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Treatment of non-metastatic CRPC (MoCRPC)

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Memorial Sloan Kettering Cancer Center

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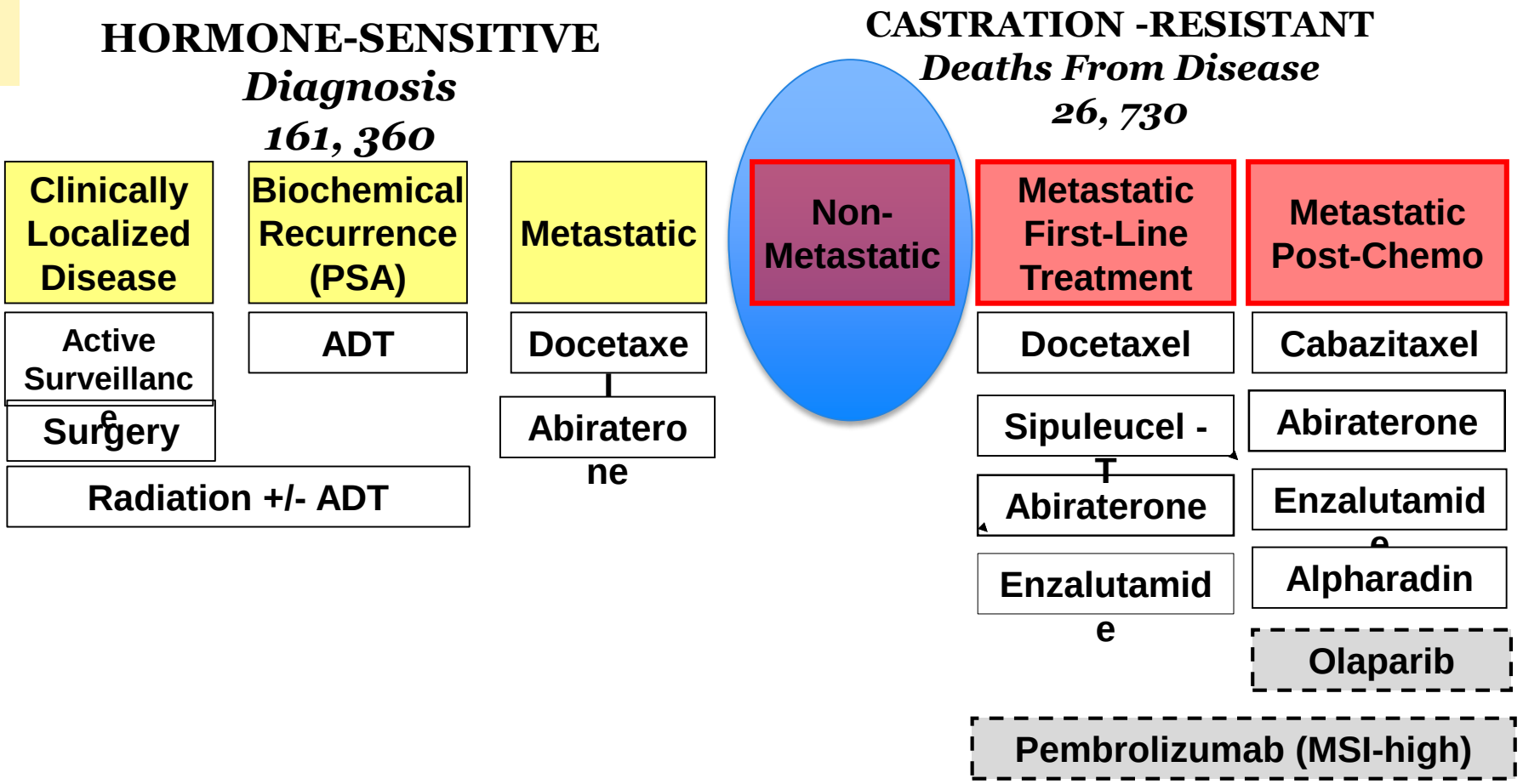
Prostate Cancer Clinical States



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What is the impetus to treat patients with Mo CRPC?

- Patient perspective
  - Fear of the rising PSA and not doing anything about it
- Clinician perspective
  - "I know they have metastases anyway"
  - "Treating early might delay symptoms and might delay use of chemotherapy"
  - "Treatment earlier might prolong survival (in mHSPC setting CHAARTED, STAMPEDE, LATITUDE)"
- But…..treating asymptomatic patients carries a certain burden of proof wherein benefit must clearly outweigh risk

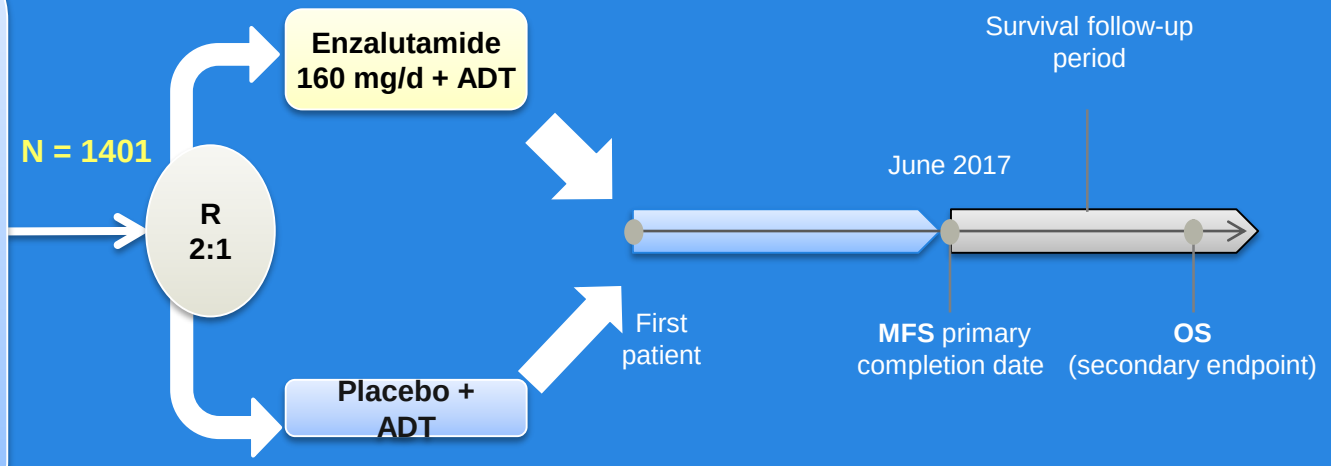
PROSPER Study Design

Key Eligibility Criteria

- M0 CRPC (central review)
- Rising PSA despite castrate testosterone (≤ 50 ng/dL)
- Baseline PSA ≥ 2 ng/mL
- PSA doubling time ≤ 10 mo

Stratification factors

- PSA doubling time (< 6 months vs 6-10 mo)
- Baseline use of bone-targeted agent (yes vs no)



Primary endpoint

- MFS

Secondary endpoints

- Time to PSA Progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life
- Safety

Statistical considerations

- MFS defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation
  - Target of 440 events provides 90% power to detect a target HR of 0.72
  - Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs. 33 months)

Abbreviations: ADT, androgen deprivation therapy; R, randomization.

Hussain et al GU ASCO 2018

Baseline Patient Characteristics (N=1401)

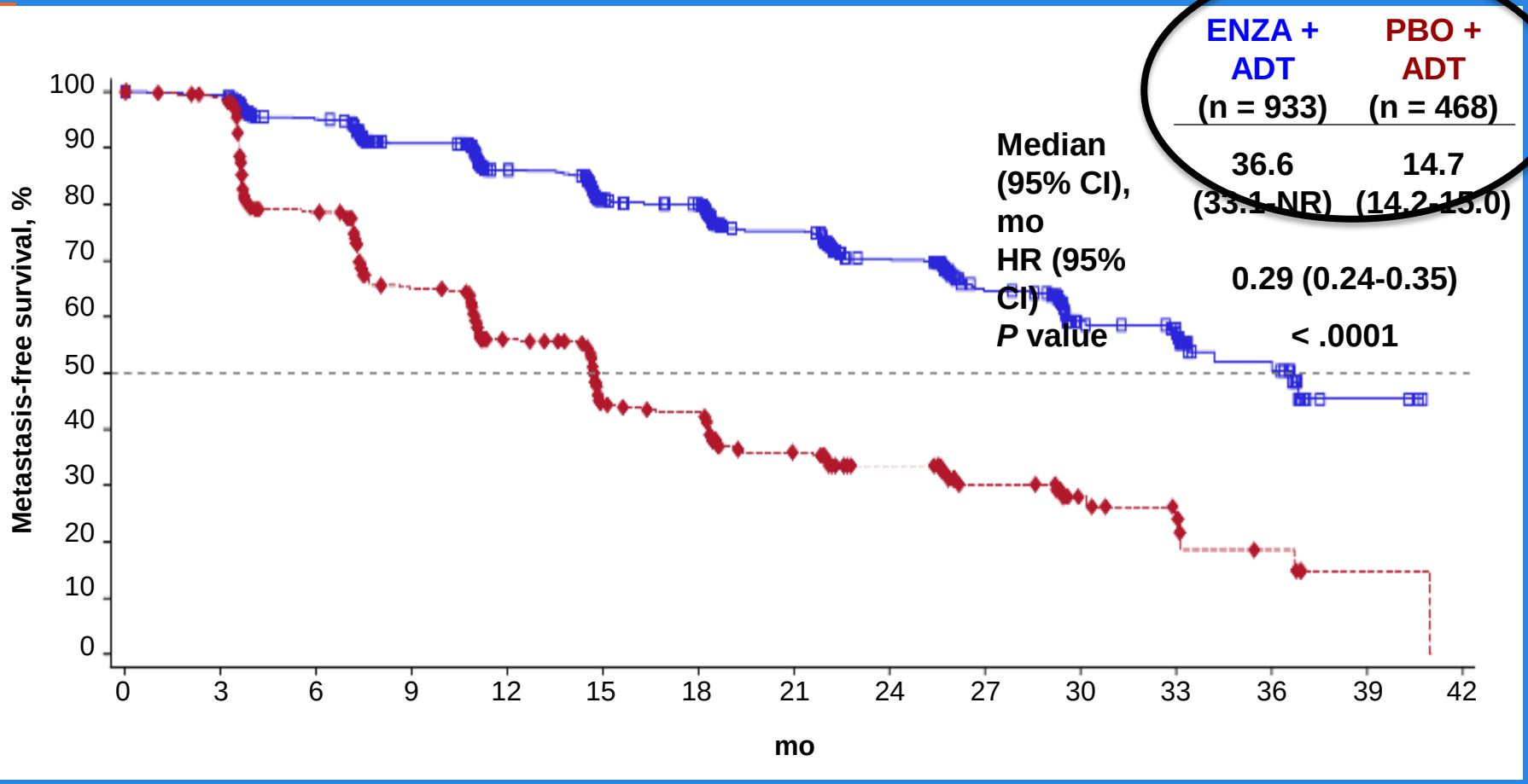
Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age (range), y	74 (50-95)	73 (63-92)
ECOG PS, no. (%) 0 1	 747 (80) 185 (20)	 382 (82) 85 (18)
Median serum PSA (range), ng/mL	11.1 (0.8-1071.1)	10.2 (0.2-467.5)
Median PSA doubling time (range), mo	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time category, no. (%) < 6 mo ≥ 6 mo	 715 (77) 217 (23)	 361 (77) 107 (23)
Baseline use of bone targeting agent, no. (%) No Yes	 828 (89) 105 (11)	 420 (90) 48 (10)
Median duration of therapy (range), mo	18.4 (0.0-41.9)	11.1 (0.0-42.8)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

- Patients enrolled: Europe (n = 654), Asia Pacific (n = 416), North America (n = 203), and South America (n = 128)

Hussain et al GU ASCO 2018

PROSPER-Primary Endpoint: MFS

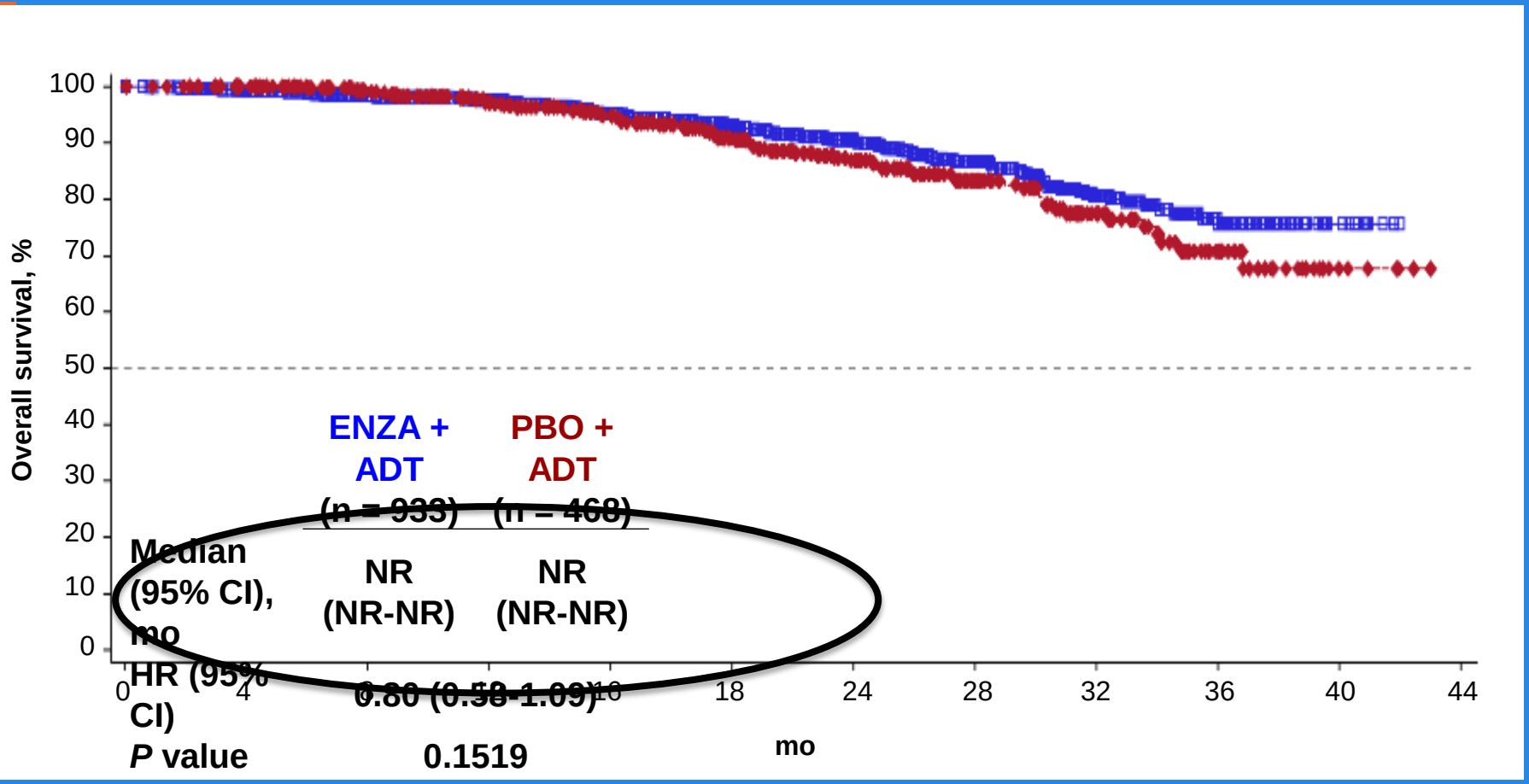


Median time to MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo.

Hussain et al GU ASCO 2018

PROSPER-Overall Survival



There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

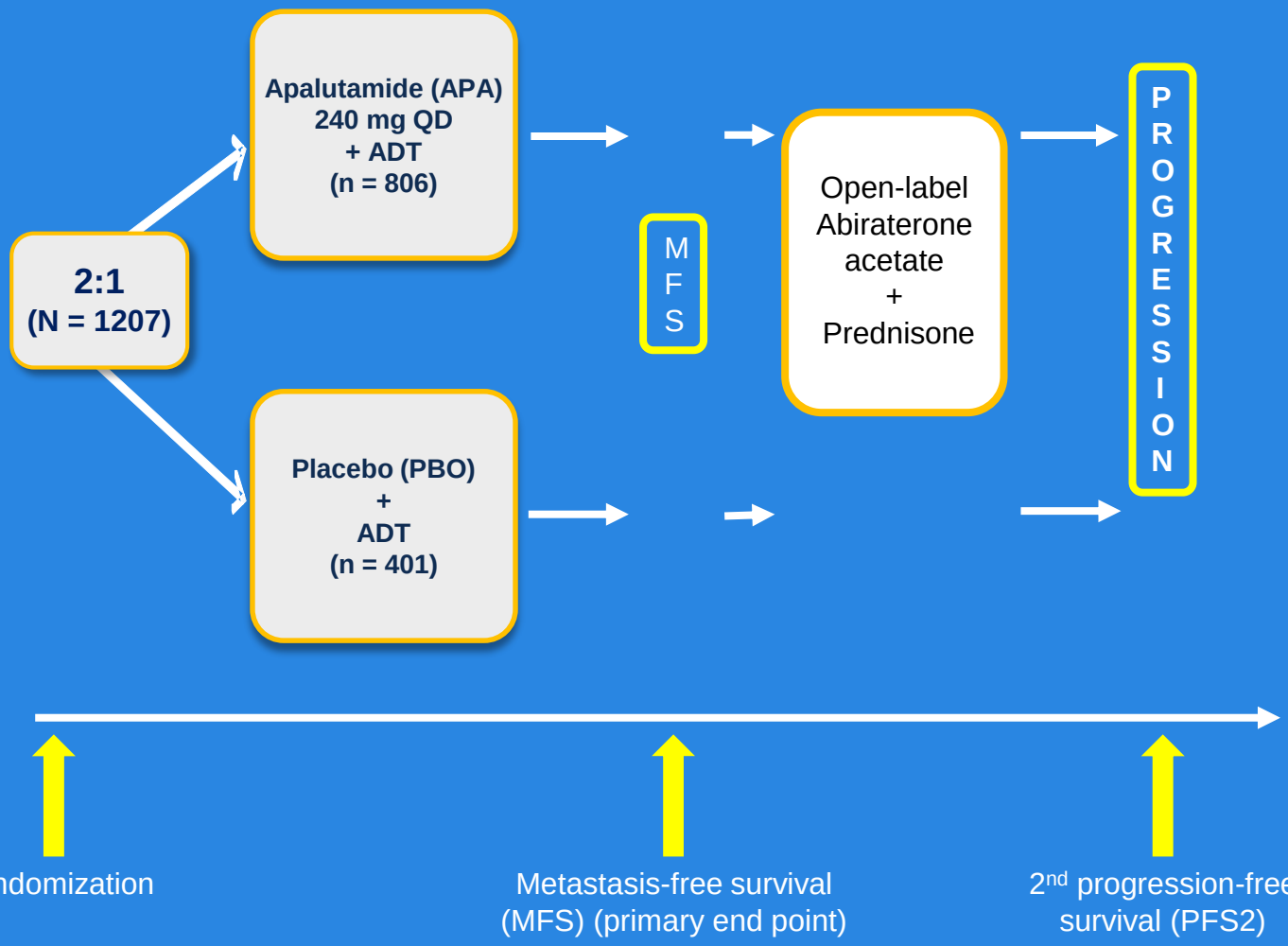
Hussain et al GU ASCO 2018

SPARTAN-Overall Study Design

Eligibility
- nmCRPC
  - Negative ^{99m}Tc bone scan
  - Negative CT of pelvis, abdomen, chest, and brain
  - Pelvic nodes < 2 cm below iliac bifurcation (N1) allowed
- PSADT ≤ 10 months

On-Study Requirement
- Continuous ADT

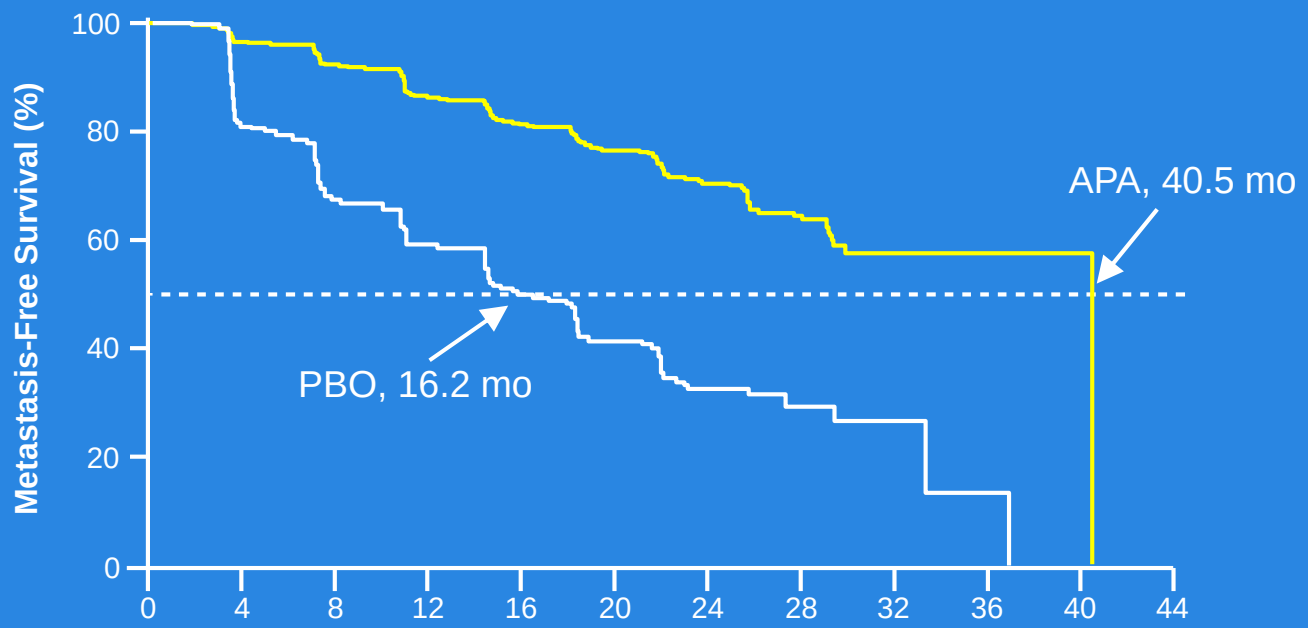
Stratifications
- PSADT > 6 mo or ≤ 6 mo
- Bone-sparing agents, y/n
- N0 or N1



Smith et al NEJM 2018

SPARTAN-Metastasis-free Survival

72% risk reduction of distant progression or death

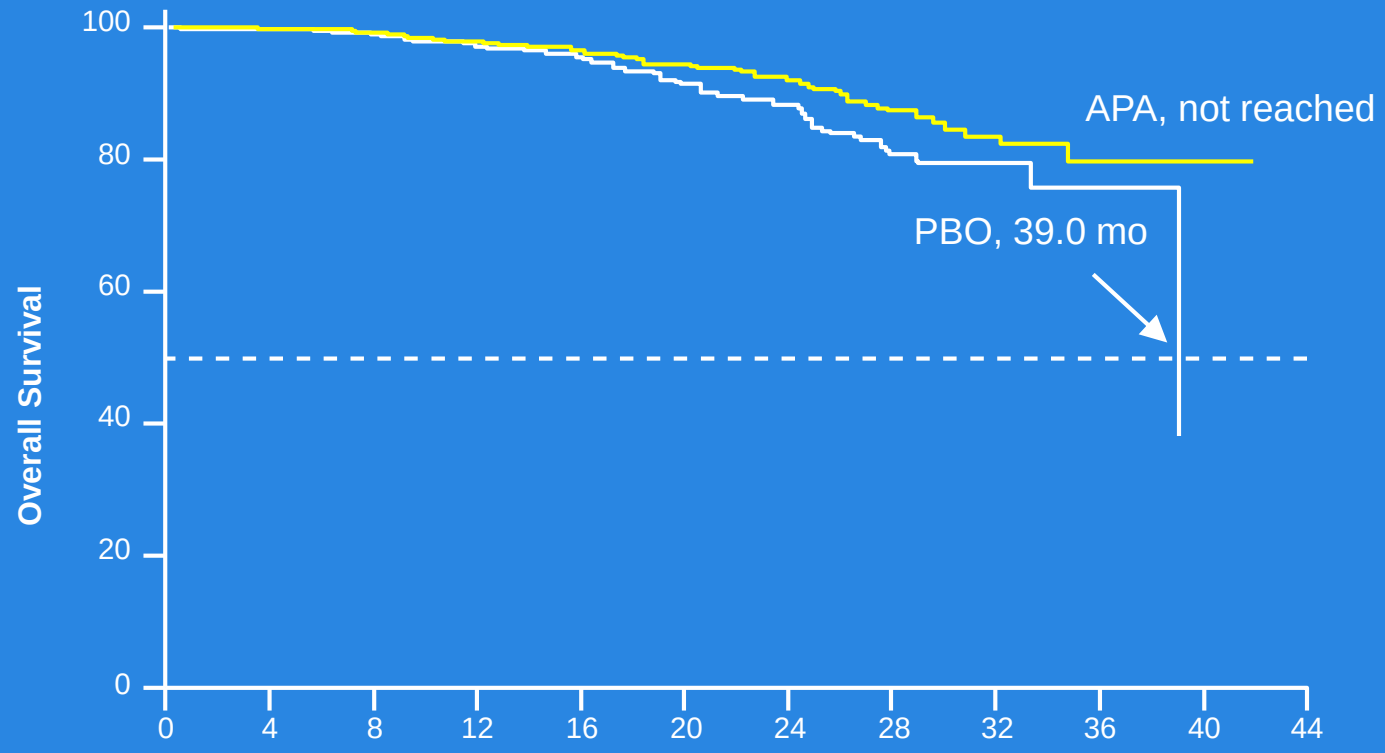


No. at risk												
APA	806	713	652	514	398	282	180	96	36	16	3	0
PBO	401	291	220	153	91	58	34	13	5	1	0	0

HR, 0.28 (95% CI, 0.23-0.35)
P < 0.0001

Smith et al NEJM 2018

SPARTAN-Overall Survival



No. at risk												
APA	806	788	756	647	527	392	275	162	64	26	4	0
PBO	401	387	374	319	248	183	126	64	29	9	0	0

HR, 0.70 (95% CI, 0.47-1.04)
P = 0.07

Smith et al NEJM 2018

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Last FDA encounter with delaying bone metastases- "MFS"

- Oncologic Drugs Advisory Committee (ODAC) voted not to recommend denosumab to prevent bone metastases in high-risk men with CRPC (2/8/2012)
- ODAC Chairman Wyndham Wilson, MD, PhD said "There's an assumption that delaying bone metastases is beneficial. We are looking at a radiographic benefit here; this is a completely artificial endpoint."

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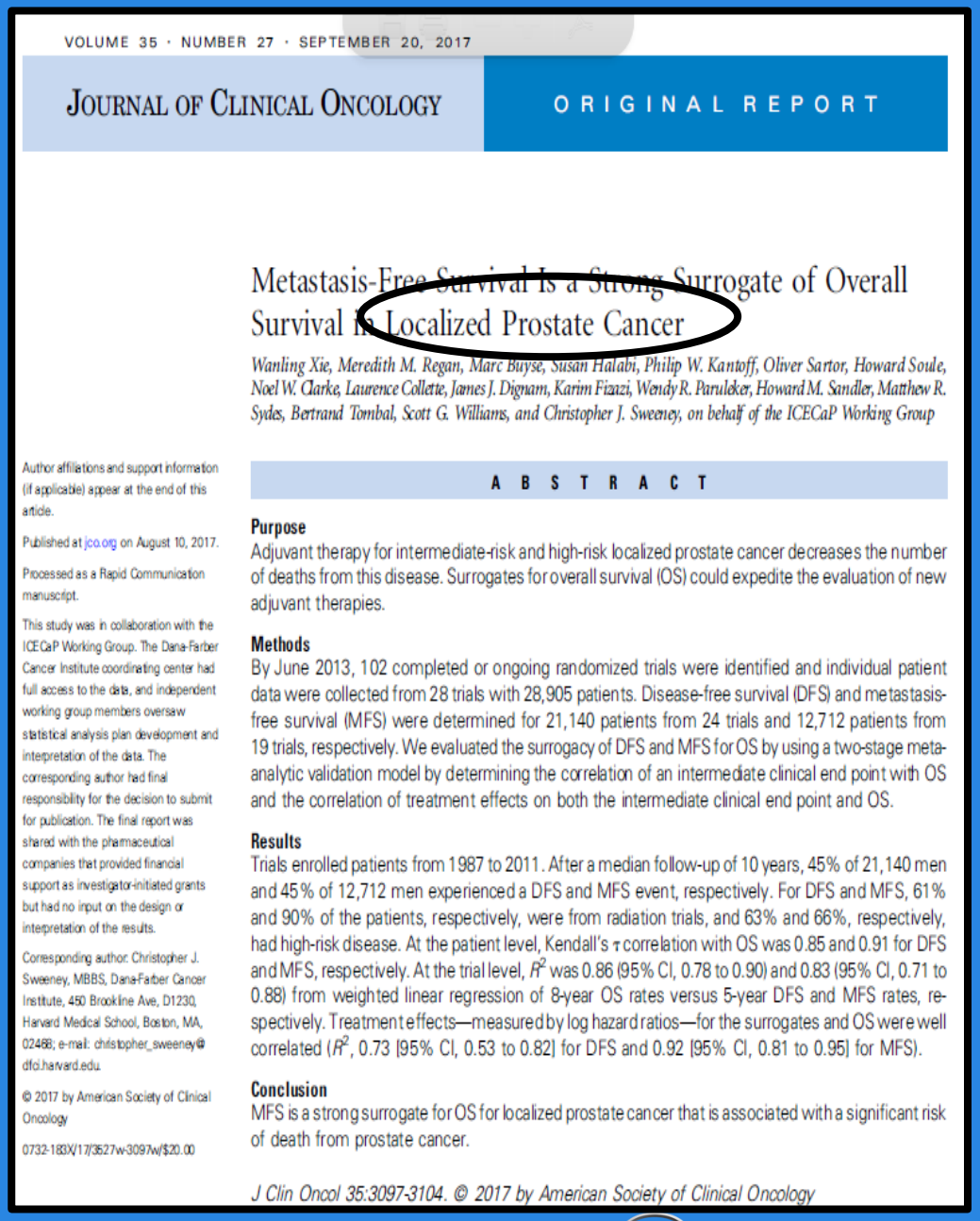
MFS as a trial endpoint-Is MFS a surrogate for OS?

Yes-from ICECaP, MFS is a surrogate for OS for men with localized disease. We don't yet know if it is for men with M0 CRPC



VOLUME 35 · NUMBER 27 · SEPTEMBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Parulekar, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on August 10, 2017.

Processed as a Rapid Communication manuscript.

This study was in collaboration with the ICECaP Working Group. The Dana-Farber Cancer Institute coordinating center had full access to the data, and independent working group members oversaw statistical analysis plan development and interpretation of the data. The corresponding author had final responsibility for the decision to submit for publication. The final report was shared with the pharmaceutical companies that provided financial support as investigator-initiated grants but had no input on the design or interpretation of the results.

Corresponding author: Christopher J. Sweeney, MBBS, Dana-Farber Cancer Institute, 450 Brookline Ave, D1230, Harvard Medical School, Boston, MA, 02468; e-mail: christopher_sweeney@dfci.harvard.edu.

0732-183X/17/3527w-3097w/$20.00

A B S T R A C T

Purpose

Adjuvant therapy for intermediate-risk and high-risk localized prostate cancer decreases the number of deaths from this disease. Surrogates for overall survival (OS) could expedite the evaluation of new adjuvant therapies.

Methods

By June 2013, 102 completed or ongoing randomized trials were identified and individual patient data were collected from 28 trials with 28,905 patients. Disease-free survival (DFS) and metastasis-free survival (MFS) were determined for 21,140 patients from 24 trials and 12,712 patients from 19 trials, respectively. We evaluated the surrogacy of DFS and MFS for OS by using a two-stage meta-analytic validation model by determining the correlation of an intermediate clinical end point with OS and the correlation of treatment effects on both the intermediate clinical end point and OS.

Results

Trials enrolled patients from 1987 to 2011. After a median follow-up of 10 years, 45% of 21,140 men and 45% of 12,712 men experienced a DFS and MFS event, respectively. For DFS and MFS, 61% and 90% of the patients, respectively, were from radiation trials, and 63% and 66%, respectively, had high-risk disease. At the patient level, Kendall's τ correlation with OS was 0.85 and 0.91 for DFS and MFS, respectively. At the trial level, R^2 was 0.86 (95% CI, 0.78 to 0.90) and 0.83 (95% CI, 0.71 to 0.88) from weighted linear regression of 8-year OS rates versus 5-year DFS and MFS rates, respectively. Treatment effects—measured by log hazard ratios—for the surrogates and OS were well correlated (R^2, 0.73 [95% CI, 0.53 to 0.82] for DFS and 0.92 [95% CI, 0.81 to 0.95] for MFS).

Conclusion

MFS is a strong surrogate for OS for localized prostate cancer that is associated with a significant risk of death from prostate cancer.

J Clin Oncol 35:3097-3104. © 2017 by American Society of Clinical Oncology

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But there are some hints of a connection between MFS and OS…

COU-302-rPFS predicts OS

VOLUME 33 · NUMBER 12 · APRIL 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Radiographic Progression-Free Survival As a Response Biomarker in Metastatic Castration-Resistant Prostate Cancer: COU-AA-302 Results

Michael J. Morris, Arturo Molina, Eric J. Small, Johann S. de Bono, Christopher J. Logothetis, Karim Fizazi, Paul de Souza, Philip W. Kantoff, Celestia S. Higano, Jinhui Li, Thian Kheoh, Steven M. Larson, Shannon L. Matheny, Vahid Naini, Tomasz Burzykowski, Thomas W. Griffin, Howard I. Scher, and Charles J. Ryan

Michael J. Morris, Steven M. Larson, and Howard I. Scher, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical

PREVAIL-rPFS predicts OS

Correlation between radiographic progression-free survival (rPFS) and overall survival (OS): Results from PREVAIL.

Presented Thursday, January 7, 2016

Authors:

Michael J. Morris, Tomasz M. Beer, Yohann Loriot, Celestia S. Higano, Andrew J. Armstrong, Cora N. Sternberg, Johann S. De Bono, Bertrand F. Tombal, Teresa Parli, Suman Bhattacharya, Andrew P. Krivoshik, De Phung, Dana E. Rathkopf; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Oregon Health & Science University Knight Cancer Institute, Portland, OR; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Seattle Cancer Care Alliance, University of Washington, Seattle, WA; Duke University Medical Center, Duke Cancer Institute Divisions of Medical Oncology and Urology, Duke University, Durham, NC; San Camillo Forlanini Hospitals, Rome, Italy; The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom; Cliniques Universitaires Saint-Luc, Brussels, Belgium; Medivation, Inc., San Francisco, CA; Medivation Inc, San Francisco, CA; Astellas Pharma Global Development, Inc., Northbrook, IL; Astellas Pharma Global Development, Inc., Leiden, Netherlands

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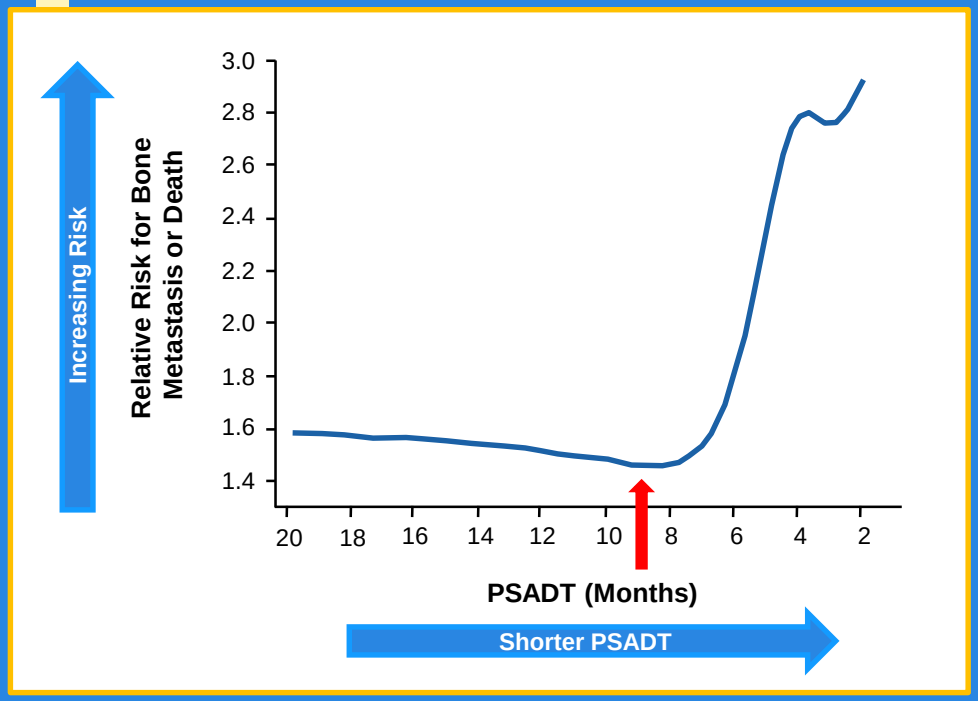
SPARTAN and PROSPER provide the first good estimate of OS in men with Mo CRPC

We know that men who have a more rapid PSADT develop metastases sooner



In SPARTAN (71%) and PROSPER (77%) had PSADT <6 months therefore patients rapidly progressing

PSADT (%)		
≤ 6 mos	71	71
> 6 mos	29	29

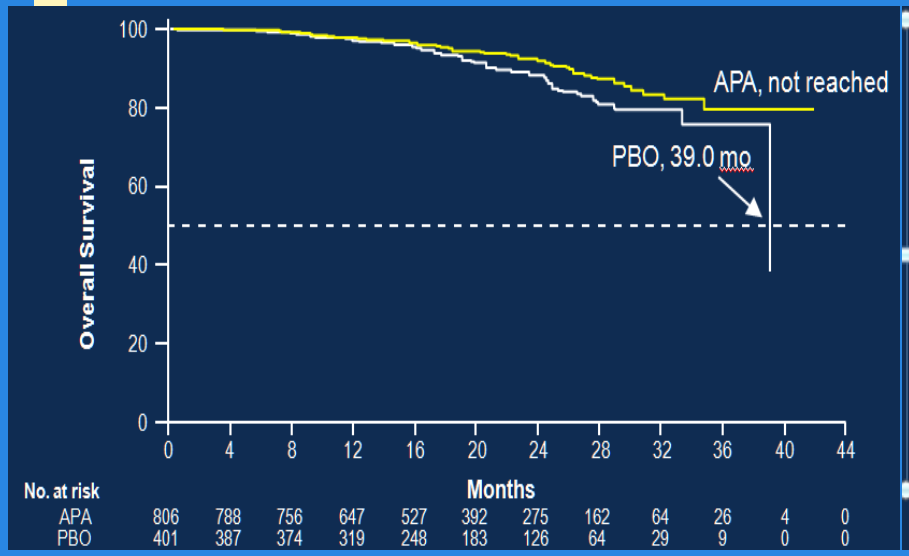
S

PSADT (%)		
< 6 mos	77	77
≥ 6 mos	23	23

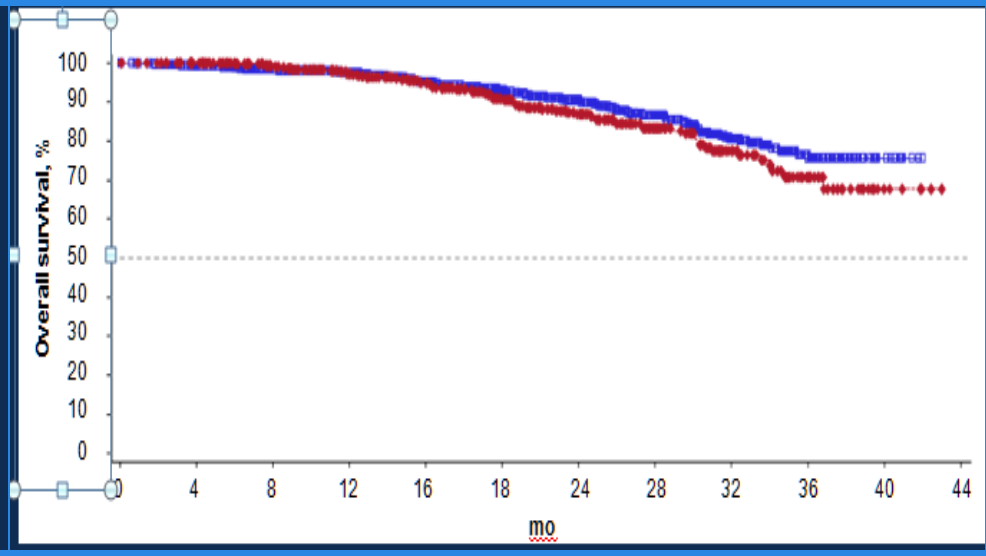
P

Smith et al J. Clin Onc 2013

The anticipated median OS for placebo patients in these trials is 5+ years



SPARTAN
Median PSADT= 4.5 mos



PROSPER
Median PSADT= 3.6 mos

Survival estimates based on SPARTAN and PROSPER for men with M0 CRPC

- Despite median PSADT 3-5 months (rapid progressers), approximate median survival for M0 CRPC is greater than 5 years
- Thus even high risk M0 patients on average live > 2 years longer than mCRPC patients
- Presumably even better for M0 CRPC patients with slower PSADT
- Thus, treatment at this stage will result in longer drug exposure and its consequences
- This is OK if clear clinical benefit is demonstrated

What constitutes clinical benefit?

- Curing men
- Prolonging survival duration
- Improving quality of life
  - Delaying or preventing SREs has been an approvable endpoint

What constitutes clinical benefit?

- Curing men-Probably not in this context

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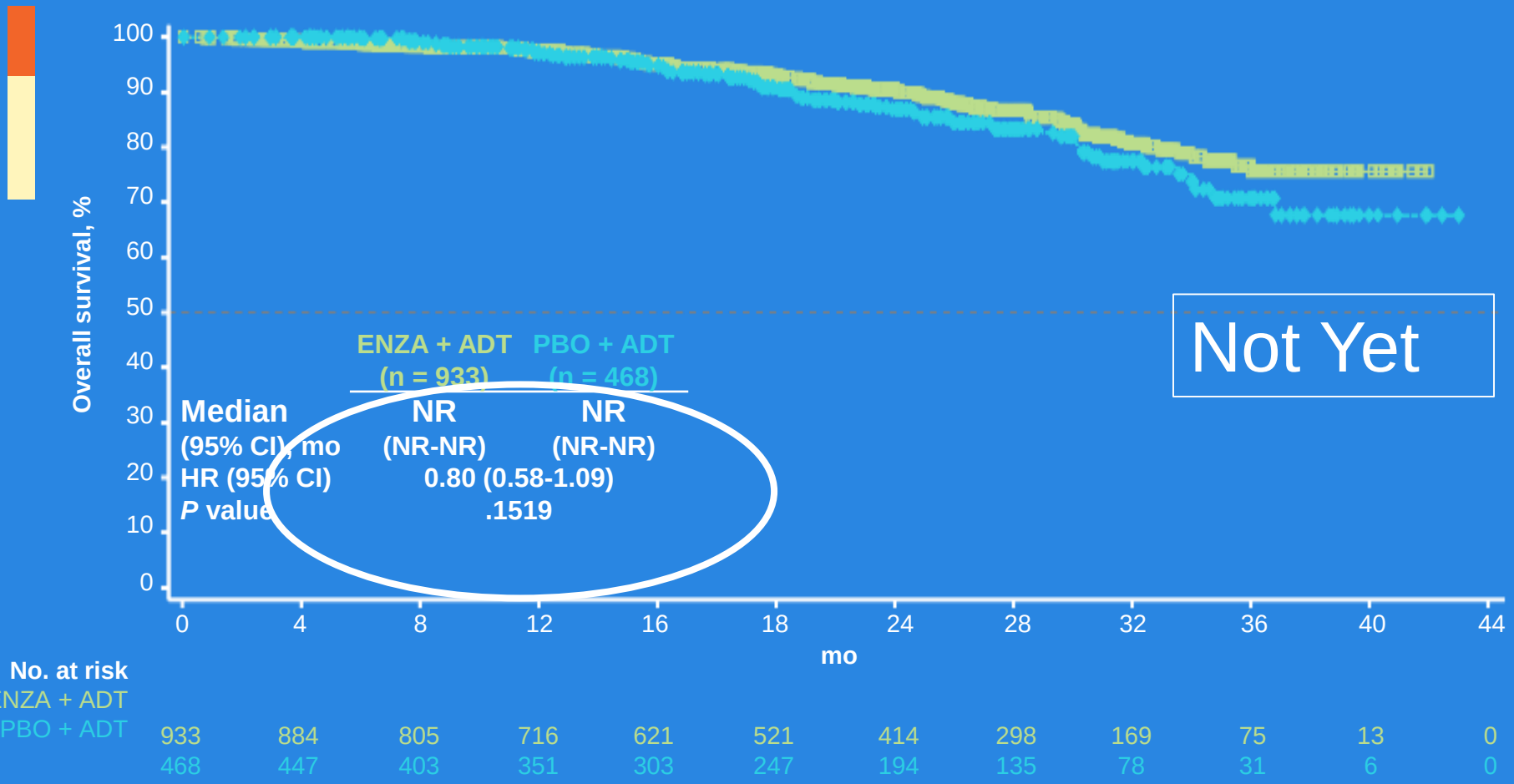
- Curing men-Probably not in this context
- Prolonging survival duration

PROSPER-Overall Survival



Not Yet

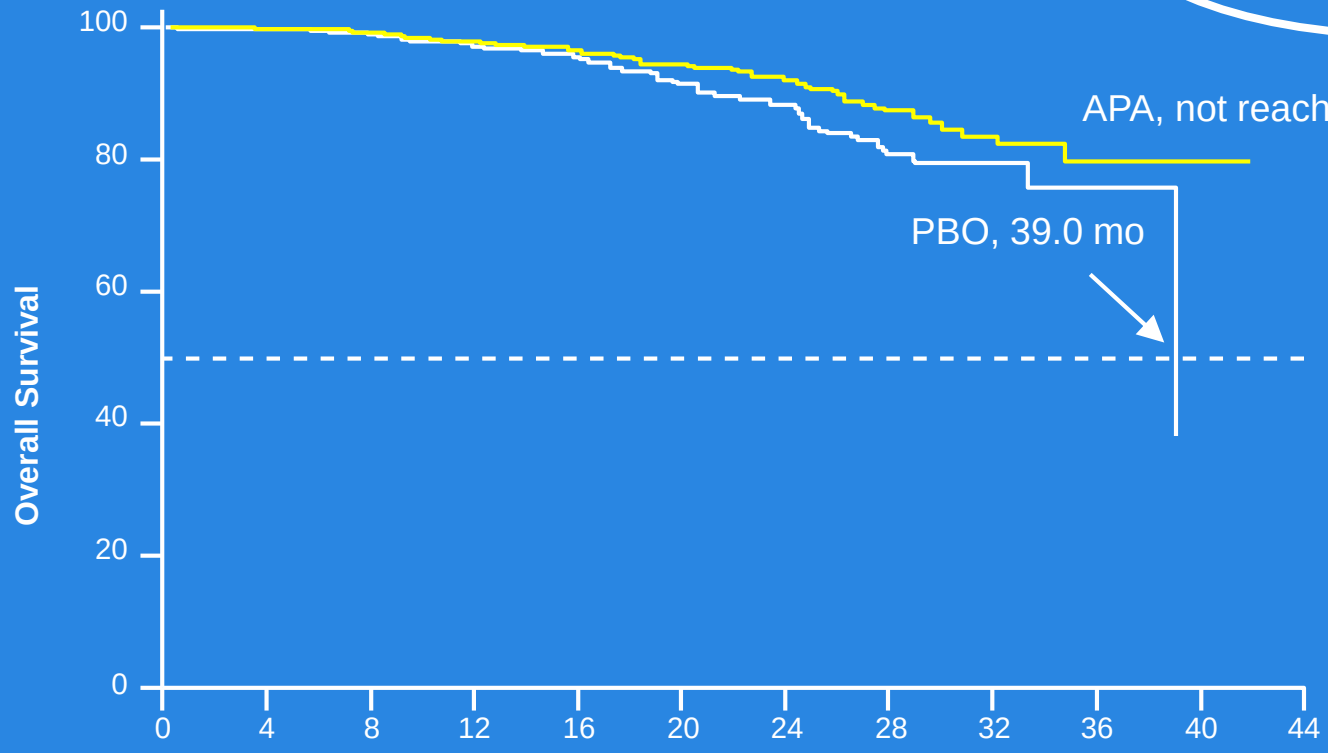
Median follow-up time was ≈ 22 months for each treatment arm

There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

Hussain et al NEJM 2018

SPARTAN-Overall Survival

HR, 0.70 (95% CI, 0.47-1.04)
P = 0.07



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No. at risk												
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Smith et al NEJM 2018

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What constitutes clinical benefit?

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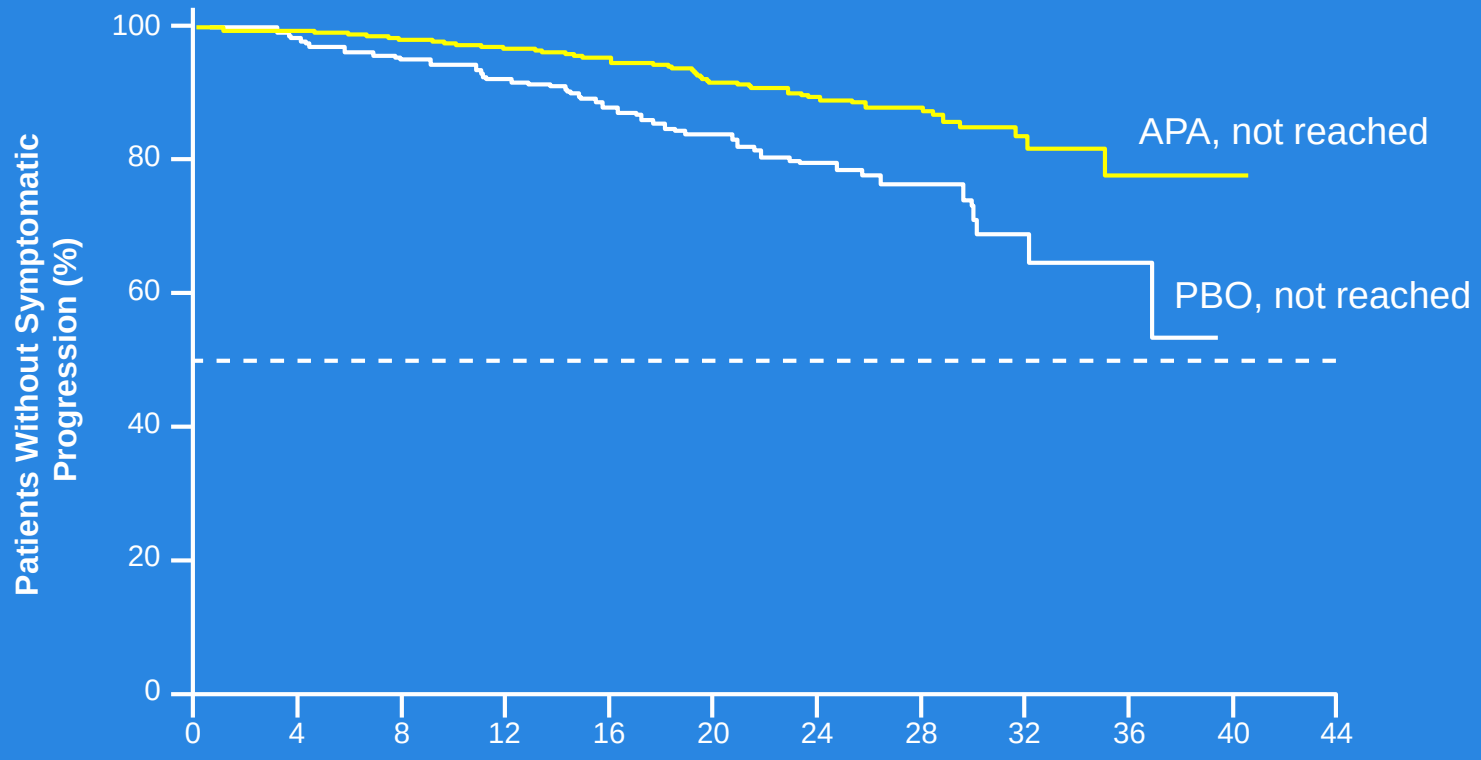
SPARTAN-Time to Symptomatic Progression

55% risk reduction of SRE, pain progression/worsening sx, clinically significant sx



No. at risk												
APA	806	769	732	601	478	344	226	127	49	19	4	0
PBO	401	373	344	270	206	152	96	45	17	7	0	0

HR, 0.45 (95% CI, 0.32-0.63)
P < 0.0001

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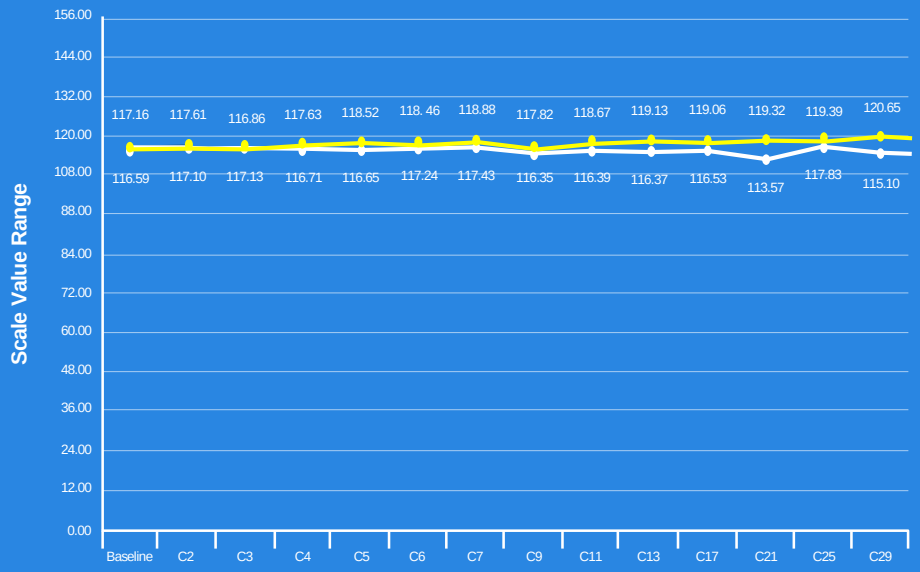
SPARTAN-Time to Symptomatic Progression

Unclear what time interval between development of radiographic metastases and initiation of abiraterone and prednisone.

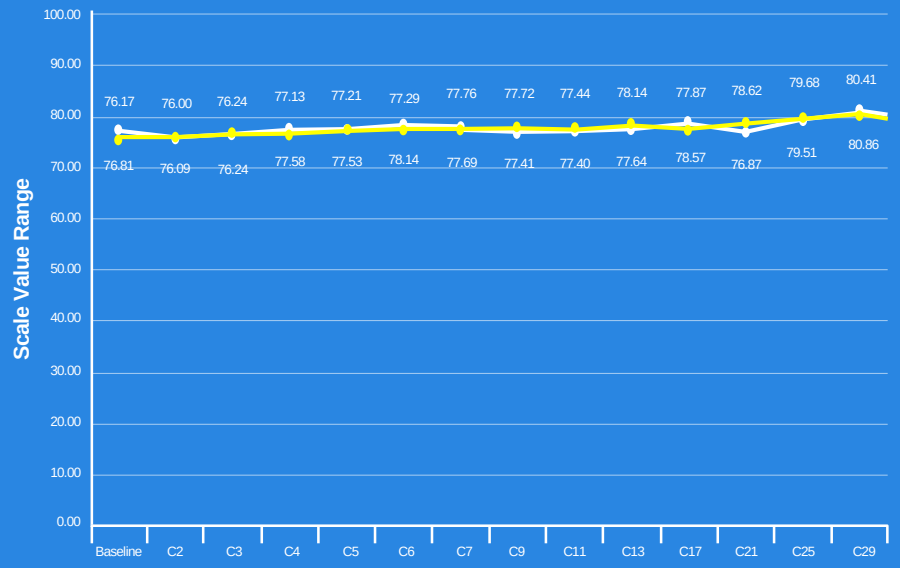
In clinical practice, could some of these patients have been treated before symptoms developed?

SPARTAN-HRQoL did not decline with the addition of APA to ADT

FACT-P



EQ5D



APA =

PBO =

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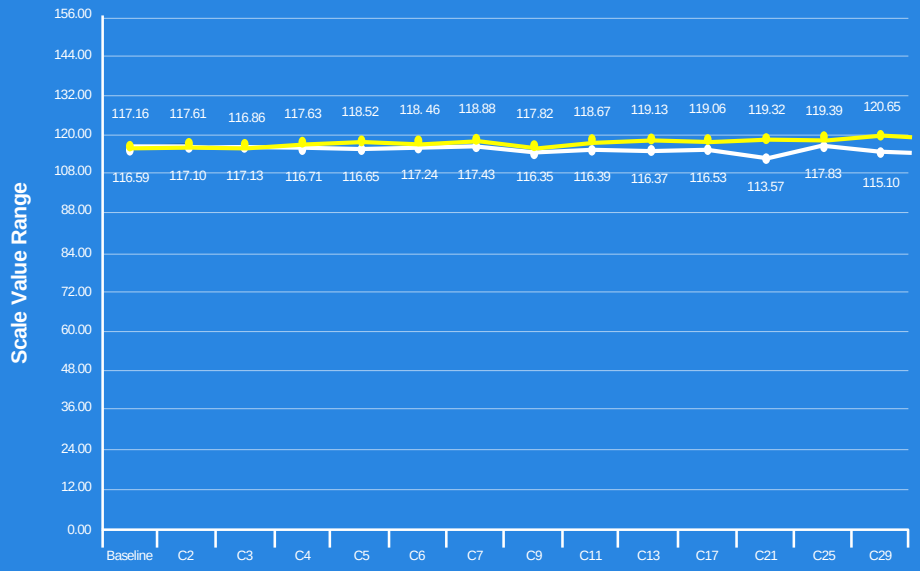
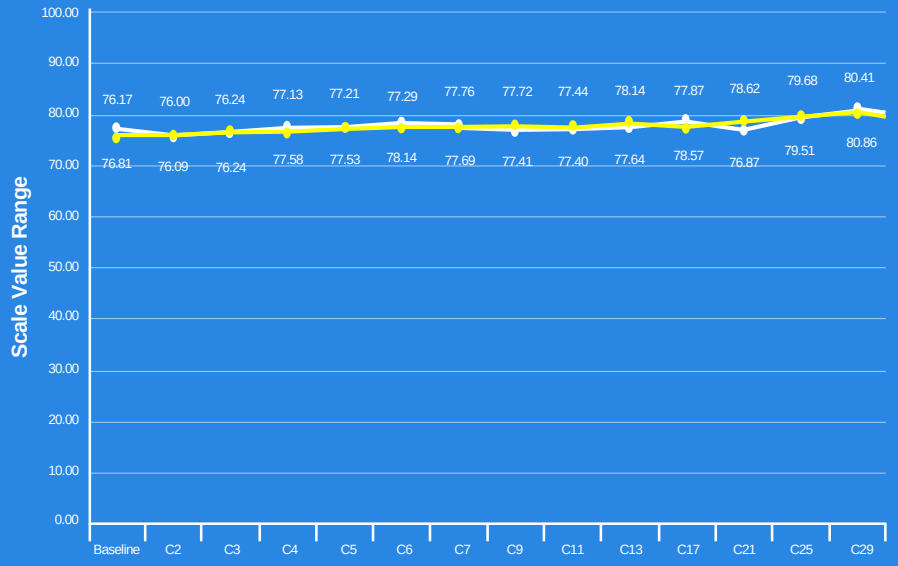
SPARTAN-In an asymptomatic population, these HRQoL instruments appear to be too insensitive to capture the psychological benefit of a decline in PSA or a delay in radiographic or symptom progression?

ACT-P



EQ5D



APA = ——

PBO = ——

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SPARTAN- Adverse Events

	APA (n = 803)		PBO (n = 398)	
	All	Gr 3/4	All	Gr 3/4
Fatigue	30.4%	0.9%	21.1%	0.3%
Rash	23.8%	5.2%	5.5%	0.3%
Weight loss	16.1%	1.1%	6.3%	0.3%
Arthralgia	15.9%	0	7.5%	0
Fall	15.6%	1.7%	9.0%	0.8%
Fracture	11.7%	2.7%	6.5%	0.8%
Hypothyroidism	8.1%	0	2.0%	0
Seizure	0.2%	0	0	0

Smith et al NEJM 2018

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Smith et al NEJM 2018

PROSPER-Progression Event by Type

Event, No. (%)	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
All progression events*	**219 (23%)**	**228 (49%)**
Radiographic progression†	187 (85%)	224 (98%)
New bone metastases	71 (32%)	79 (35%)
New soft-tissue metastases	109 (50%)	132 (58%)
Concurrent new bone and soft-tissue metastases	7 (3%)	13 (6%)
Death without documented radiographic progression within 112 days of study treatment discontinuation†	32 (15%)	4 (2%)

- The proportion of progression events in the enzalutamide arm was 50% less than that of the placebo arm

*Event percentages are based on total number of patients randomized in each arm (enzalutamide + ADT, n = 933; placebo + ADT, n = 468)

†Partition of event percentages are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228).

Hussain et al GU ASCO 2018

Conclusions

- APA and ENZA delay MFS in men with Mo CRPC an impressive 2 years.
- These drugs are very biologically active.
- This potentially gives us 2 new options for men with Mo CRPC.
- Delaying the onset of disease-related symptoms, as seen in SPARTAN, represents clinical benefit.

Conclusions

- BUT-Clinical benefit not yet fully determined.
- Some untoward effects need to be better defined
  - More deaths from other causes-needs to be understood to minimize risk
  - More side effects-falls, fractures etc.-need to better understand who is at high risk to minimize risk
- My confidence in declaring a new SOC for non-metastatic CRPC would be greater with further scrutiny of the toxicities and understanding how care patterns in these studies compare with actual practice.
- The number of M0 patients may diminish considerably with improvement in imaging techniques.

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Thank you