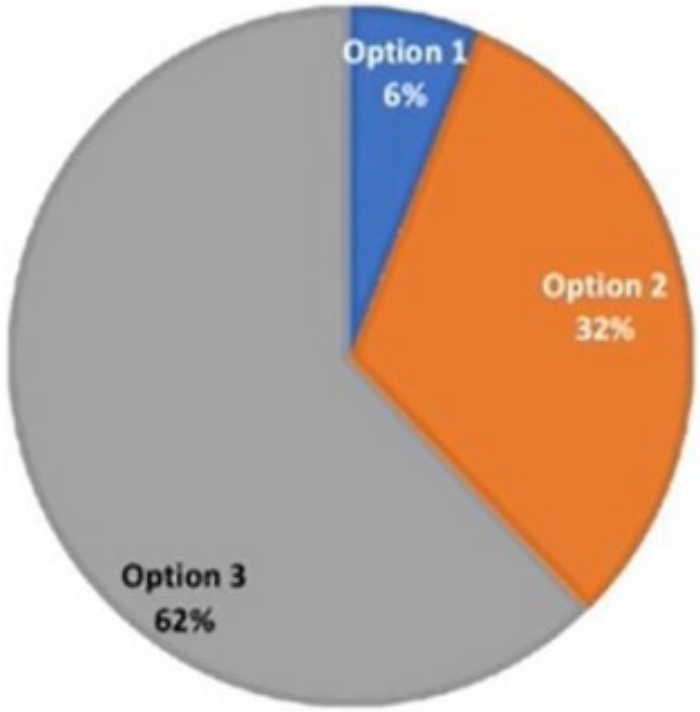
115. For the majority of patients with a PSA doubling-time ≤10 months imaged initially with PSMA PET demonstrating 1-3 lesions, would you go back and perform conventional imaging (CT + bone scintigraphy) to define whether disease state is nmCRPC by conventional imaging?

1. Yes
2. Yes, but only in order to access standard option apalutamide, darolutamide, or enzalutamide
3. No
4. Abstain/unqualified to answer



Option	Votes
Option 1	6
Option 2	32
Option 3	61
Option 4	5
Total votes	104

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

Aprile 2017	PSA 0,3 ng/ml	Testosterone tot 20 ng/dl
Settembre 2017	PSA 0,6 ng/ml	
Gennaio 2018	PSA 0,8 ng/ml	
Aprile 2018	PSA 1,1 ng/ml	
Settembre 2018	PSA 1,5 ng/ml	
Dicembre 2018	**PSA 2,1 ng/ml**	

PSADT 8 mesi

TMD

Dicembre 2018 Scintigrafia ossea: negativa per secondarismi

TAC: lifonodo iliaco esterno destro di 10 mm

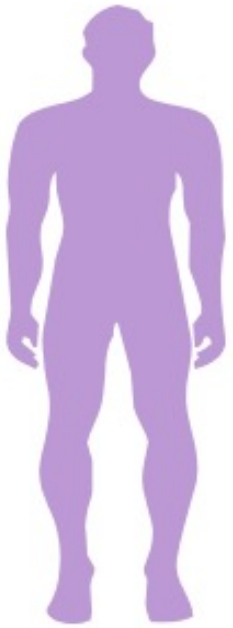
TMD

Dicembre 2018 PET-TC Colina: confermata debole captazione a livello del linfonodo iliaco esterno destro (suv max 3,8)

How do we stage this patient?

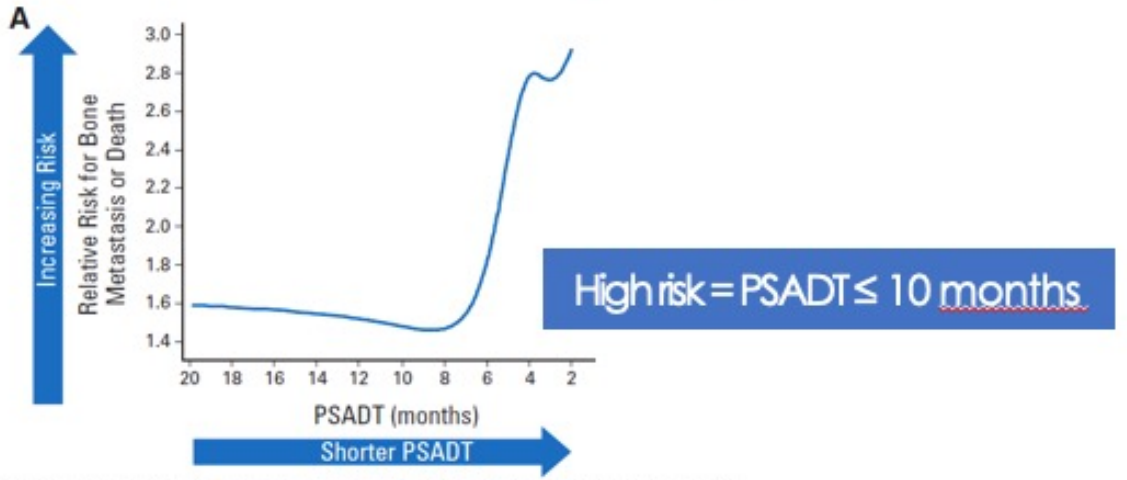
High Risk nmCRPC

The target population is at high risk of developing metastases and progressing to mCRPC



High risk nmCRPC patient

- Has had prostate cancer for several years
- Has HRQoL comparable to the general population[1]
- His PSA levels are rising, with PSADT ≤10 months which means he is at high risk of progressing to mCRPC[2,3]



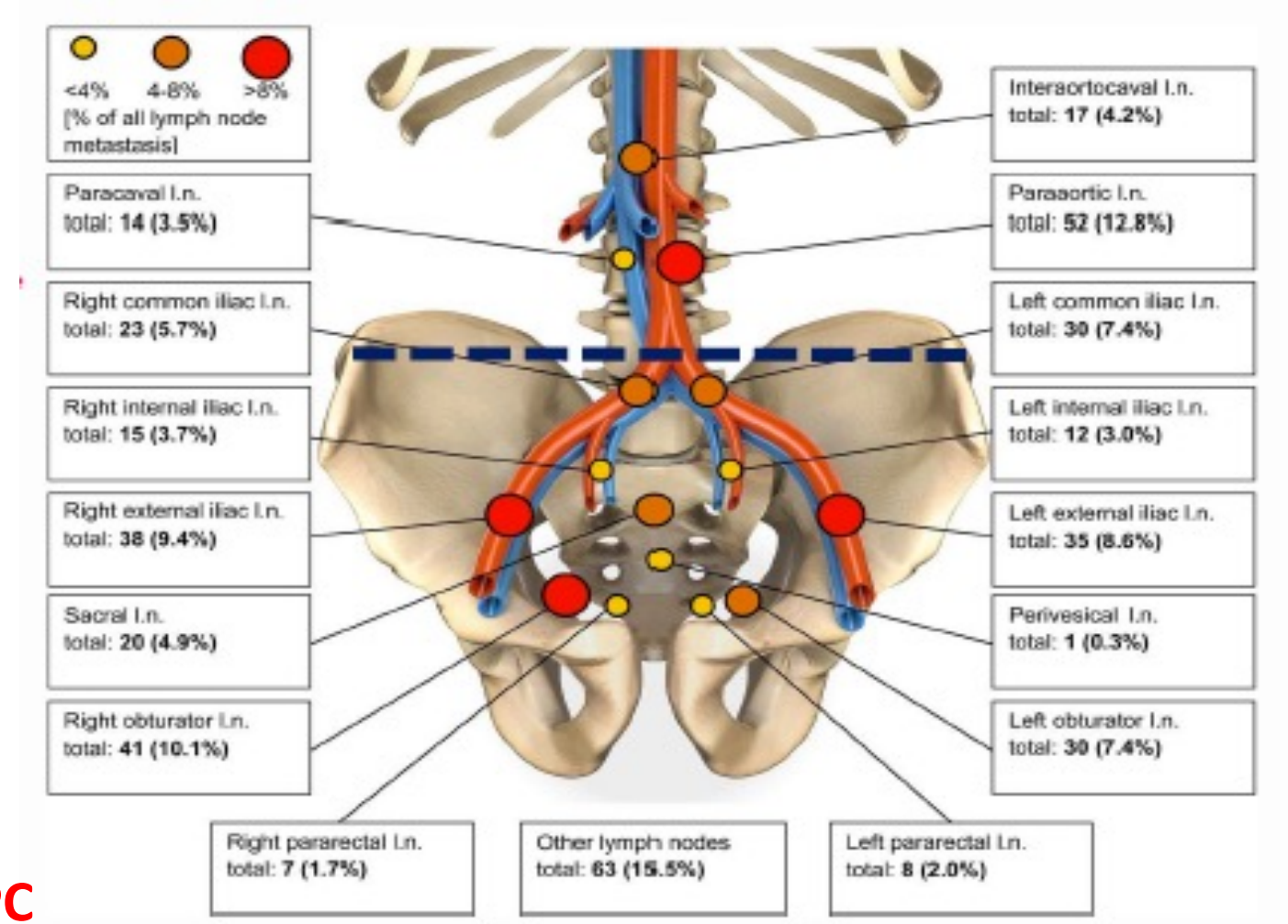
- Is worried about developing metastases[4,5]

1. Saad F, et al. 2018.
2. Aly M et al, 2017.
3. Moreira DM, et al. 2016.
4. Clinical Outcomes Solutions. 2018.
5. Janssen. *(Data on file)*.

Who are N1 patients?

- **N0** no regional lymph nodes metastasis
- **N1** regional lymph node metastasis (nodes of the true pelvis, which are essentially the pelvic nodes below the bifurcation of the common iliac arteries)

- **M1a** non-regional lymph nodes(s)
- **M1b** bone(s)
- **M1c** other site(s)



- N status was assessed by CT scan

- **Presence of local relapse, or residual tumour was considered within nmCRPC**

FOCUS on Study characteristics

SPARTAN	PROSPER	ARAMIS
Apalutamide	**Enzalutamide**	**Darolutamide**
- M0 N0-1 CRPC	- M0 **N0** CRPC	- M0 N0-1 CRPC
- PSA rising	- PSA rising	- PSA rising
- PSA ≥ 2 ng/ml	- PSA ≥ 2 ng/ml	- PSA ≥ 2 ng/ml
- PSAdt ≤ 10 mo	- PSAdt ≤ 10 mo	- PSAdt ≤ 10 mo

Quale Opzione terapeutica?

1. Manipolazione ormonale (aggiunta antiandrogeno, cambio LHRH agonista, cambio LHRH antagonista)

2. Follow-up

3. Trattamento diretto alle metastatsi

4. Apalutamide, Darolutamide, Enzalutamide

Metastasis-directed therpy for oligoprogressive mCRPC

Retrospective series

Rference	n.pts.	Treatment	% 2-years Distant PFS	Median systemic therapy–free surv
Muldermans, *2016*	*50*	**SBRT** (BED 30-50 Gy)	45	NR
Triggiani, *2019*	*86*	**SBRT** (BED 80 Gy)	33.7	21.8 months

Lack of prospective data
Unknown effect on OS

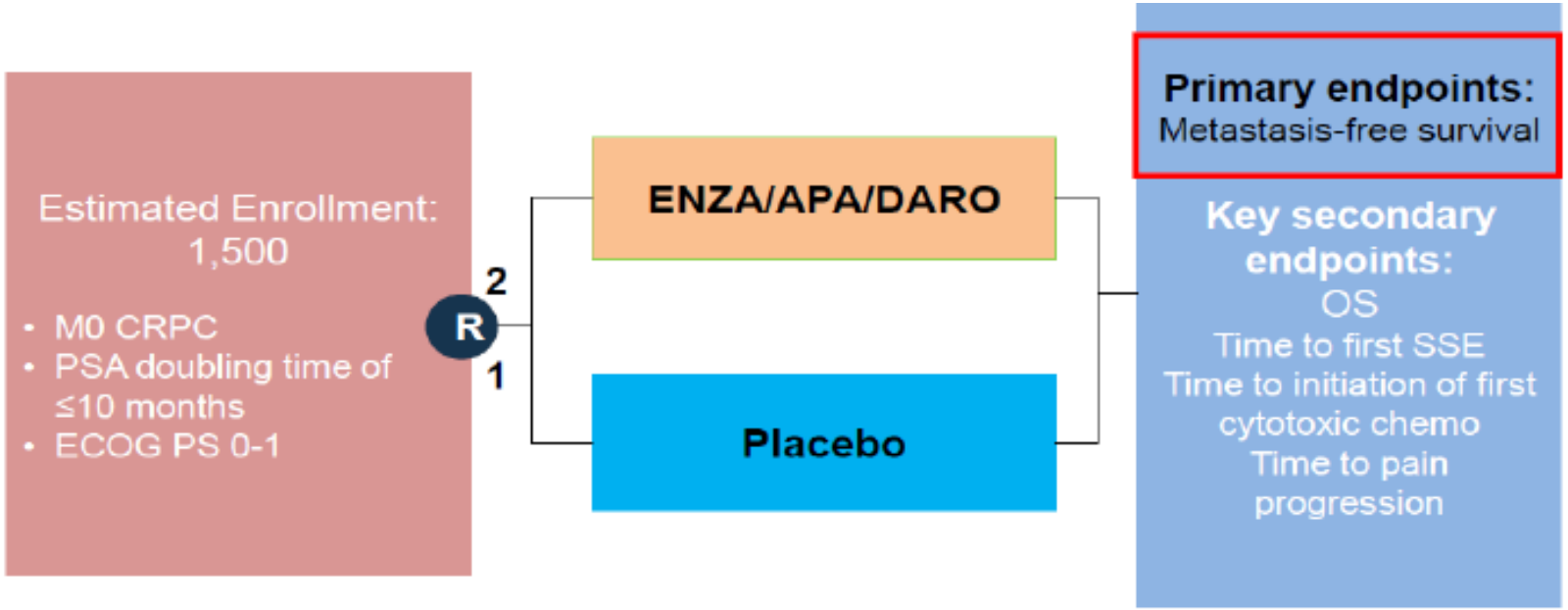
	% Grading	
Toxicity	**G1**	**G2**
Pain flare	9	3
Gastrointestinal	3	-
Genitourinary	1	3

Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: A position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO)

In an asymptomatic or minimally symptomatic mCRPC patient with a PSA doubling time > 6 months, time to castration-resistant phenotipe > 12 months, and oligometastases up to three nodal or bone lesions detected by metabolic imaging, RT with radical intent to metastatic sites could be offered as alternative to ARTA to delay systemic treatment

D'Angelillo at Al. Crit. Rev Oncol Hematol 2019

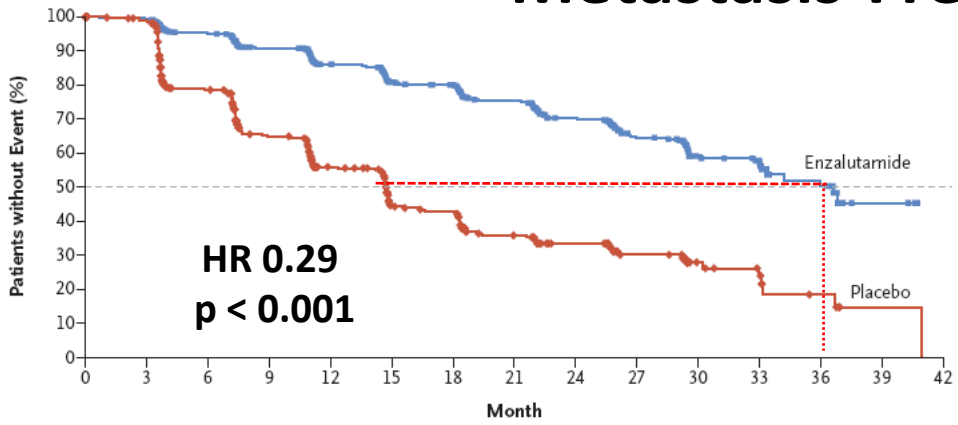
Phase III randomized trials in High-Risk nmCRPC



Similar trials with Enzalutamide (PROSPER)[1], Apalutamide (SPARTAN)[2], Darolutamide (ARAMIS)[3]

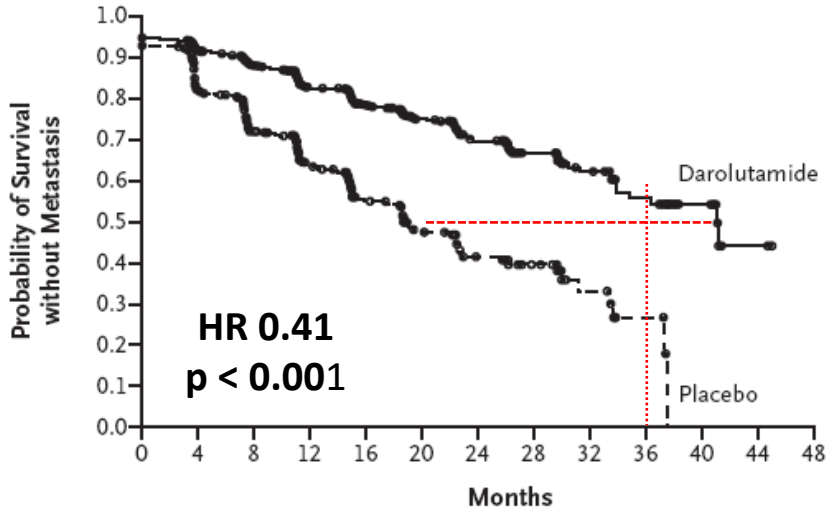
1.Hussain, NEJM 2018; 2.Matthew, NJM 2018; 3.Fizazi, NEJM 2019

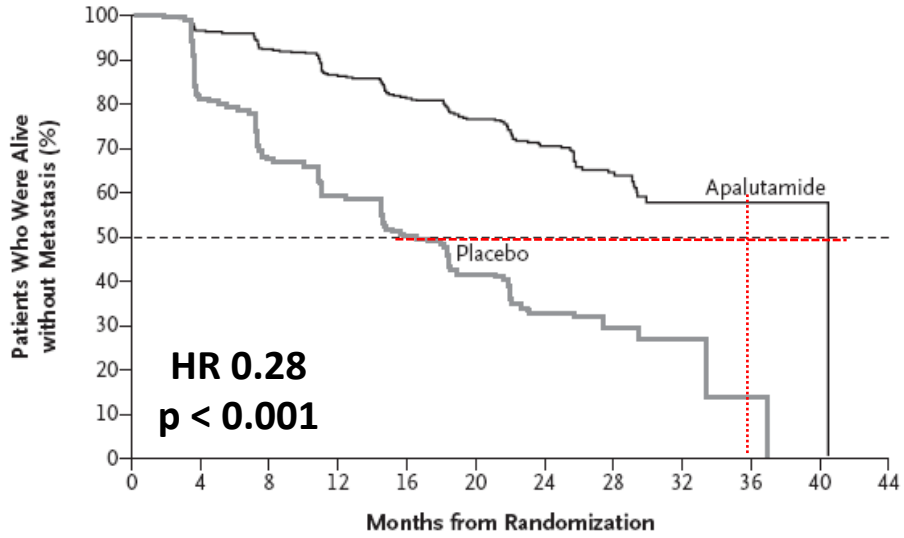
Metastasis-Free survival



Enzalutamide

Apalutamide



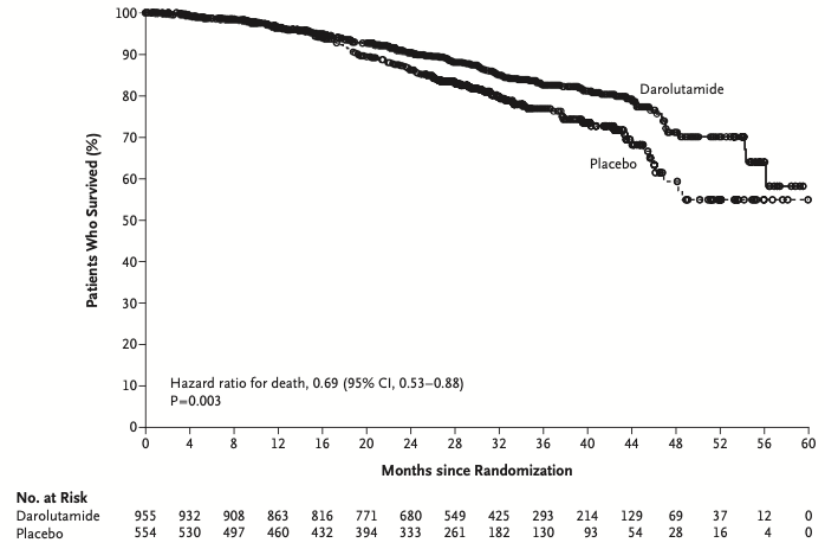


Darolutamide

1.Hussain, NEJM 2018; 2.Matthew, NJM 2018; 3.Fizazi, NEJM 2019

Overall survival and New Hormonal Agents in M0 CRPC

Darolutamide

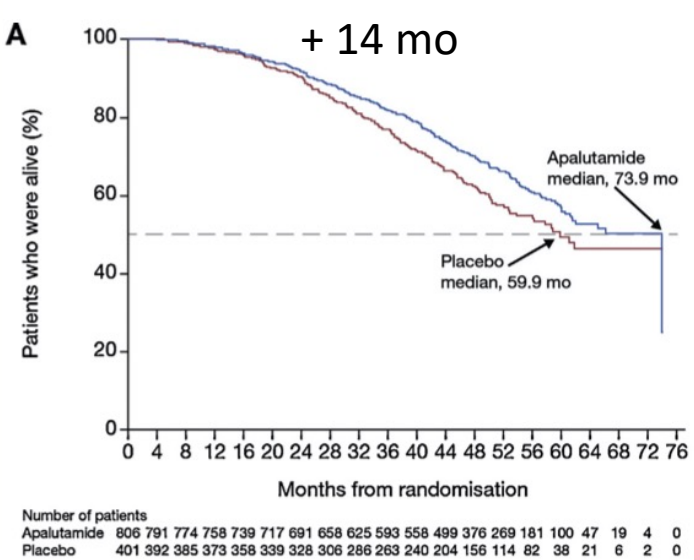


HR 0.69

Fizazi, NEJM 2020

Apalutamide

+ 14 mo

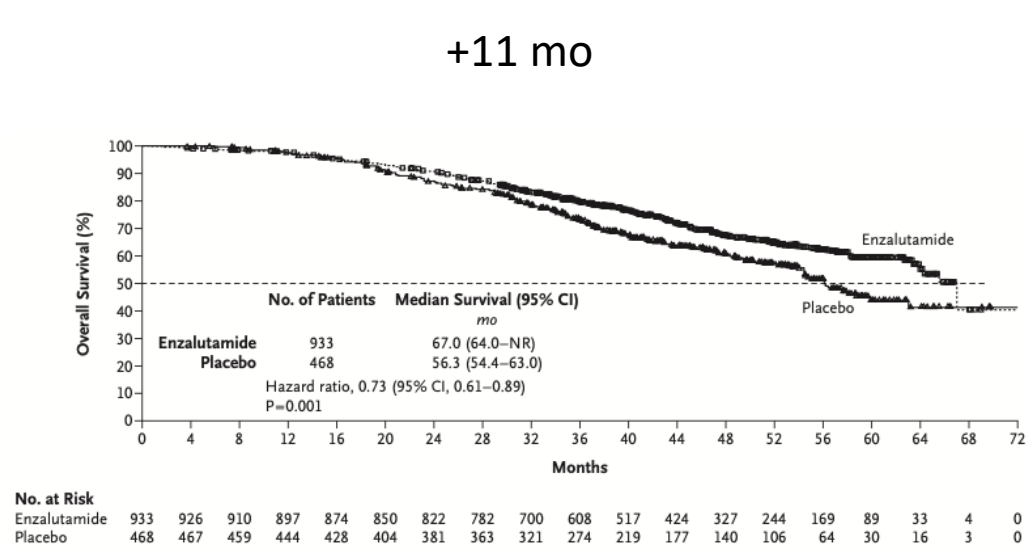


HR 0.78

Smith, Eur Urol 2020

Enzalutaide

+11 mo



HR 0.73

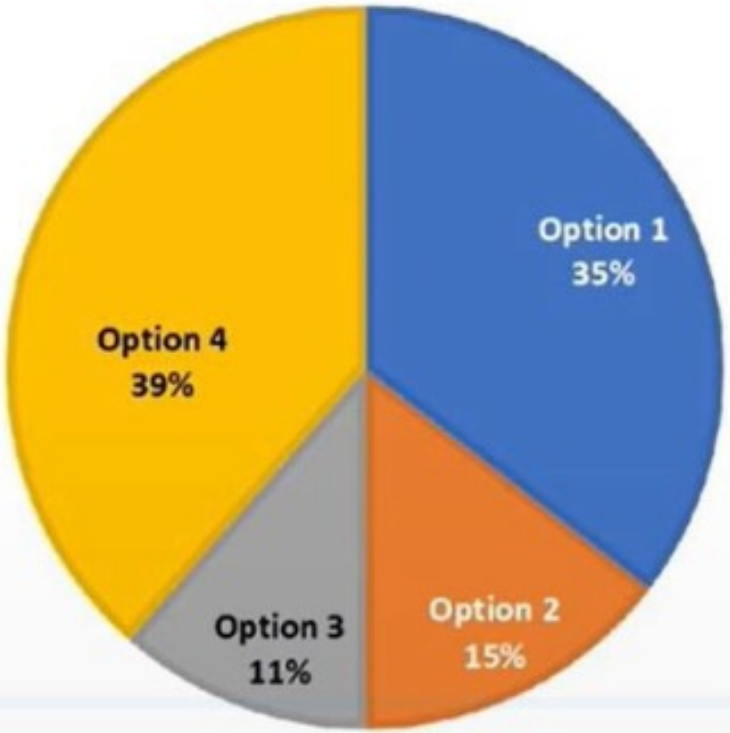
Sternberg, NEJM 2020

APCCC
ADVANCED PROSTATE CANCER CONSENSUS CONFERENCE
www.apccc.org

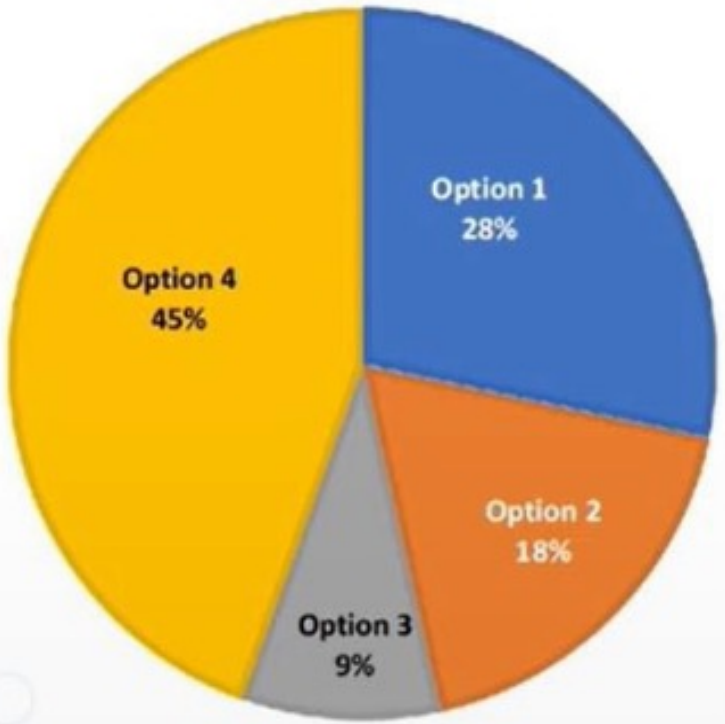
116 and 117 For the majority of patients with nmCRPC on conventional imaging with a PSA doubling-time ≤10 months what is your preferred treatment if the PSMA PET shows:

1. Treat as nmCRPC with standard option: apalutamide, darolutamide, or enzalutamide
2. Treat as mCRPC with standard option
3. Metastases directed therapy (MDT) alone
4. MDT plus systemic therapy (either for nmCRPC or mCRPC)
5. Abstain/unqualified to answer (including I do not recommend PSMA PET)

1 - 3 lesions in distant lymph nodes



1 - 3 lesions in lymph nodes and bone



Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

TMD Dicembre 2018: **RT stereotassica (36 Gy in 6 fx) + Apalutamide uso compassionevole**.

Marzo 2019 PSA 0.06 *Inizio Denosumab 60 mg semestrale*

TAC (lug 2019) non più evidente linfonodo
TAC (feb 2020) negativa
TAC + Scintigrafia ossea (Dic 2020) negativa
TAC (Dic 2021) negativa

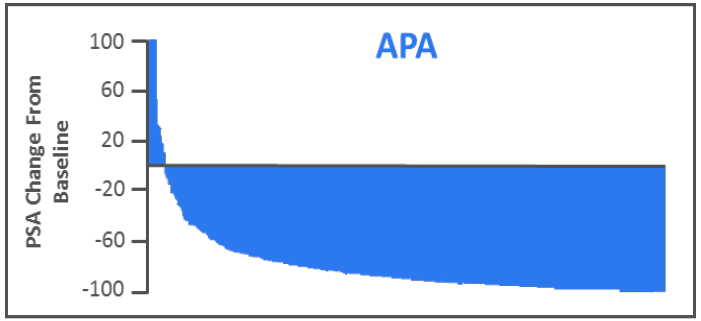
Eventi Avversi:

- aumento colesterolo totale trattato con utilizzo di statine (insorgenza: dopo 6 mesi di trattamento)

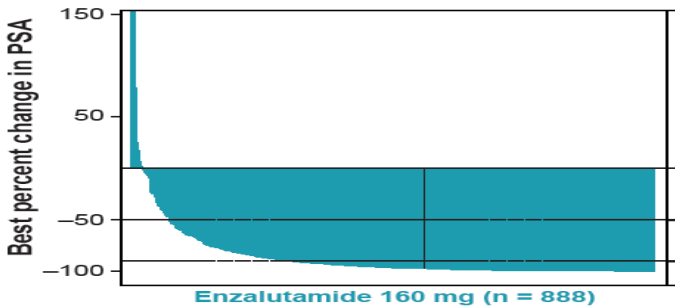
Maggio 2022 PSA 0.0 Testosterone totale indosabile Asintomatico (77 anni)
Programmata TAC dic 2022.

PSA response

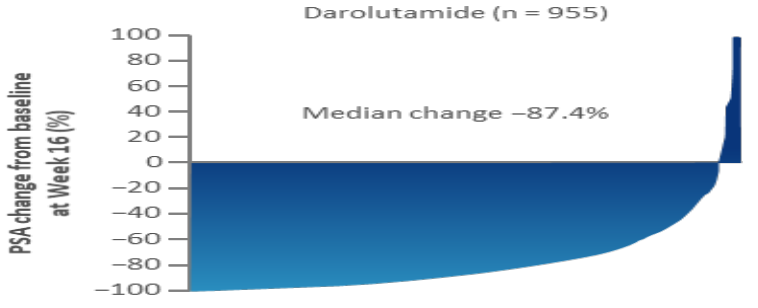
SPARTAN: ≥50% PSA decline: 93%



PROSPER: ≥50% PSA decline: 76.3%



ARAMIS: ≥50% PSA decline: 83.3%

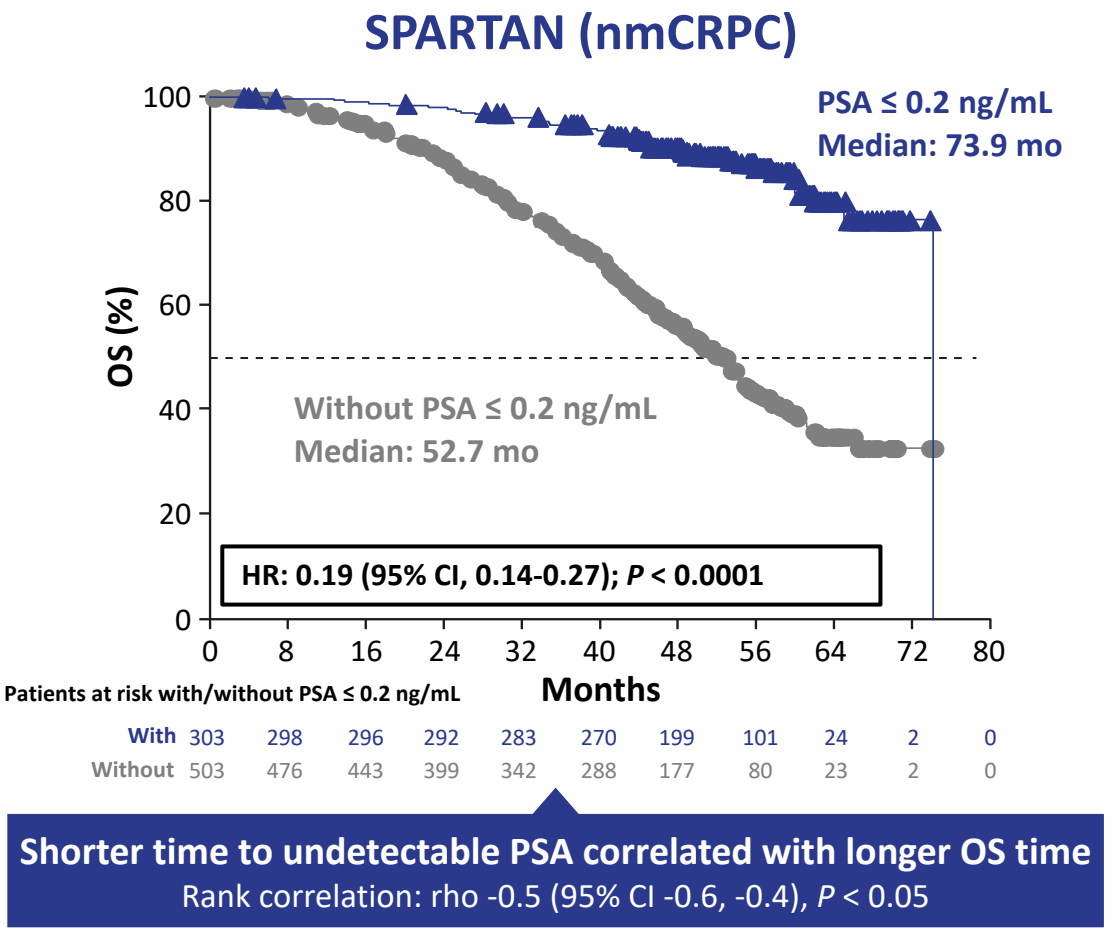


	SPARTAN		PROSPER		ARAMIS	
	APA (n = 806)	PBO (n = 401)	ENZA (n = 933)	PBO (n = 468)	DARO (n = 955)	PBO (n = 554)
≥50% PSA decline	**93%**	**2%**	**76.3%**	**2.4%**	**83.3%**	**8.1%**
P value	NR		<0.0001		<0.001	
≥90% PSA decline	**66%**	**NR**	**55.9%**	**0.4%**	**51%**	**2%**
P value	NR		<0.0001		<0.001	

Small ES, et al. Oral presentation. AUA 2018 (Abstract PD10-11); Smith MR, et al. N Engl J Med. 2018 Apr 12;378(15):1408-1418 (and Suppl and protocol); Sternberg CN, et al. Poster presented at EAU 2018 (abstract 604); Tammela T, et al. Oral presentation. EAU 2019 (Breaking news session 3BN); Hussain M, et al. N Engl J Med. 2018 Jun 28;378(26):2465-2474 (and Suppl and Protocol)

Achievement of Undetectable PSA Was Associated With Improved OS

OS by achievement of ≤ 0.2 ng/mL PSA with APA + ADT



Shorter time to undetectable PSA correlated with longer OS time

Rank correlation: rho -0.5 (95% CI -0.6, -0.4), $P < 0.05$

SAFETY AT SIMILAR TREATMENT EXPOSURE

Treatment option	APA + ADT	ENZA + ADT	DARO +ADT
Any AEs	✓	✓	✓
SAEs	✓	✓	✓
G3-4 AEs	✓	✓	NR
Rash	✗	NR	✗
Fatigue+asthenia	✓	✗	✗
Hypertension	✓	✗	✓
Falls	✗	✗	✓
Fractures	✗	NR	✗
Cognitive/memory impairment and loss of consciousness/ syncope	✗	✗	✓

✓ < 1.5x increase in AEs vs control

✗ ≥ 1.5x increase in AEs vs control

AEs of interest exposure adjusted (ASCO 2020)

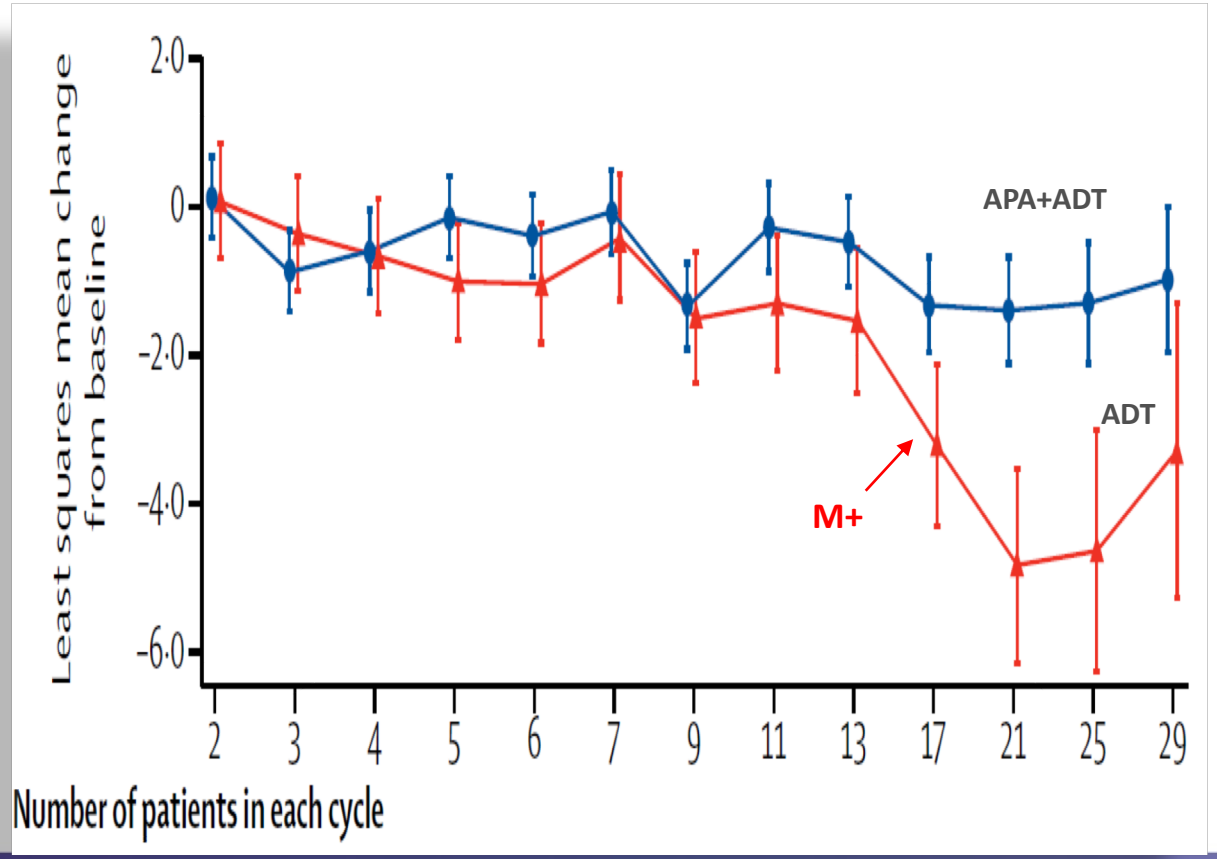
Treatment option	APA + ADT	ENZA + ADT	DARO +ADT
any grade AEs	NA	✓	NA
SAEs	✓	✓	NA
grade ≥3 AEs	✓	✓	NA
AEs of special interest			
Rash	✗	✓	✗
Fatigue	NA	✓	✓
Hypertension	NA	✓	✓
Falls	✓	✗	✓
Fractures	✓	✗	✓
Cognitive/memory impairment and loss of consciousness/ syncope	NA	✗	✓

✓ < 1.5x increase in AEs vs control

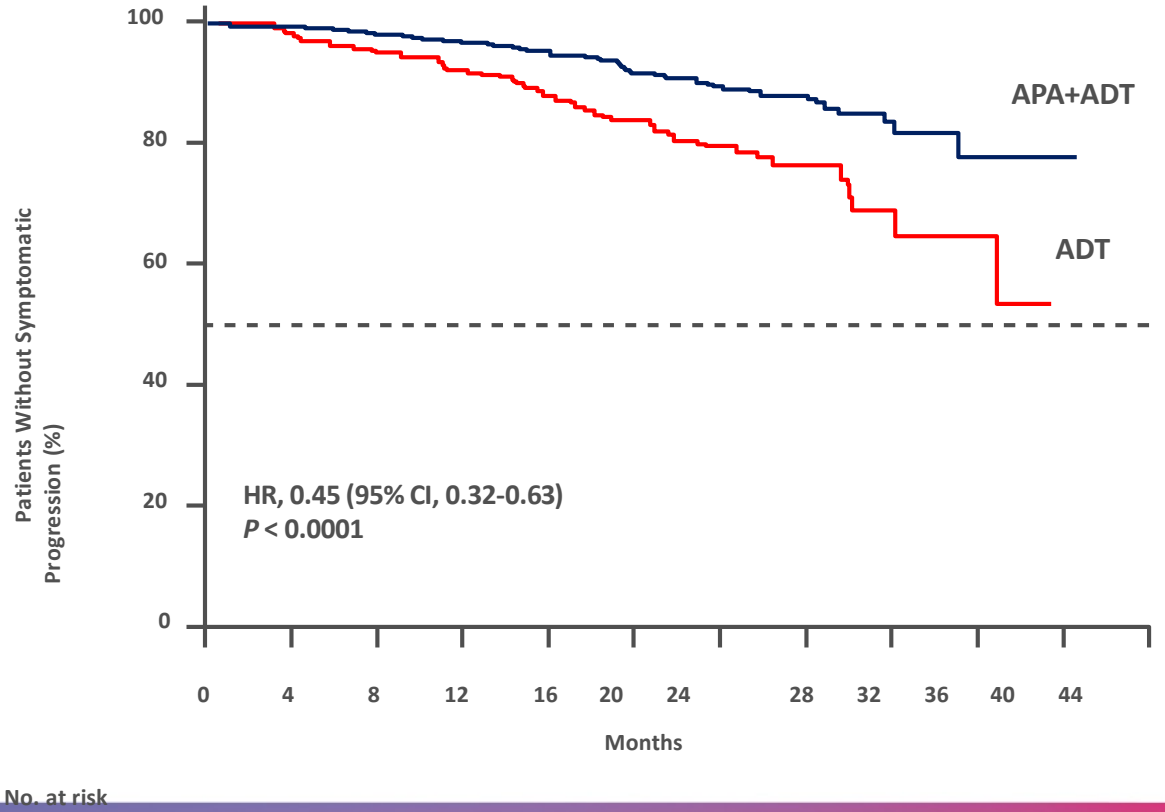
✗ ≥ 1.5x increase in AEs vs control

Significato clinico del ritardo della metastasi: Apalutamide ritarda il decadimento della QoL e la progressione dei sintomi

Variazioni nella Qol dal basale (Fact-P)



Tempo alla progressione dei sintomi

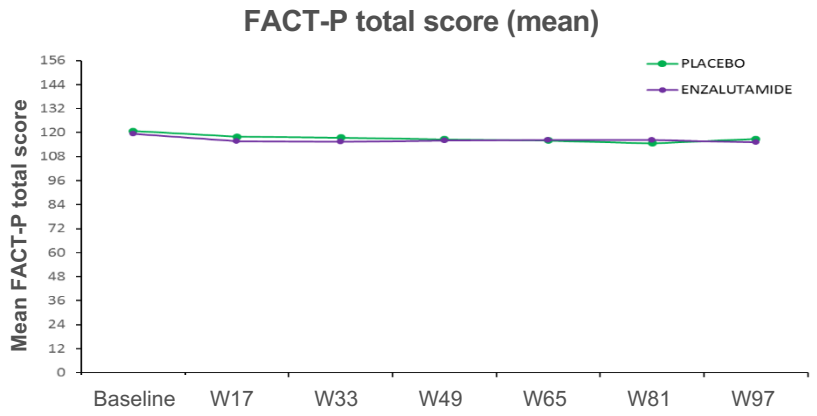


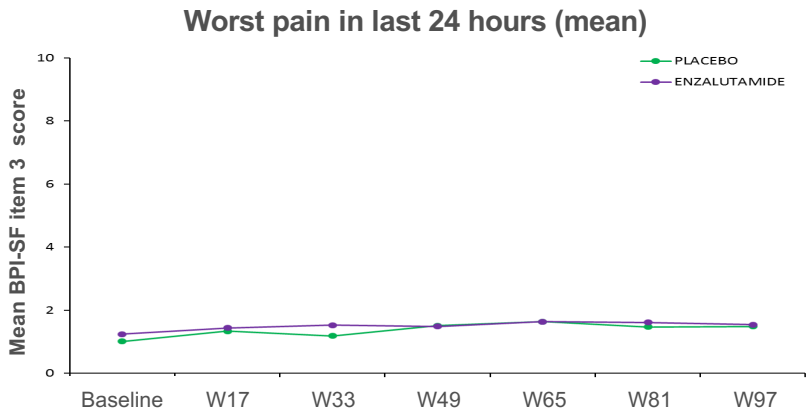
[1]Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.

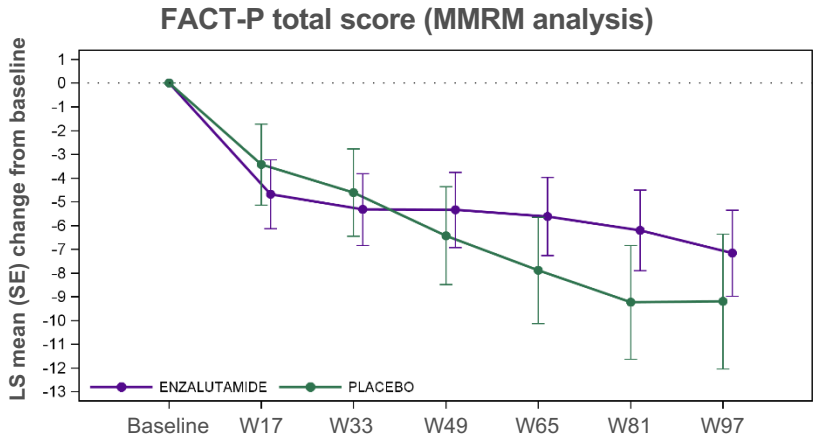
[1]Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.

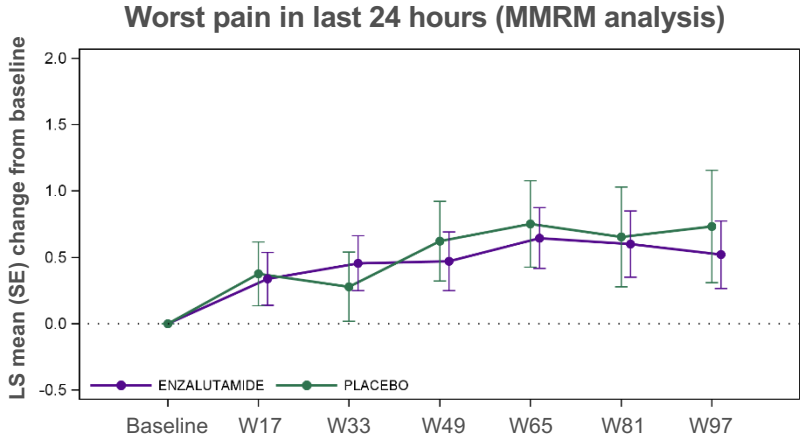
PROSPER: Enzalutamide QoL was similar to placebo

- Changes in mean FACT-P total score at each visit compared with baseline indicated a small deterioration in health status with both ENZA and placebo.





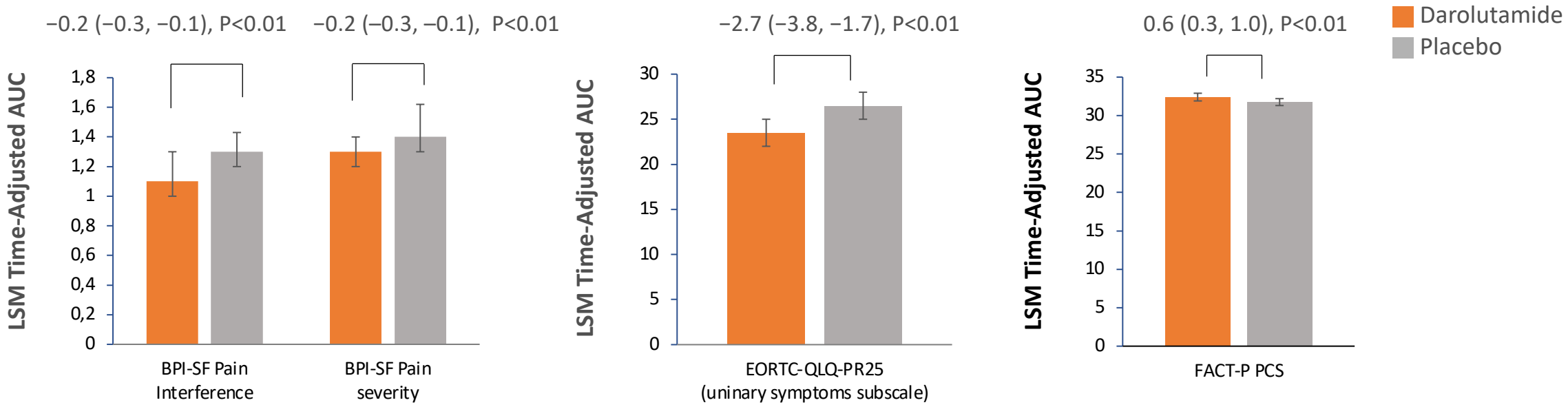




No statistically or clinically meaningful change in FACT-P total score or worst pain, was observed over 97 weeks*

Saad F, et al. Poster presented at AUA 2018 (abstract MP52-19)

ARAMIS: Health-related quality of life outcomes



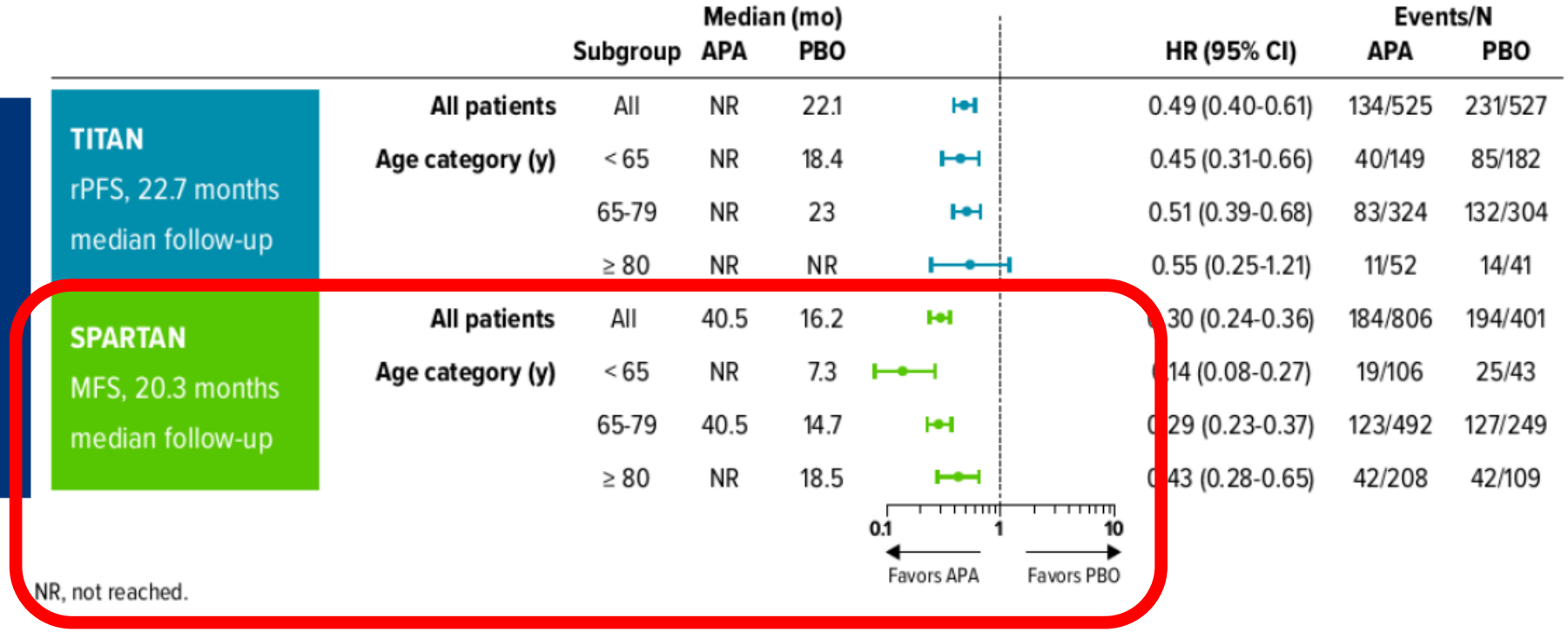
Patient-reported scores tended to favor darolutamide for pain and urinary symptoms; differences did not reach clinically meaningful tresholds

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.

Fizazi K, et al. Oral presentation at ASCO GU 2019; February 14-16. abstract 140.

TITAN and SPARTAN Patients Derived Benefit With APA Regardless of Age: Primary/Co-Primary Outcomes

- rPFS was improved with APA in < 65 and 65-79 year age groups in TITAN
- MFS was improved with APA in SPARTAN patients of all ages



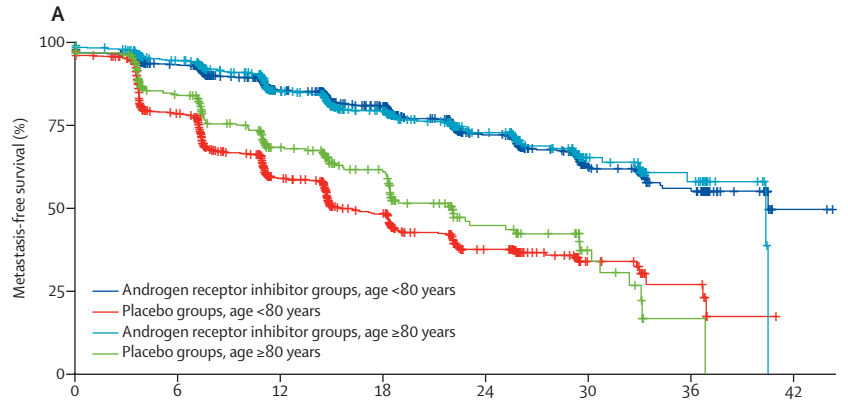
ESMO 2021

Survival outcomes in older men with non-metastatic castration-resistant prostate cancer treated with androgen receptor inhibitors: a US Food and Drug Administration pooled analysis of patient-level data from three randomised trials

Jaleh Fallah, Lijun Zhang*, Anup Amatya, Yutao Gong , Bellinda King-Kallimanis , Vishal Bhatnagar, Chana Weinstock, Daniel L Suzma Sundeep Agrawal, Elaine Chang, Mitchell S Anscher, Dow-Chung Chi, James X Xu, Jamie R Brewer, Michael H Brave, Mehrnoosh Hadadi, Marc R Theoret, Paul G Kluetz, Kirsten B Goldberg, Amna Ibrahim, Shenghui Tang, Richard Pazdur, Julia A Beaver, Laleh Amiri-Kordestar Harpreet Singh*

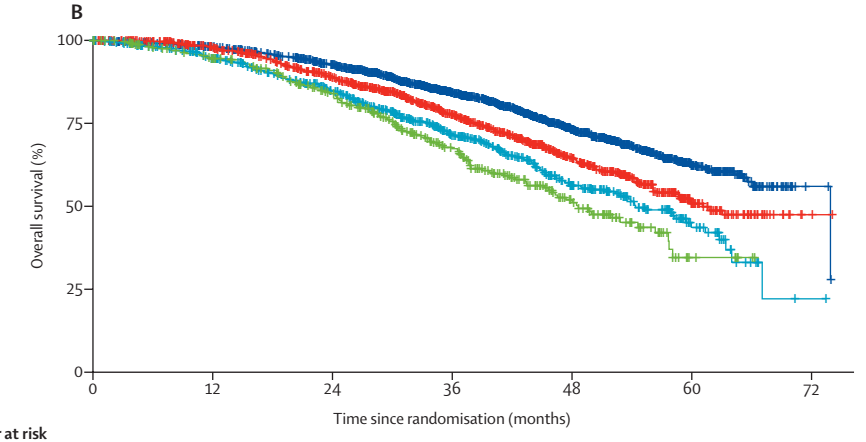
www.thelancet.com/oncology **Vol 22 September 2021**

MFS



Number at risk (number censored)								
Androgen receptor inhibitor groups, age <80 years	2019 (0)	1704 (183)	1183 (580)	905 (798)	479 (1149)	152 (1434)	66 (1510)	2 (1572)
Placebo groups, age <80 years	1075 (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)

OS



Number at risk (number censored)							
Androgen receptor inhibitor groups, age <80 years	2019 (0)	1916 (65)	1707 (173)	1187 (554)	630 (987)	157 (1397)	3 (1543)
Placebo groups, age <80 years	1075 (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)

Figure 2: **Kaplan-Meier curves of survival outcomes**
(A) Metastasis-free survival. (B) Overall survival.

	Androgen receptor inhibitor groups	Placebo groups
Age ≥80 years		
Participants	573	292
FACT-P total score at baseline	116·70 (19·62)	115·87 (16·10)
FACT-P total score at week 16	114·66 (20·27)	113·94 (17·94)
Change in FACT-P total score	2·13 (16·15)	2·10 (13·81)
Age <80 years		
Participants	1828	958
FACT-P total score at baseline	117·70 (18·23)	117·57 (18·88)
FACT-P total score at week 16	116·31 (19·37)	115·91(20·11)
Change in FACT-P total score	1·41 (13·79)	1·65 (14·68)

Data are n or mean (SD). 466 patients did not complete a patient-reported outcomes assessment. FACT-P=Functional Assessment of Cancer Therapy—Prostate questionnaire.

Table 4: **FACT-P scores by age and treatment group**

The findings of this pooled analysis support the use of androgen receptor inhibitors in older patients with non-metastatic castration-resistant prostate cancer. Incorporating geriatric assessment tools in the care of older adults with prostate cancer might help clinicians to offer individualised treatment to each patient, on the basis of the patient's health status, and the drug's safety and efficacy profile.

Dosage compliance and Food Impact

Treatment option	APA+ADT	ENZA+ADT	DARO+ADT
Study	**SPARTAN[1,2]**	**PROSPER[3]**	**ARAMIS[4]**
Dosing	Apalutamide 240 mg QD + ADT with or without food	Enzalutamide 160 mg QD + ADT with or without food	Darolutamide 600 mg BID (2 x 300 mg tablets BID with food; total 1200 mg/d) + ADT
Oral administration	✓	✓	✓
Food impact	✓	✓	✗
Once daily	✓	✓	✗

Not head-to-head trials

1. Smith MR, et al. N Engl J Med. 2018 Apr 12;378(15):1408-1418 (and Suppl and protocol); 2. Smith MR, et al. Poster presented at AACR 2018 (Abstract 2605); 3.Hussain M, et al. N Engl J Med. 2018 Jun 28;378(26):2465-2474 (and Suppl and Protocol); 4. Fizazi K, et al. N Engl J Med. 2019 Feb 14. (and suppl appendix and protocol)