PROSTATE CANCER NEWS

uno scenario che sta cambiando

Prof. **Bernardo Rocco**

Cronaca sul nmCRPC: Opportunità terapeutiche, identificazione e trattamento

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Who are these patients? Medical definition

1) Biochemical progression despite castrate levels of testosterone

2) Absence of metastasis

3) Asymptomatic

Saad, Lancet 2018

1) Biochemical progression despite castration levels of testosterone

M0 CRPC : Biochemical progression <u>while on ADT</u> + Castration = Serum testosterone levels below 50 ng/dL

Definition of <u>biochemical progression:</u>

Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

Adapted from: Scher HI et al. J Clin Oncol. 2016;34(12):1402-1418; Mottet, N, et al. (2017). EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. Available from: http://uroweb.org/guideline/prostate-cancer/ (Access Date: August 2017); Hong JH, Kim IY. Korean J Urol. 2014 Mar;55(3):153-60

2) Absence of metastases

M0 CRPC :

Biochemical progression <u>while on ADT</u>

+

Castration = Serum testosterone levels below 50 ng/dL

+

No evidence of metastasis with CT/bone scan

Absence of *<u>distant</u>* metastasis

Adapted from: Scher HI et al. J Clin Oncol. 2016;34(12):1402-1418; Mottet, N, et al. (2017). EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. Available from: http://uroweb.org/guideline/prostate-cancer/ (Access Date: August 2017); Hong JH, Kim IY. Korean J Urol. 2014 Mar;55(3):153-60

3) Asymptomatic

Stage of the Disease

M0 - CRPC

Year 1

QoL

Sintomi

I sintomi sono lievi e principalmente funzionali (disuria ecc)

QoL

QoL simile alla popolazione generale Non ci sono limitazioni alle attività quotidiane[2]

Who is the castration resistant but non metastatic patient?

- **Median bone metastasis-free survival without treatment**: ranges 25–30 months
- **nmCRPC remaining bone metastases free at 2 years:** 70% of men
  (Smith MR, JCO 2005; Crawford ED, Urology 2014)
- **Diagnosis of nmCRPC:** Imaging modalities recommended by EAU Guidelines for initial assessment include 99mTc bone scan and abdomen/pelvis/chest CT

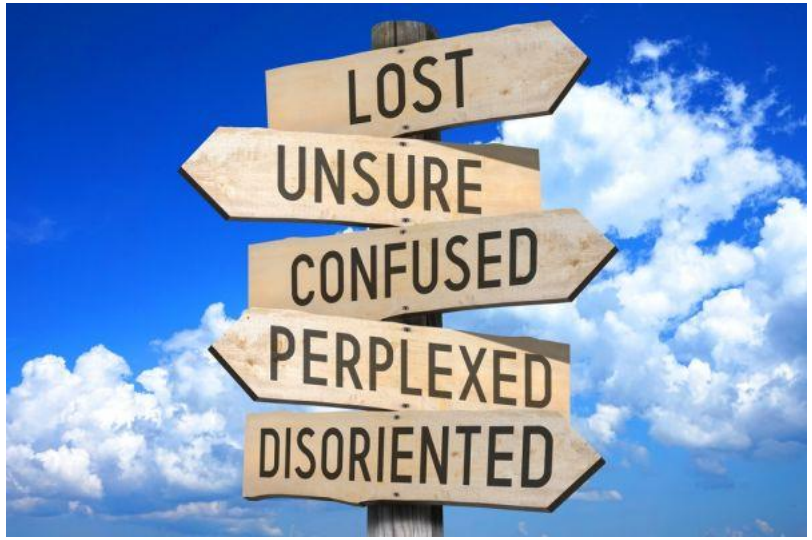
Who are these patients? Patient's perspective

- Area of unmet medical need
- Historically understudied setting of PC patients
- Disease progression is a constant concern for patients with non-M CRPC

  (anxiety about mortality, loss of wellbeing)

Saad et al, Lancet 2018

WHAT SHOULD WE DO WITH THESE PATIENTS Mo-CRPC?



Are all these M0CRPC patients equal?

Medical definition:

- Rising PSA despite castrate levels of testosterone
- Absence of metastasis
- Asyntomatic

NO

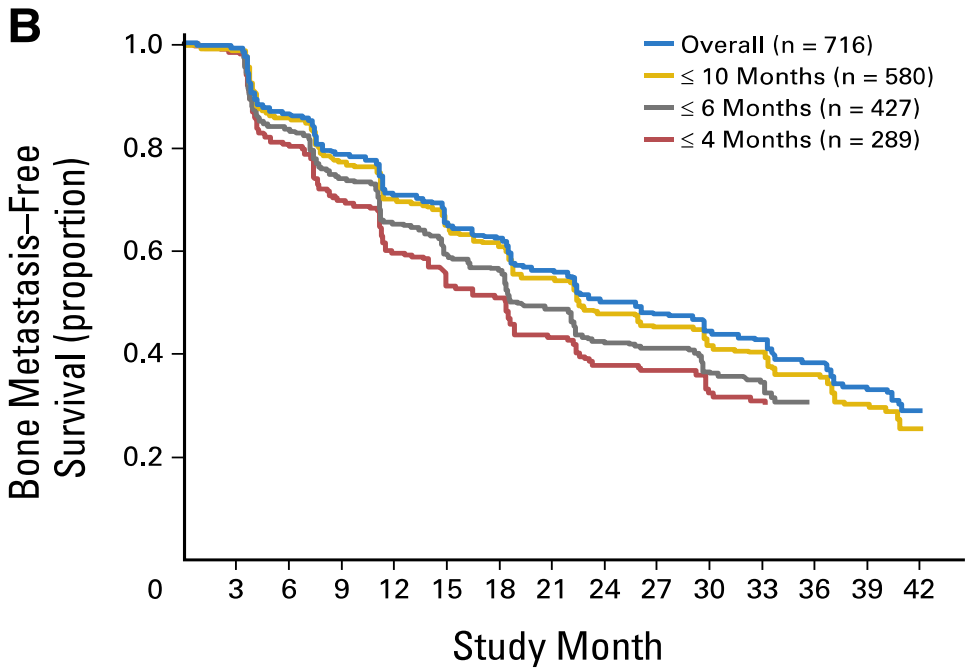
Heterogeneous group

- PSA doubling time

PSA Doubling Time

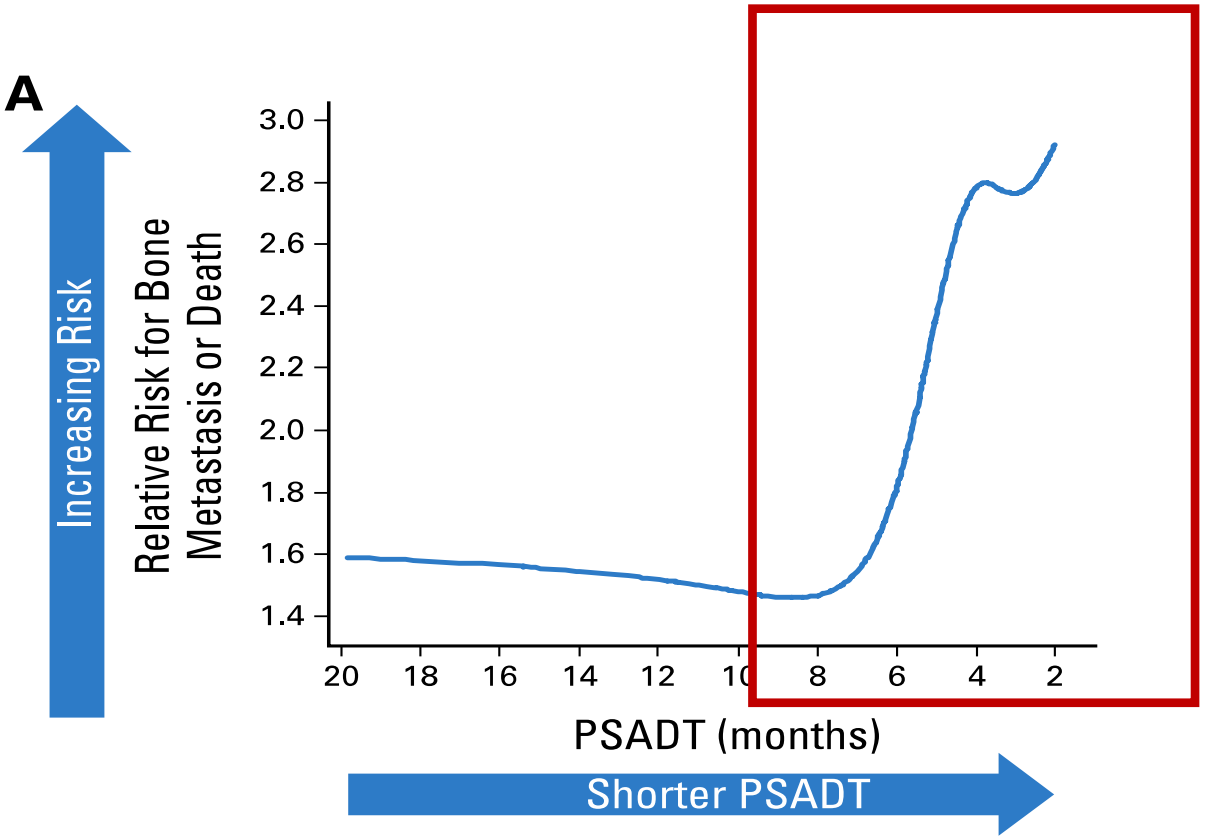
Analysis of the placebo arm (from Denosumab trial) correlated PSA-DT with outcomes, identifying a higher relative risk of bone mets* or death for PSA DT < 8 months

(*Conventional diagnostic imaging)



Smith et al, Clin Oncol 2013

PSA Doubling Time



Relative risk for bone MFS over PSADT

High Risk M0 CRPC

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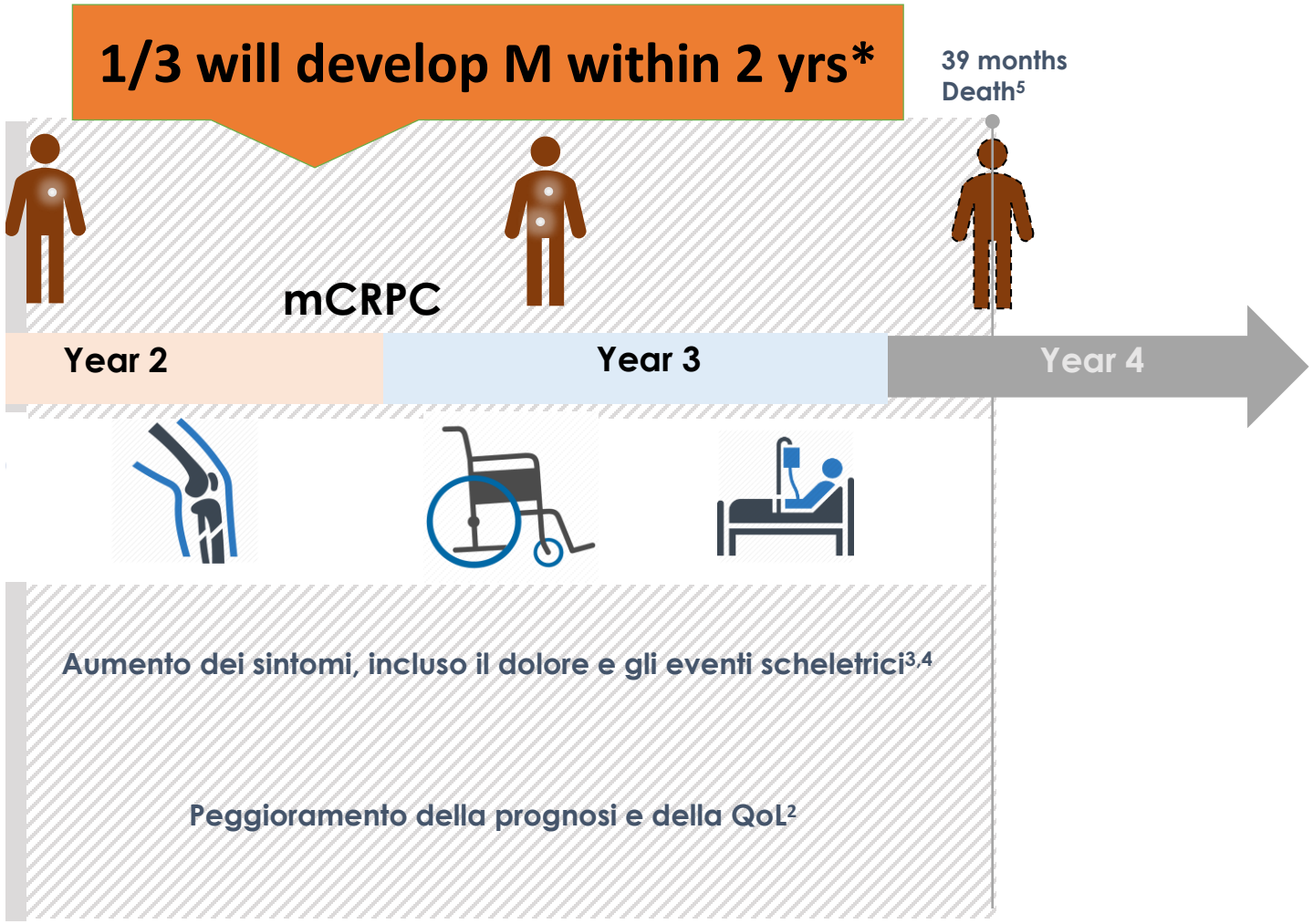
Progression to symptomatic



*Smith et al, JJ Clin Oncol 2005

Medical Need of M0CR PC

- Up to now, patients have been treated with ADT until developmentof mets and afterwards treated as M-CRPC [2-5]
- ADT manipulation has been so long the gold standard therapy for M0 CRPC[4-5]
- Up to now, **no treatment had advantage in OS[1]**

Need: novel agents to delay metastatic status

1. Luo J, et al. Oncology (Williston Park). 2016 Apr;30(4):336-44; 2. Mottet, N, et al. (2017). EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. Available from: http://uroweb.org/guideline/prostate-cancer/ (Access Date: August 2017); 3. Parker C, et al. Ann Oncol. 2015;26(suppl 5):v69-v77; 4. NCCN Clinical Practice Guidelines in Oncology – Prostate Cancer. Version 2-2017 – Feb 11, 2017; 5. Lowrance WT, et al. J Urol. 2016;195:1444-1452; 6. Zytiga SmPC; 7. XTANDI SmPC; 8. XOFIGO SmPC; 9. Taxotere SmP; 10. Jevtana SmPC

EAU GUIDELINES 2018

Recommendations	Strength rating
Do not treat patients for non-metastatic CRPC outside of a clinical trial.	Strong

Guidelines for non-meta

2019

Recommendation	Strength rating
Offer apalutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT ≤ 10 months) to prolong time to metastases.	Strong

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D.,
Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D.,
Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D.,
Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D.,
Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D.,
Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D.,
Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D.,
for the SPARTAN Investigators*

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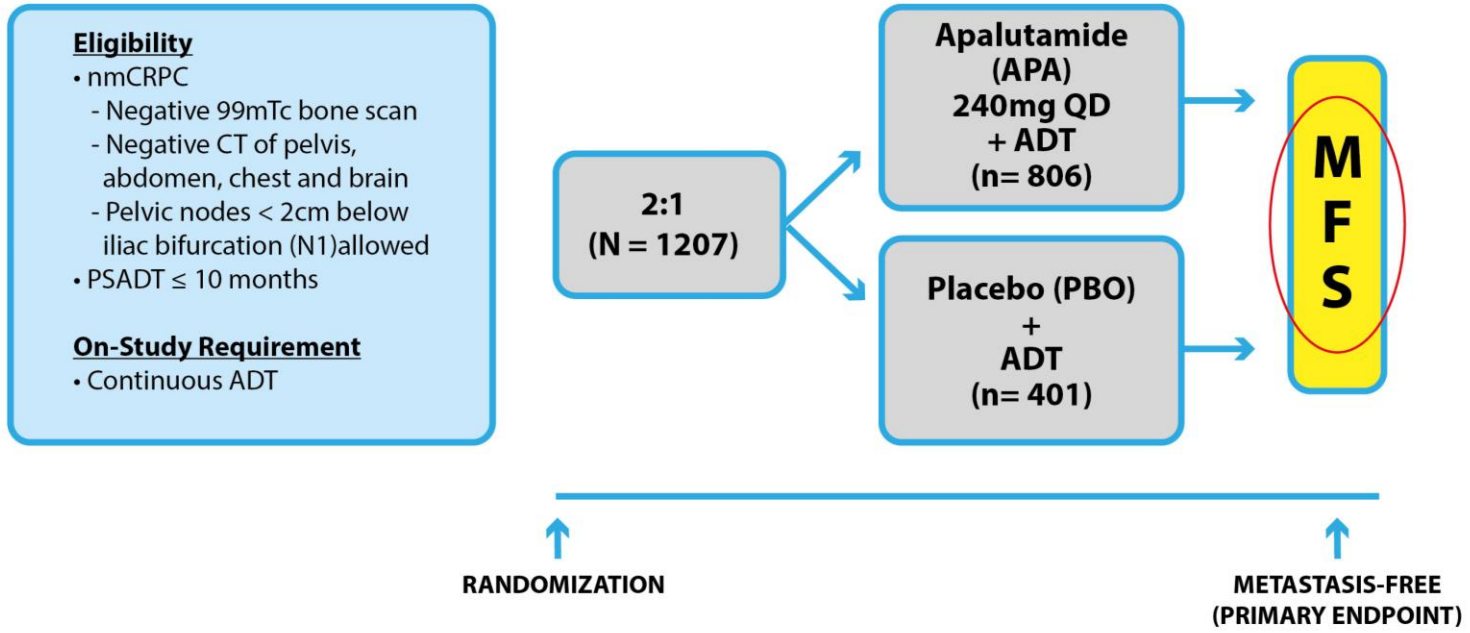
SPARTAN trial design: Apalutamide in non metastatic CRPC (PSA DT<10m)



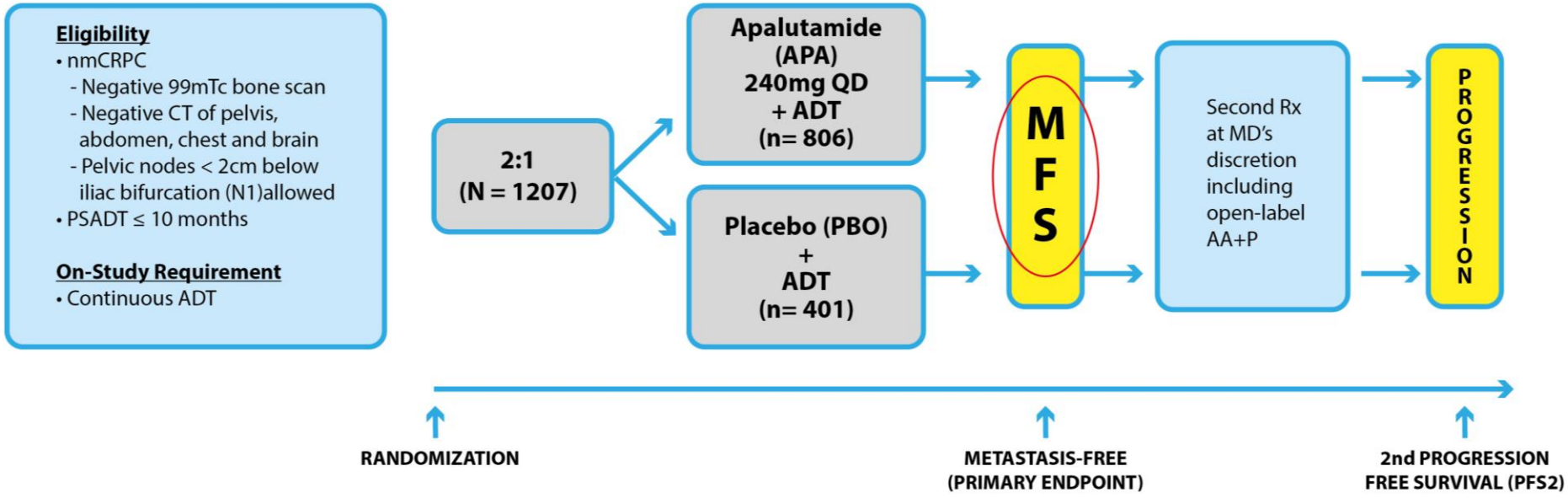
Key eligibility:

- M0CRPC
- PSD DT < 10 mo

Endpoints:

- 1ry: MFS
- 2ry: OS
  - Time to symptom progression
  - PFS2
  - QoL

SPARTAN trial design: Apalutamide in non metastatic CRPC (PSA DT<10m)



Key eligibility:

- M0CRPC
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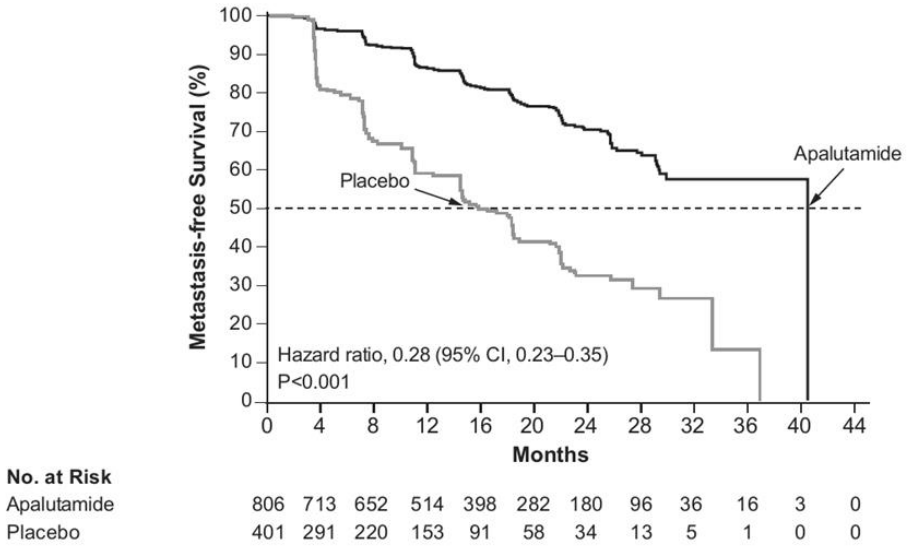
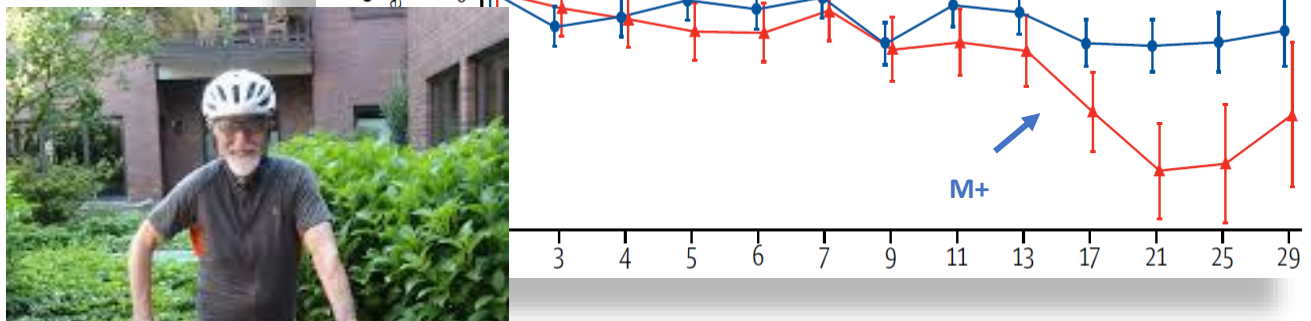
  Time to symptom progression
  PFS2
  QoL

SPARTAN Apalutamide

Primary Endpoint: Metastasis-free Survival



Quality of Life maintained with APA



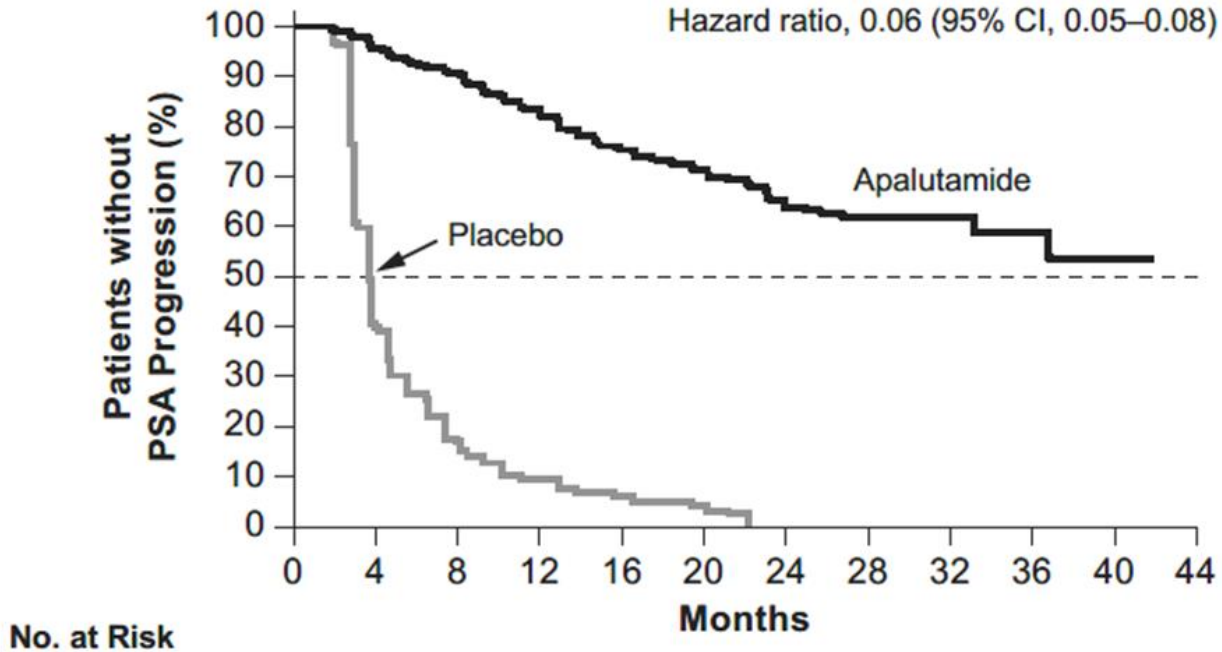
- Metastases delayed > 2 years
- **MFS: risk reduction 72%**

- QoL maintained in apa arm

Smith MR et al. N Engl J Med. 2018
Saad F at al., Lancet Oncology 2018

SPARTAN: 94% PSA progression risk reduction

Time to PSA Progression



Smith MR et al. N Engl J Med. 2018

SPARTAN Summary of Adverse Events

Adverse Event	APA + ADT (n = 803)	PBO + ADT (n = 398)
	no of patients (%)	
Any adverse event	775 (96.5)	371 (93.2)
Grade 3 or 4 adverse event	362 (45.1)	136 (34.2)
Any serious adverse event	199 (24.8)	92 (23.1)
Any adverse event leading to treatment discontinuation	85 (10.6)	28 (7.0)
Adverse event leading to death	10 (1.2)	1 (0.3)

Smith MR et al. N Engl J Med. 2018

Is the clinical advantage gained with new hormonal agents maintained with 2nd line treatment or is resistance expected?

A concern:
Could new hormonal agents in an early setting account for mechanisms of further resistance?

	Baseline		EOT[a]	
	APA	PBO	APA	PBO
ARV7	3/60 (5%)	5/66 (8%)	9/96 (9%)	13/104 (13%)
AR mutations (actionable LBD mutations)	2/66 (3%)	2/67 (3%)	10/118 (8%)	8/122 (7%)
AR amplification	4/66 (6%)	2/67 (3%)	18/118 (15%)	18/122 (15%)
Total AR anomalies	8/50 (16%)	8/60 (13%)	19/93 (20%)	30/100 (30%)

[a]EOT is at first MFS event or discontinuation of treatment.

AR anomalies at APA progression did not increase over baseline (20 vs 16%)

80% of patients at end of APA treatment did not show AR abnormalities

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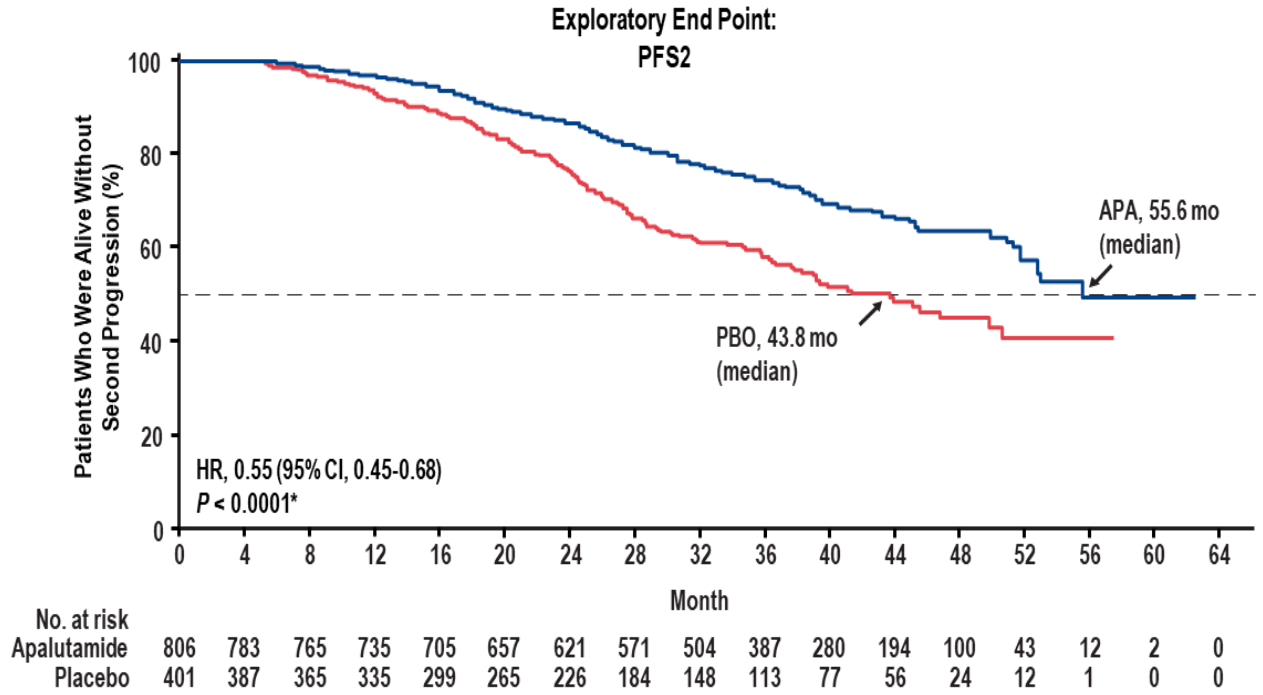
Patients in APA arm maintain the clinical advantage at the second line

45% lower risk of progression at apa + 2nd line

(PSA, radiographic, symptomatic, or any combination)



- 69% of placebo-treated patients and 40% of apalutamide-treated patients received subsequent life-prolonging therapy
- The most commonly received subsequent therapy was AAP

Small et al., ESMO 2019

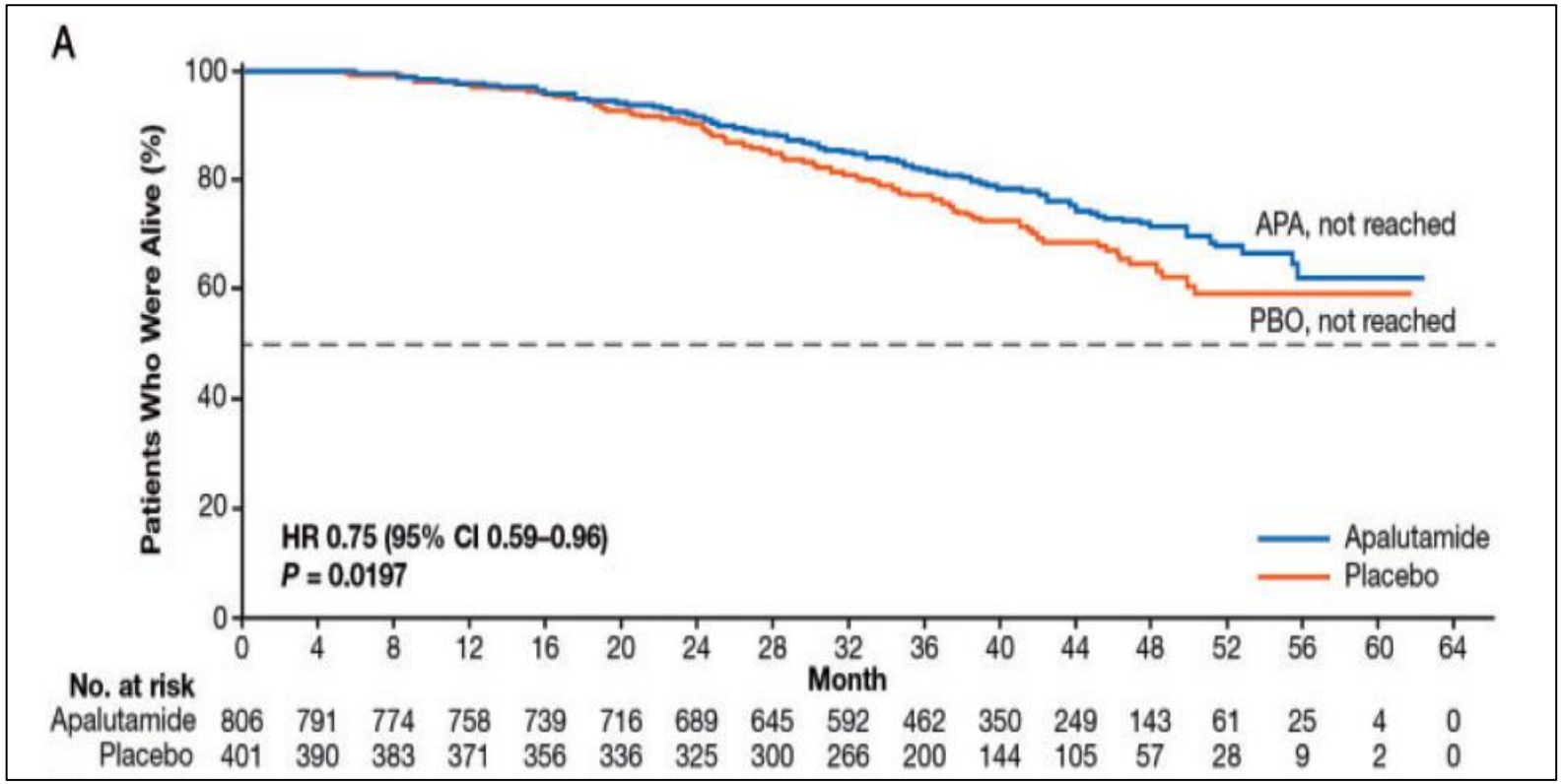
Survival outcomes ➔ Median OS not (yet) reached


ESMO

ORIGINAL ARTICLE

Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer

APA was associated with a 25% reduction in risk of death at 41 mo (HR 0.75)



Small et al., ESMO 2019

Conclusions

- M0 CRPC patients: *emerged* area of previously unmet need
- High-risk (PSA DT <10m) M0 CRPC: higher risk of early metastatic progression
- Novel hormonal agents able to delay metastasis and improve major oncological endpoints
- Final survival analysis will be available once all requisite events have occurred (*but promising novel interim analysis*)