Prostate cancer from PSA elevation to late stage: therapeutic algorithm

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Disclosures

- Dr Mukherji has received travel support/honoraria from MSD, Pfizer, Amgen, Astellas, Jannsen, Roche, Merck Serono and BMS

Outline

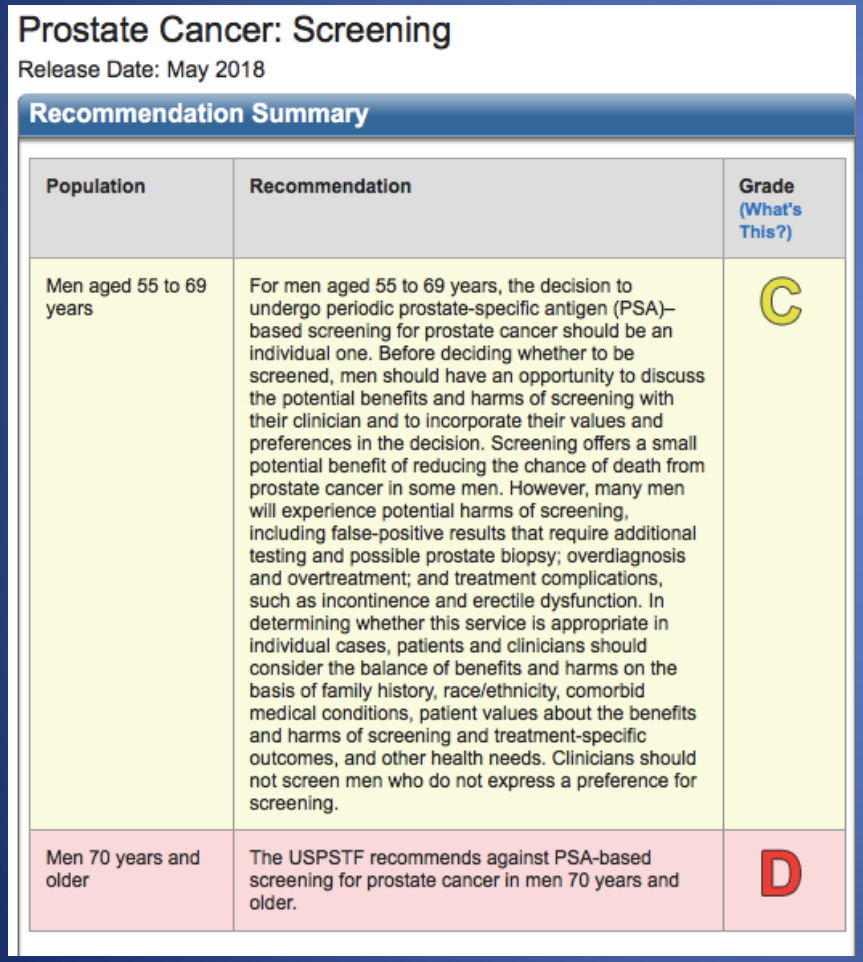
- Update on screening recommendations
- Diagnosis and treatment options for localized disease
- Advanced disease – castration sensitive
- Advanced disease – castration resistant
- Hot topics and future directions

Case 1

- Mr X is a 65 year-old male with controlled hypertension coming to see his cardiologist for an annual check-up
- He has no family history of prostate cancer, he asks about PSA screening
- What should we advise him?

Prostate cancer screening

Prostate Cancer Screening: USPTF 2018



Prostate Cancer: Screening

Release Date: May 2018

Recommendation Summary

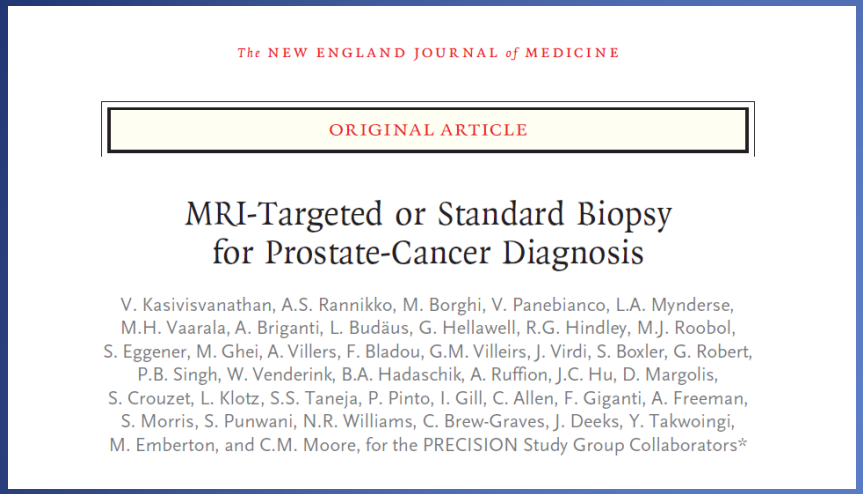
Population	Recommendation	Grade (What's This?)
Men aged 55 to 69 years	For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.	C
Men 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.	D

- Age 55-69
- Individual decision on PSA screening
- No screening ≥70

Case continued

- Mr X has a PSA test with his annual lab tests – it is 6.5
- Looking back in his file – his PSA 2 years ago was 2.5
- He has no symptoms and no abnormalities on DRE

MRI +/- targeted biopsy superior to standard biopsy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

- Avoids biopsy in low-risk
- Increased diagnosis of clinically-significant cancer
- Decrease in diagnosis of clinically insignificant cancer

March 2018

Case continued

- Mr X has a PSA test with his annual lab tests – it is 6.5
- Looking back in his file – his PSA 2 years ago was 2.5
- He has no symptoms and no abnormalities on DRE
- MRI shows suspicious PIRADS 4 lesion, targeted biopsy shows Gleason 3+3 = 6 (Gleason grade group 1) adenocarcinoma in 2/7 cores 10%

New Gleason Grade Groups

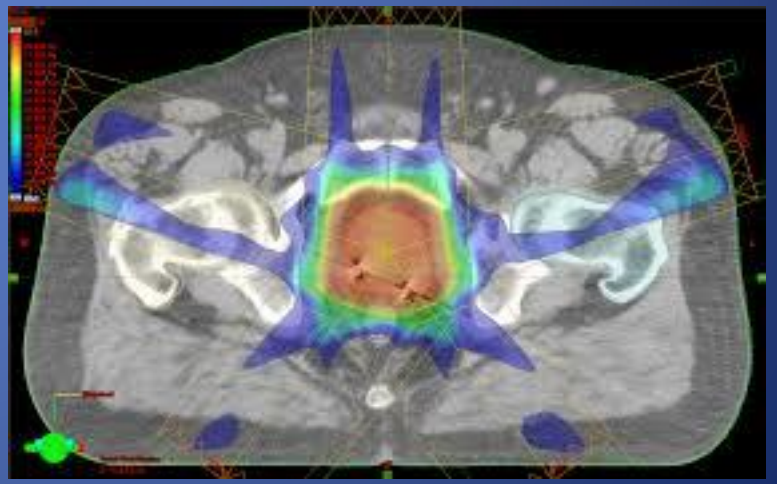
Table 1: Risk of PSA Relapse 5 Years Following Radical Prostatectomy, Based on Various Biopsy Gleason Scores.

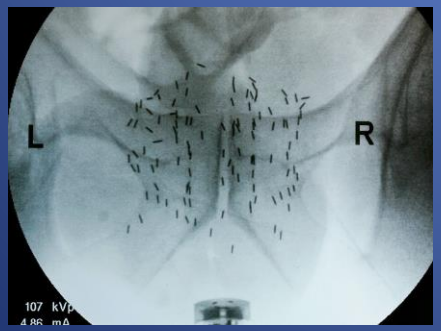
Group 1	Gleason Score 6	5%
Group 2	Gleason Score 3+4=7	17%
Group 3	Gleason Score 4+3=7	35%
Group 4	Gleason Score 4+4=8	37%
Group 5	Gleason Score 9-10	76%

Epstein et al European Urology 2016

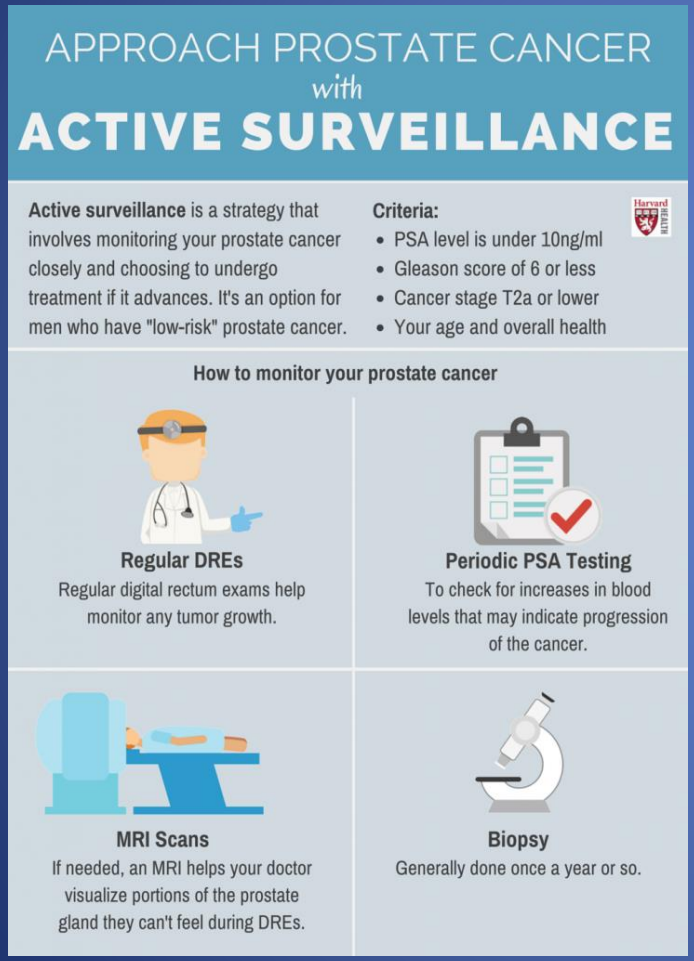
Treatment options for localized disease

- Active Surveillance
- Radical prostatectomy
- Radical radiation therapy
- Brachytherapy
- Watchful waiting (unfit for curative therapy)



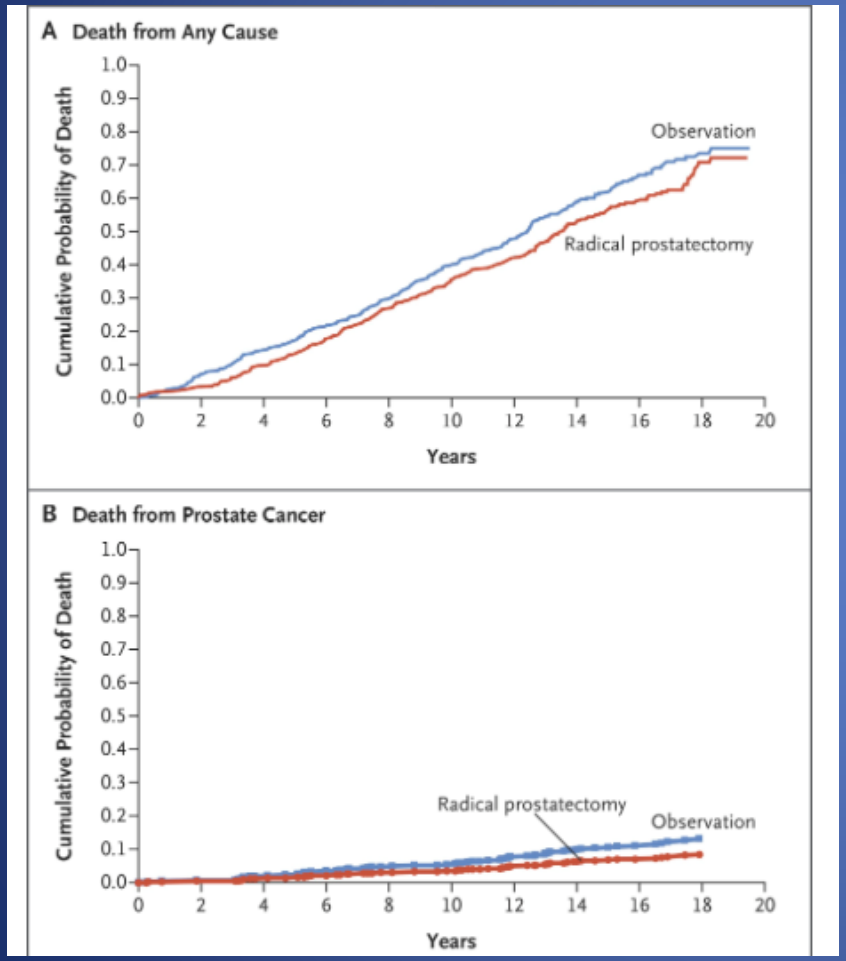


Active Surveillance



- Low risk disease
- Avoids over-treatment
- Requires motivated and non-anxious patient!

PIVOT study: 19 years follow-up



- Patients randomized to surveillance vs prostatectomy
- No significant difference in prostate cancer mortality

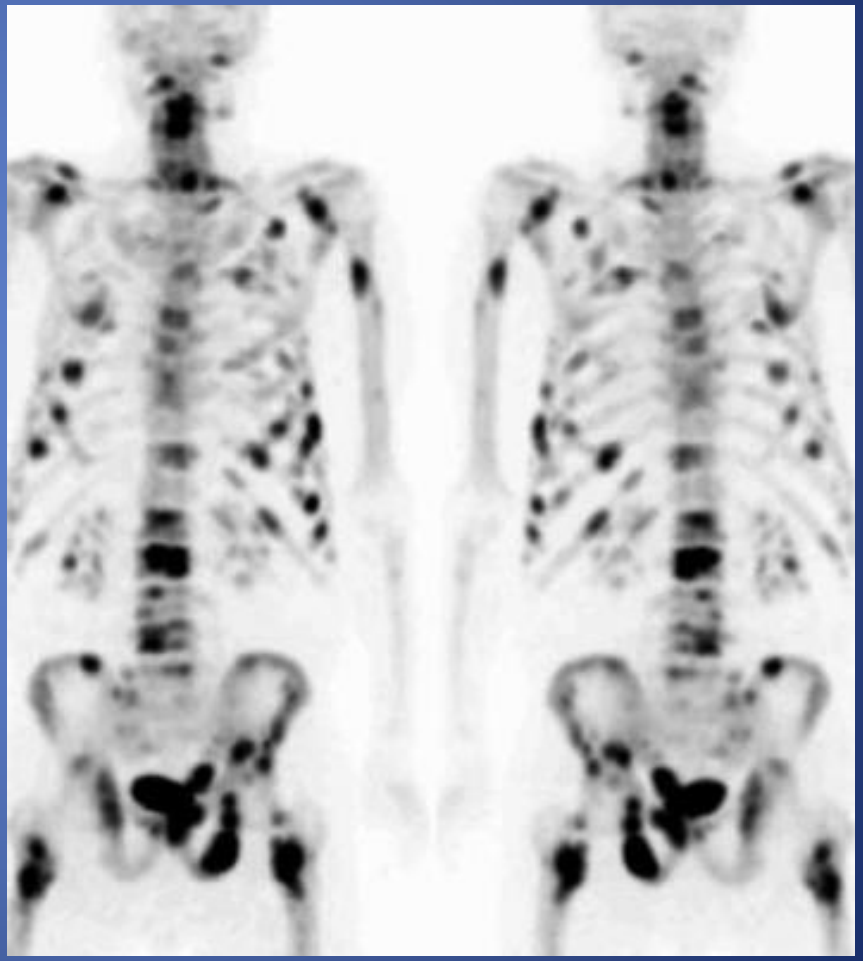
Wilt et al NEJM 2017

Outline

- Update on screening recommendations
- Diagnosis and treatment options for localized disease
- Advanced disease – castration sensitive
- Advanced disease – castration resistant
- Hot topics and future directions

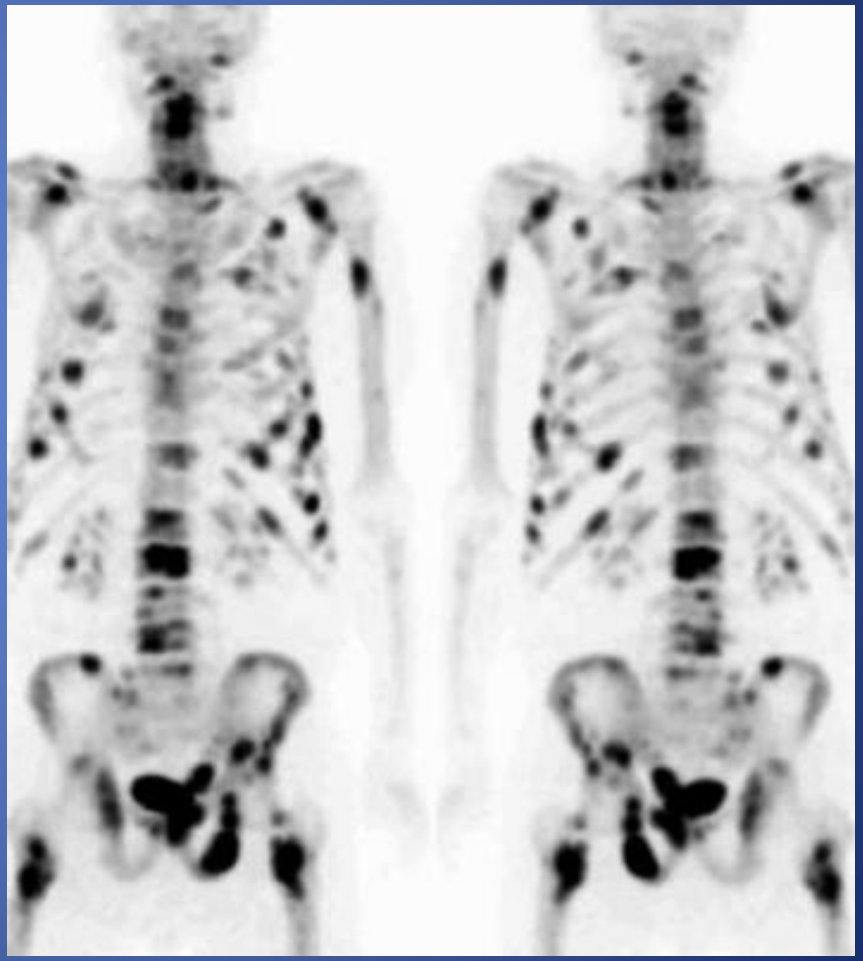
Case 2

- Mr Y is a 65 year-old presenting with back pain
- PSA is 100
- Imaging shows multiple bone metastasis



Case 2

- Options for treatment?
- Life expectancy?



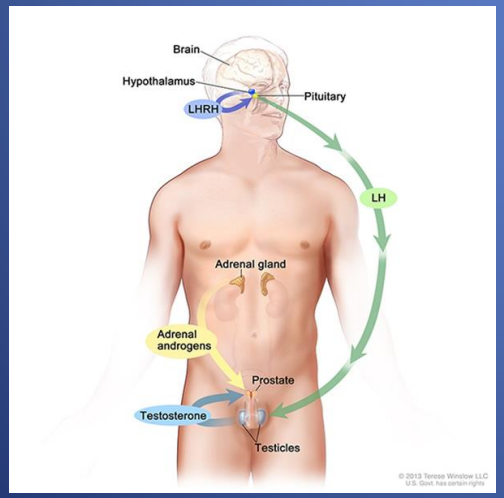
Treatment of hormone-sensitive metastatic disease

Androgen deprivation therapy

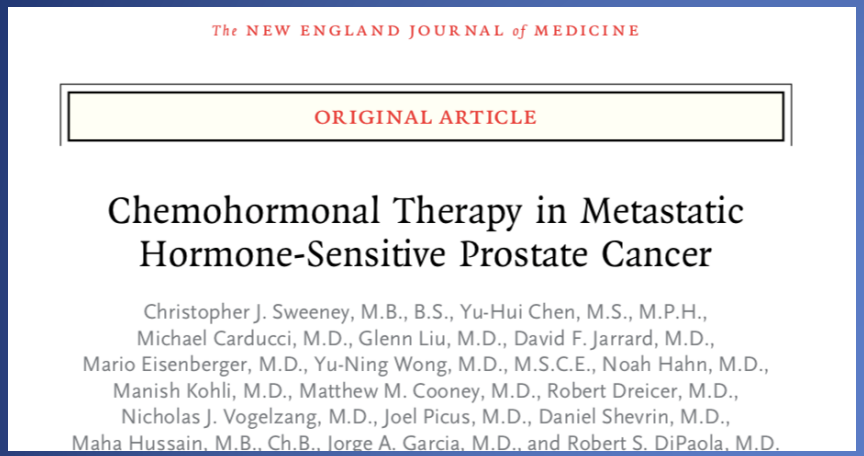
- Surgical orchiectomy
- Anti-androgen followed by LHRH-agonist
- LHRH antagonist

Additional systemic therapy

- Docetaxel chemotherapy (6 cycles)
- Abiraterone plus prednisone (until progression)



Improved survival with addition of systemic therapy to ADT



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ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

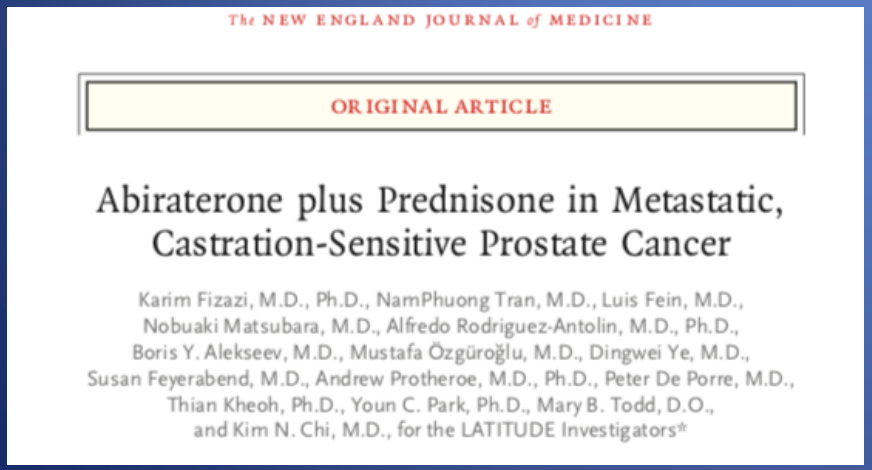
Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators*

Summary

Background Long-term hormone therapy has been the standard of care for advanced prostate cancer since the 1940s. STAMPEDE is a randomised controlled trial using a multiarm, multistage platform design. It recruits men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy. We report primary survival results for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone.

Lancet 2016; 387: 1163–77

Published Online December 21, 2015



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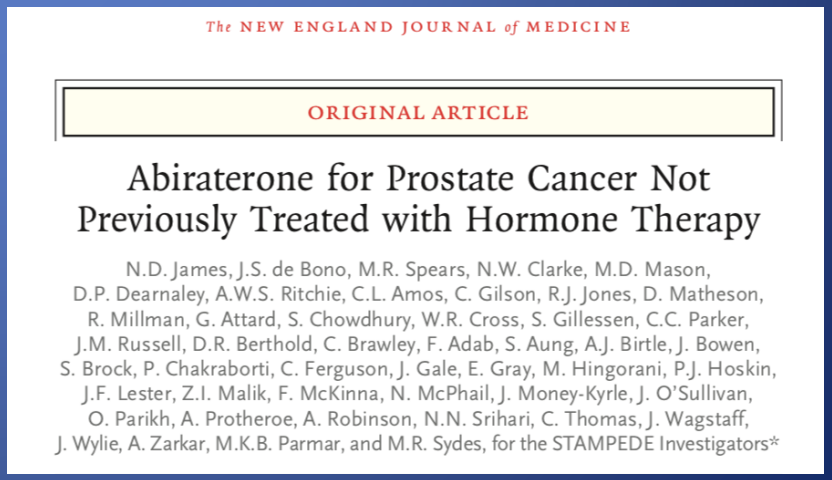

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Sweeney NEJM 2015, James lancet 2016, Fizazi NEJM 2017, James NEJM 2017

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mOS 57.6 vs 44m

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mOS 71 vs 81m

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See Comment page 1135

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mOS 35m vs NR

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3yearOS 76% vs 83%

Sweeney NEJM 2015, James lancet 2016, Fizazi NEJM 2017, James NEJM 2017

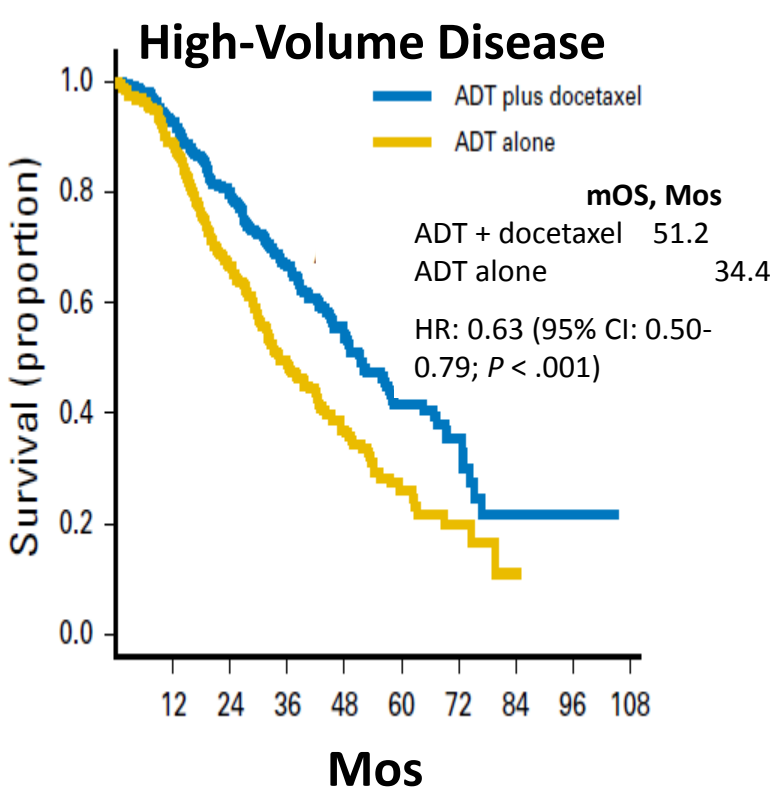
Consensus, Controversy, and Change in Hormone-Naive Metastatic Prostate Cancer: 2018

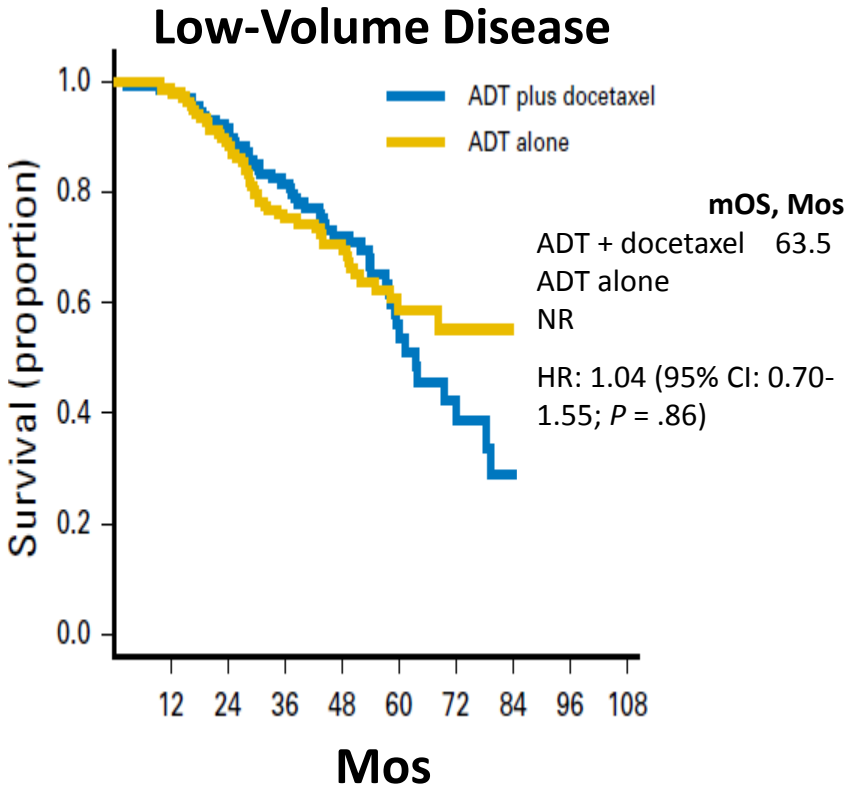
- **Consensus:** docetaxel + ADT appropriate for high-volume metastatic disease
- **Controversy:** docetaxel + ADT quite debatable for low-volume metastases
  - New CHAARTED data negative for low volume subset[1]
- **Change:** STAMPEDE[2] and LATITUDE[3] in 2017 are the recent game changers (ADT ± abiraterone)
  - ADT + abiraterone = ADT + docetaxel[4]

1. Kyriakopoulos, et al. J Clin Oncol;36:1080-1087. 2. James ND, et al. N Engl J Med. 2017;377:338-351.
3. Fizazi K, et al. N Engl J Med. 2017;377:352-360. 4. Sydes MR, et al. Ann Oncol. 2018;[Epub ahead of print].

Phase III CHAARTED Trial Long-term Follow-up: High-Volume vs Low-Volume Disease

- Median follow-up of 53.7 mos in patients with metastatic hormone-sensitive prostate cancer randomized to ADT + docetaxel vs ADT alone (N = 790)





Kyriakopoulos CE, et al. J Clin Oncol. 2018;36:1080-1087.

2 New Abiraterone Studies in Castrate-Sensitive Metastatic Disease: Inclusion Criteria

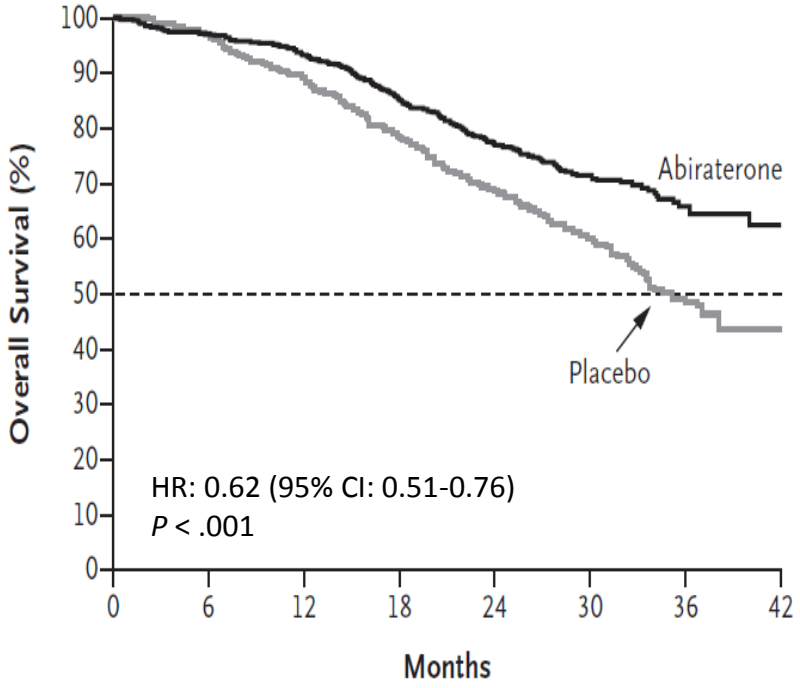
- **LATITUDE**[1]
  - At least 2 of the following 3 features: Gleason score ≥ 8, measurable visceral metastasis, ≥ 3 bone lesions
- **STAMPEDE**[2]
  - Newly diagnosed metastatic disease. Pelvic node–positive, or high-risk locally advanced with ≥ 2 high-risk features (Gleason score 8-10, T3-T4, PSA ≥ 40 ng/mL)
  - Relapsing after local therapy with high-risk features: PSA > 4 ng/mL with doubling time < 6 mos, PSA > 20 ng/mL, metastatic or nodal relapse,
    < 12m of total ADT including interval > 12m without treatment

1. Fizazi K, et al. N Engl J Med. 2017;377:352-360. 2. James ND, et al. N Engl J Med. 2017;377:338-351.

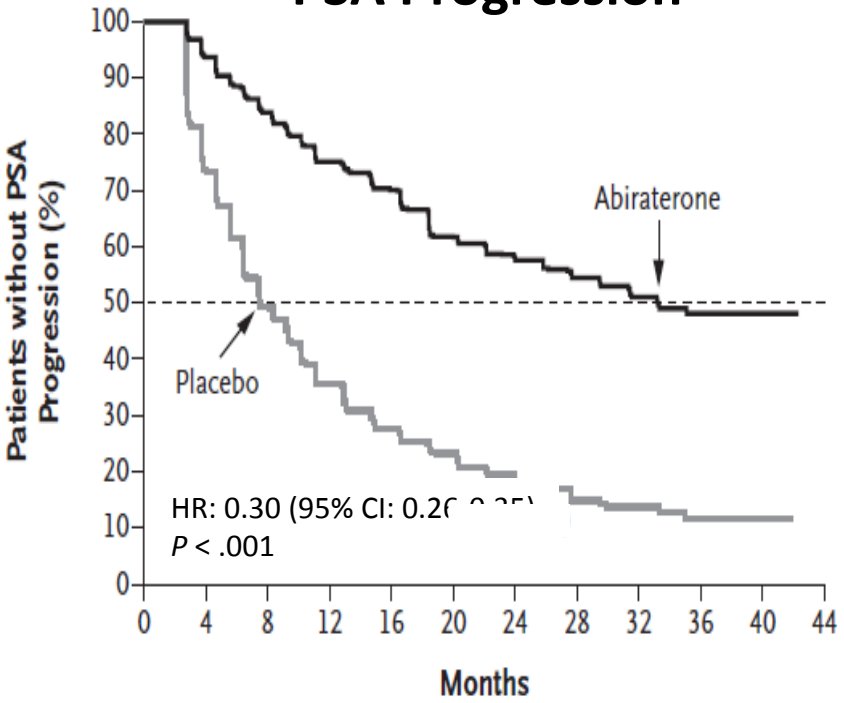
LATITUDE: ADT + Abiraterone + Prednisone vs ADT + Dual Placebo in Metastatic Castrate-Sensitive PC

- Randomized, double-blind phase III trial in patients with newly diagnosed disease (N = 1199)

Survival



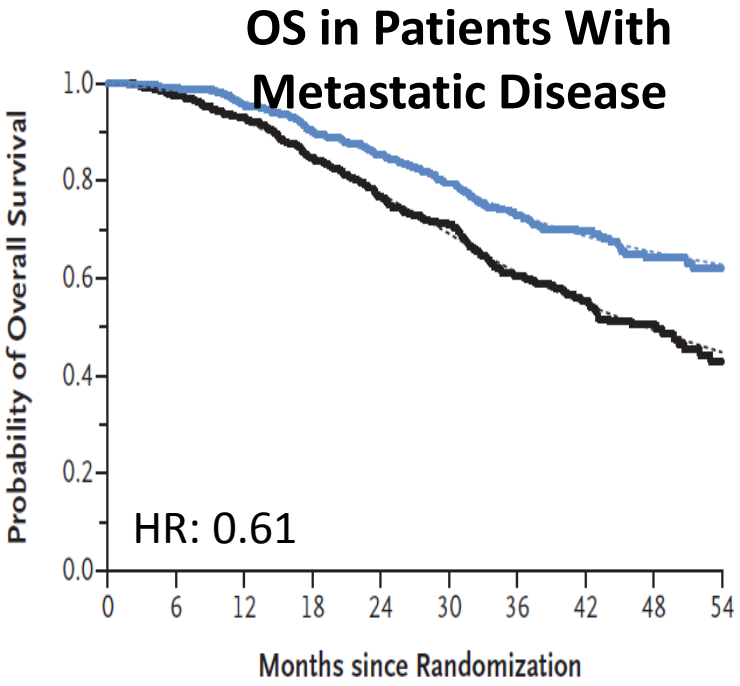
PSA Progression

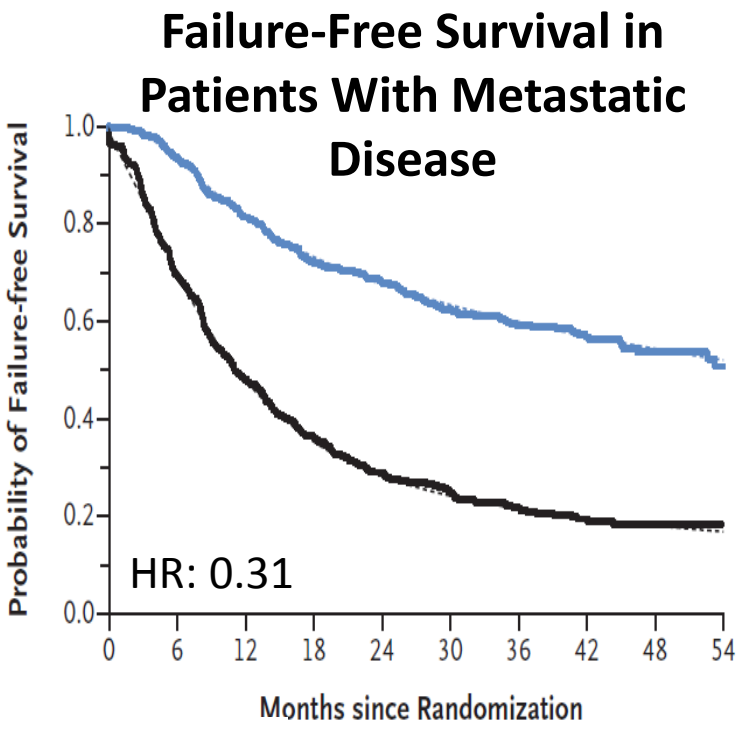


Fizazi K, et al. N Engl J Med. 2017;377:352-360.

STAMPEDE: ADT + Abiraterone + Prednisolone vs ADT Alone

- Randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)





Combination therapy*

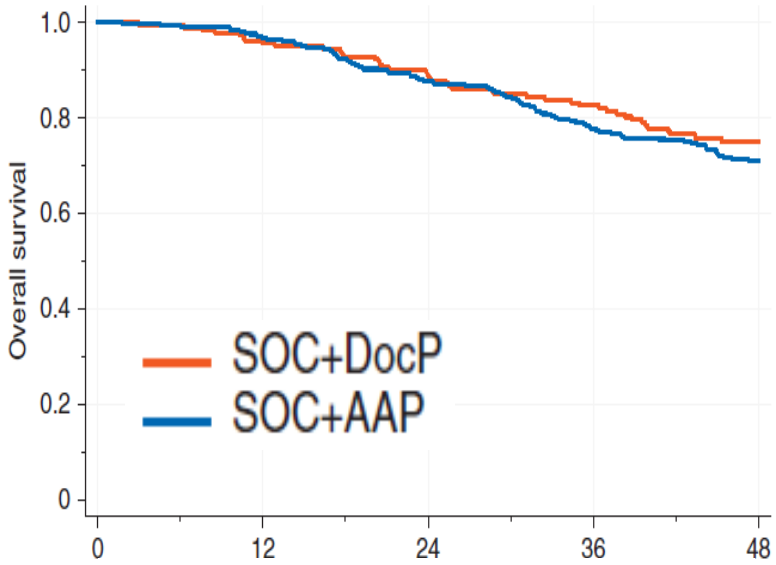
ADT alone*

*By Kaplan-Meier estimates.

James ND, et al. N Engl J Med. 2017;377:338-351. C
NCT00268476.

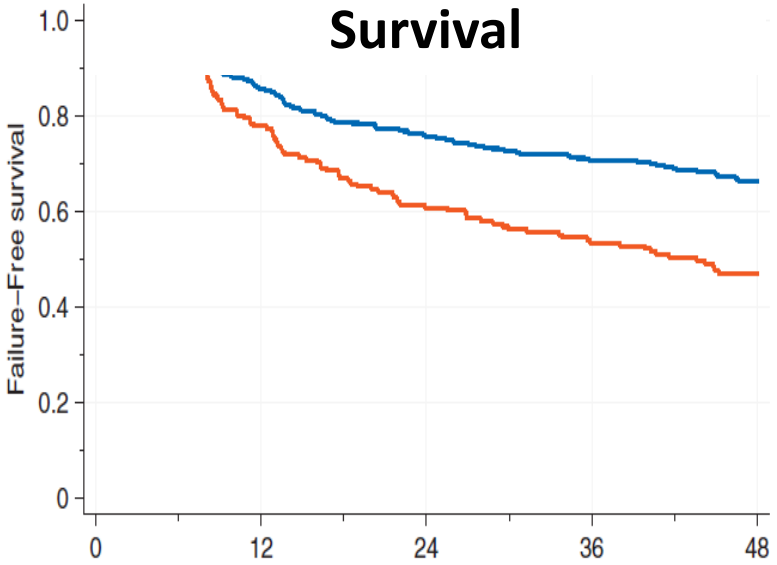
STAMPEDE: Direct Comparison of ADT + Docetaxel + Prednisolone vs ADT + Abiraterone + Prednisolone

Kaplan-Meier OS



Number of patients (events)																										
SOC+DocP	189	(1)	183	(7)	175	(5)	168	(7)	158	(7)	146	(4)	139	(10)	112	(2)	74									
SOC+AAP	377	(3)	371	(9)	358	(16)	339	(17)	320	(12)	307	(24)	278	(9)	240	(12)	161									

Kaplan-Meier Failure-Free Survival



Number of patients (events)																										
SOC+DocP	189	(11)	172	(29)	142	(20)	121	(11)	109	(8)	99	(5)	92	(5)	77	(5)	49									
SOC+AAP	377	(16)	358	(37)	316	(25)	286	(11)	270	(11)	256	(7)	242	(5)	211	(7)	141									

Sydes MR, et al. Ann Oncol. 2018;[Epub ahead of print].

High risk vs high volume?

BACKGROUND

	Pt N°	Median F/U (mo)	HR
LATITUDE M1 "high risk"	1199	30.4	**0.62** (0.51-0.76)
STAMPEDE AAP M0+M1	1917	40	**0.63** (0.52-0.76)
STAMPEDE AAP (M1)	1002	40	**0.61** (0.49-0.75)
STAMPEDE AAP (M0)	915	40	**0.75** (0.48-1.18)

Guidance Versus Licensing

What do we mean by "Risk" or "Volume?"

Definition		
CHAARTED (volume)	High	Visceral metastases AND/OR ≥4 Bone metastasis (≥1 outside vertebral column or spine)
LATITUDE (risk)	High	≥2 high risk features • ≥3 Bone metastasis • Visceral metastasis • ≥Gleason 8

MUNICH 2018 ESMO congress

Hoyle ESM 2018

Abirtaterone improved OS in low risk/ low volume HS-MPC

SUMMARY

- Abiraterone + Prednisolone + ADT improves all survival endpoints in mHNPC
- No evidence of subgroup interaction
  - All endpoints
  - Stratification independent
- Individual risk/volume variation
  - 18.2%

Overall	Overall Survival (HR)	p value
STAMPEDE M1 Cohort	**0.61** (0.49-0.79)	p<0.001

Low	Overall Survival (HR)	p value
STAMPEDE Low Risk	**0.66** (0.44-0.98)	p=0.041
STAMPEDE Low Volume	**0.64** (0.42-0.97)	p=0.034

High	Overall Survival (HR)	p value
LATITUDE High Risk	**0.62** (0.51-0.76)	<0.001
STAMPEDE High Risk	**0.54** (0.41-0.74)	<0.001
STAMPEDE High Volume	**0.60** (0.46-0.78)	<0.001

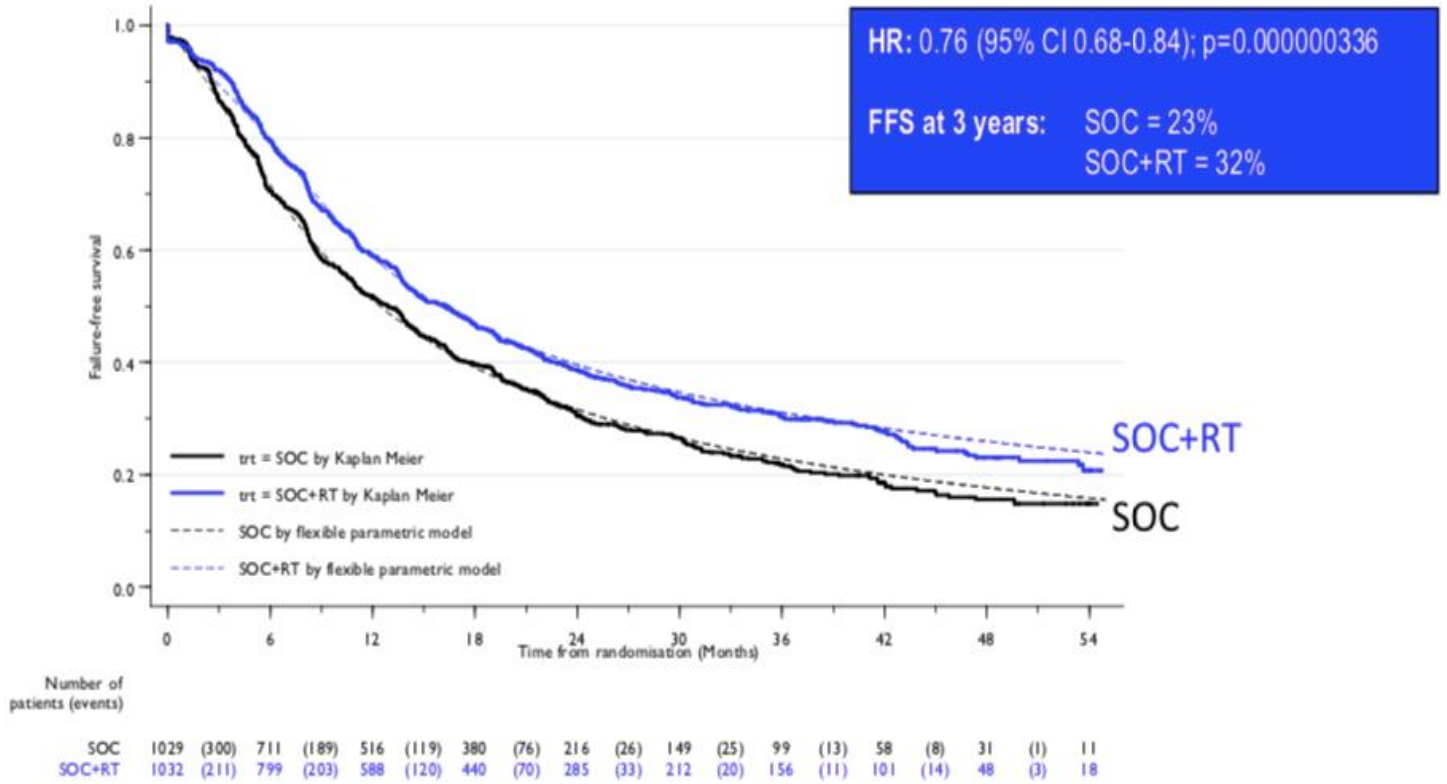
MUNICH 2018 ESMO congress

Hoyle ESM 2018

STAMPEDE: Radiation to primary?

Failure-free survival: all patients

Events 758 SOC | 685 SOC+RT



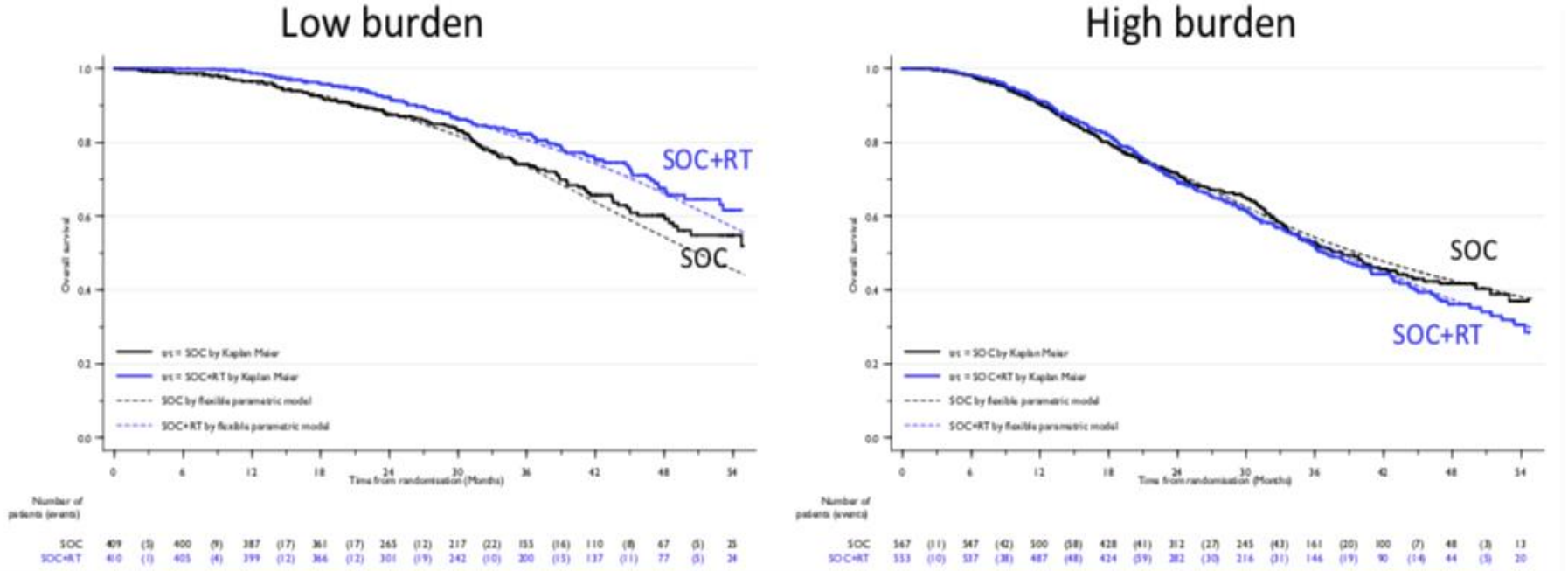
MUNICH 2018 ESMO congress

MRC CTU at UCL

Parker ESMO 2018

STAMPEDE: Radiation to primary?

Overall survival: metastatic burden subgroup analysis



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

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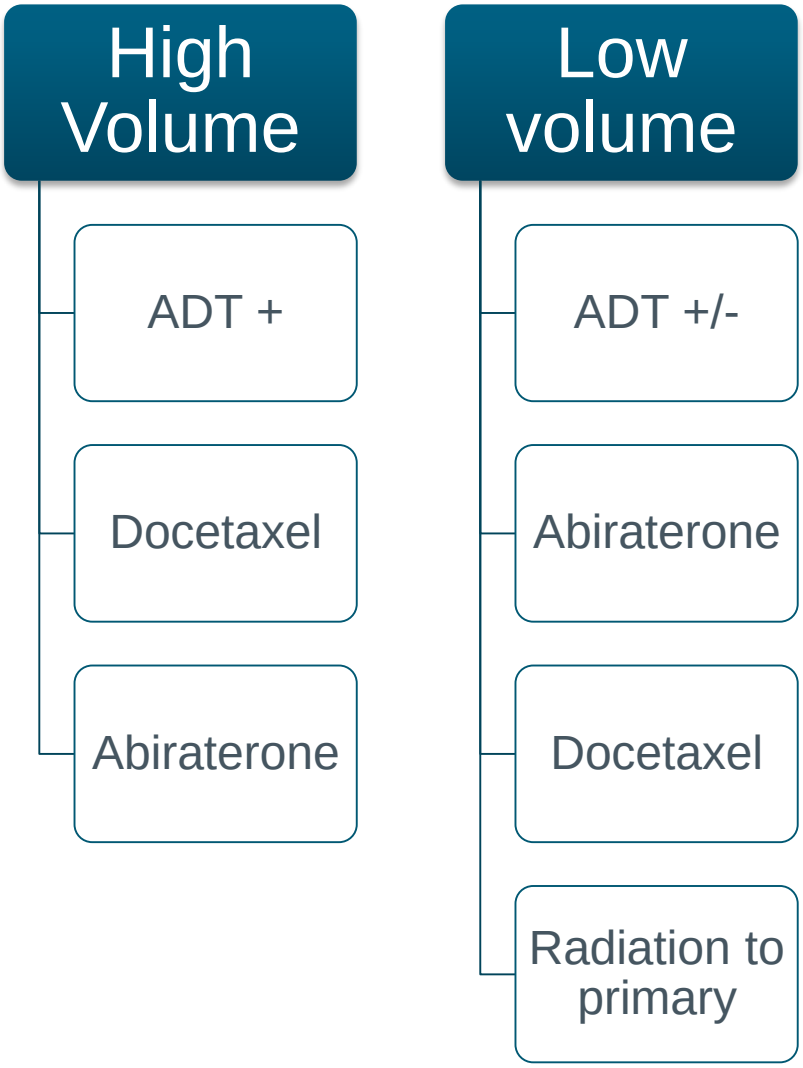
Parker ESMO 2018

Consensus, Controversy, and Change in Hormone-Naive Metastatic Prostate Cancer: 2019

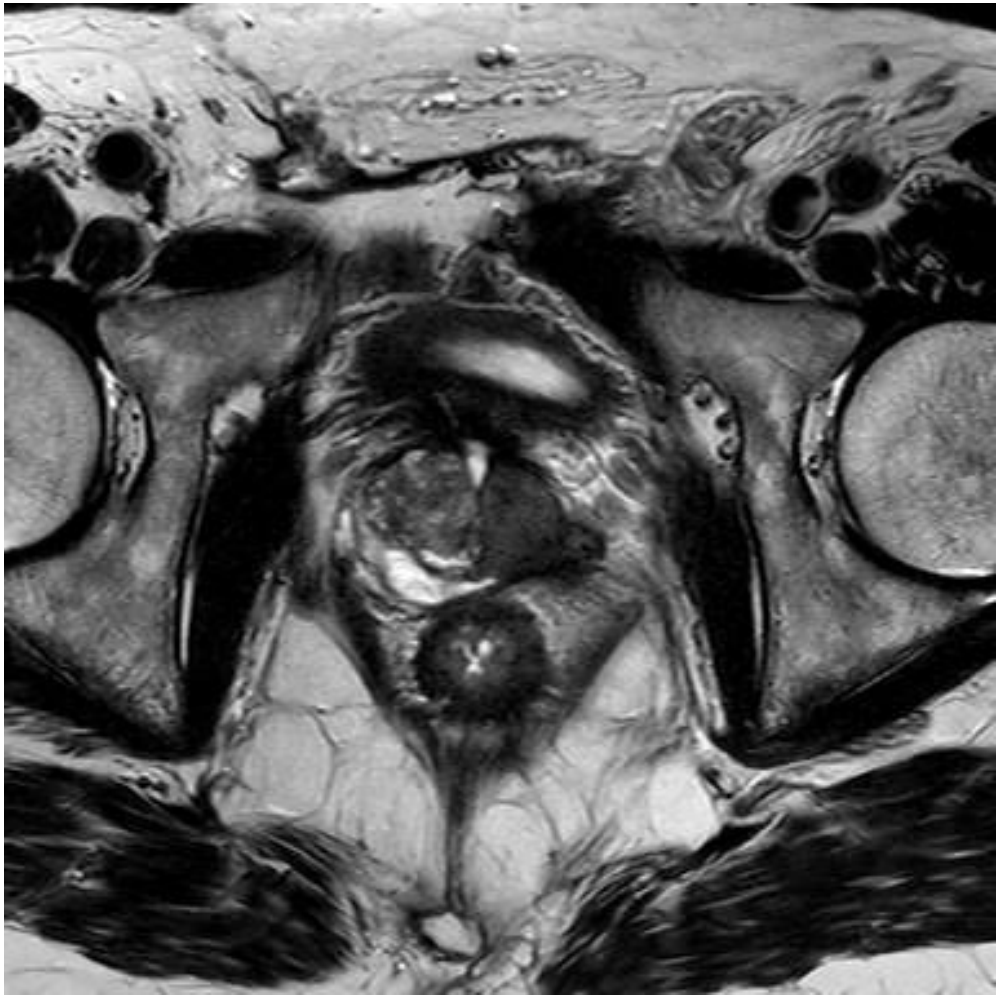
- **Consensus:** docetaxel or abiraterone + ADT appropriate for high-volume metastatic disease
- **Controversy:** docetaxel + ADT quite debatable for low-volume metastases
  - New CHAARTED data negative for low volume subset
  - Abiraterone has stronger data for OS benefit in low volume (ESMO 2018)
- **Change: Consider radiation to primary in low-volume disease (ESMO 2018)**

Hormone/castration-sensitive advanced prostate cancer

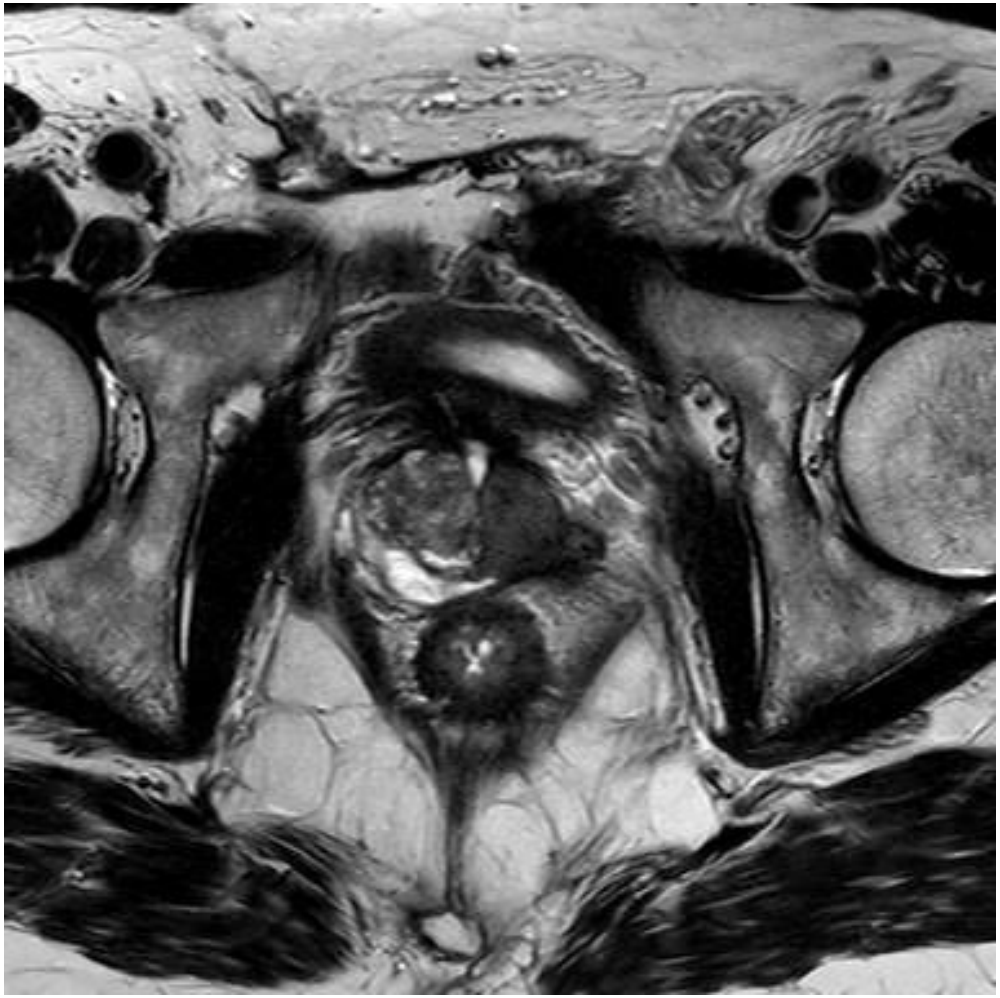


Case 3

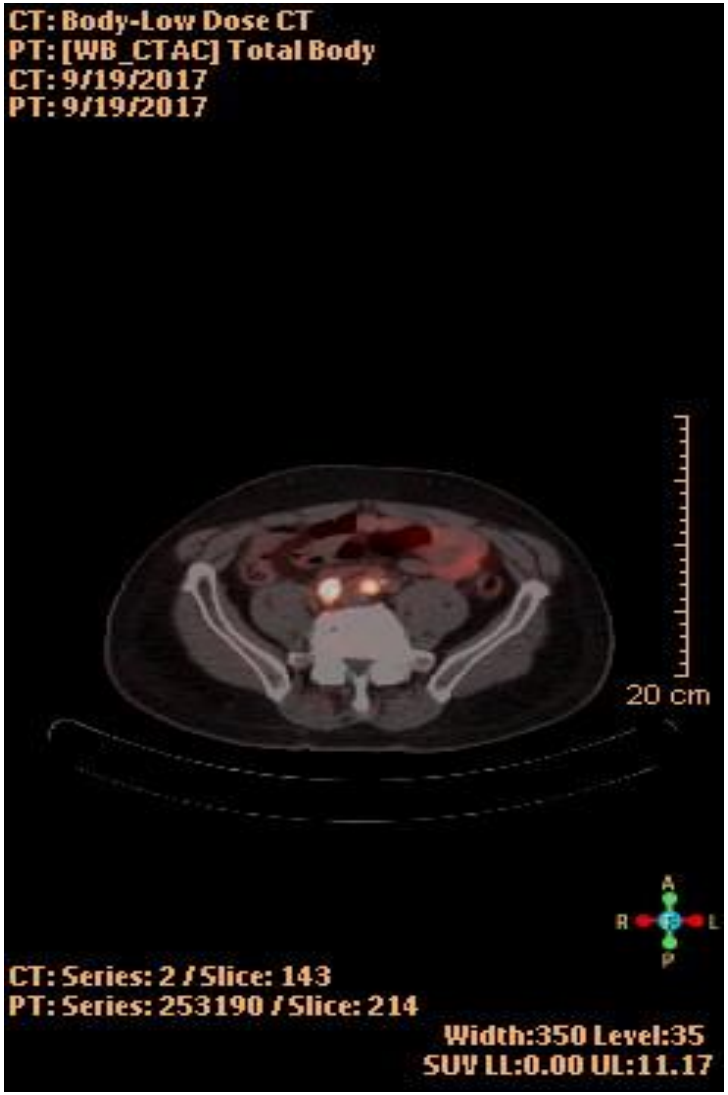
- 69 year old fit gentleman
- 3 episodes acute urinary retention
- Sept 2017 PSA 7.6 (2.87 Mar 2013)
- MRI prostate requested



Gleason 8 (grade group 4) on the left



PET-PSMA



Multiple radiotracer-avid small lymph nodes in the right external iliac, right common iliac, left common iliac, retrocaval, para caval regions measuring up to 1.2 x 0.5 cm with SUVmax 31

Case 3 discussion

- Hormone sensitive metastatic prostate ca detected on PET-PSMA
- Locally-advanced disease with 3 episodes of retention

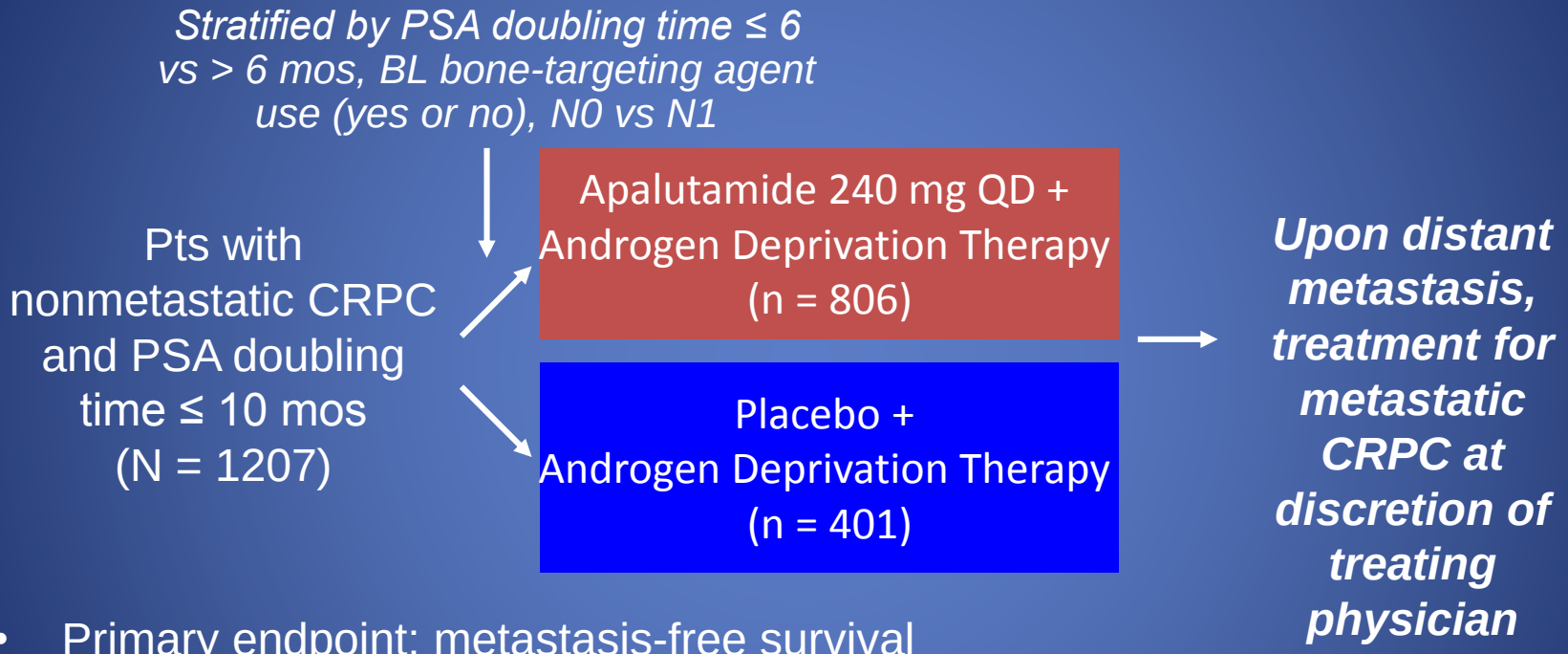
Options:

- ADT alone
- Surgery
- Role for systemic therapy?
- Role for radiation?

Outline

- Update on screening recommendations
- Diagnosis and treatment options for localized disease
- Advanced disease – castration sensitive
- Advanced disease – castration resistant
- Hot topics and future directions

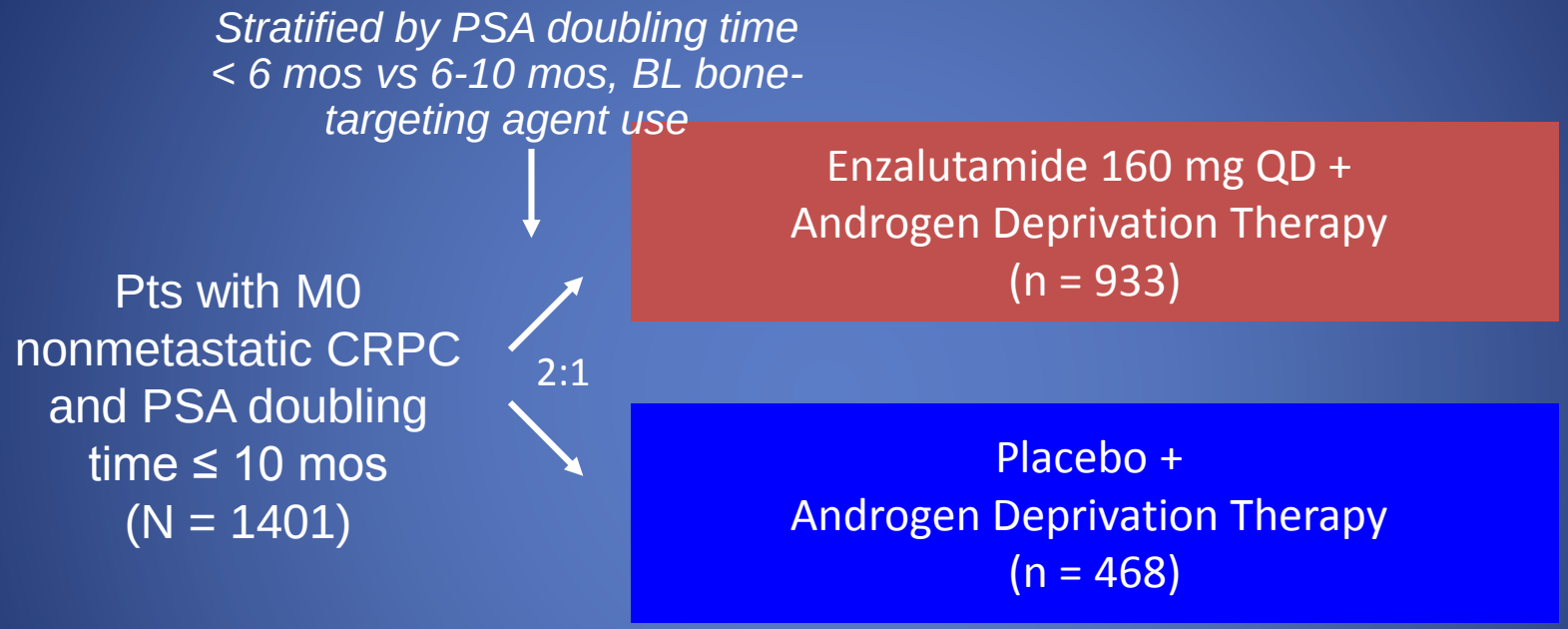
Apalutamide vs Placebo in Nonmetastatic CRPC (SPARTAN): Phase III Study Design



- Primary endpoint: metastasis-free survival
- Secondary endpoints including: time to metastasis, PFS, time to symptomatic progression, OS, time to chemotherapy
- Exploratory endpoints: time to PSA progression, PSA response rate, PFS2, PRO

Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;

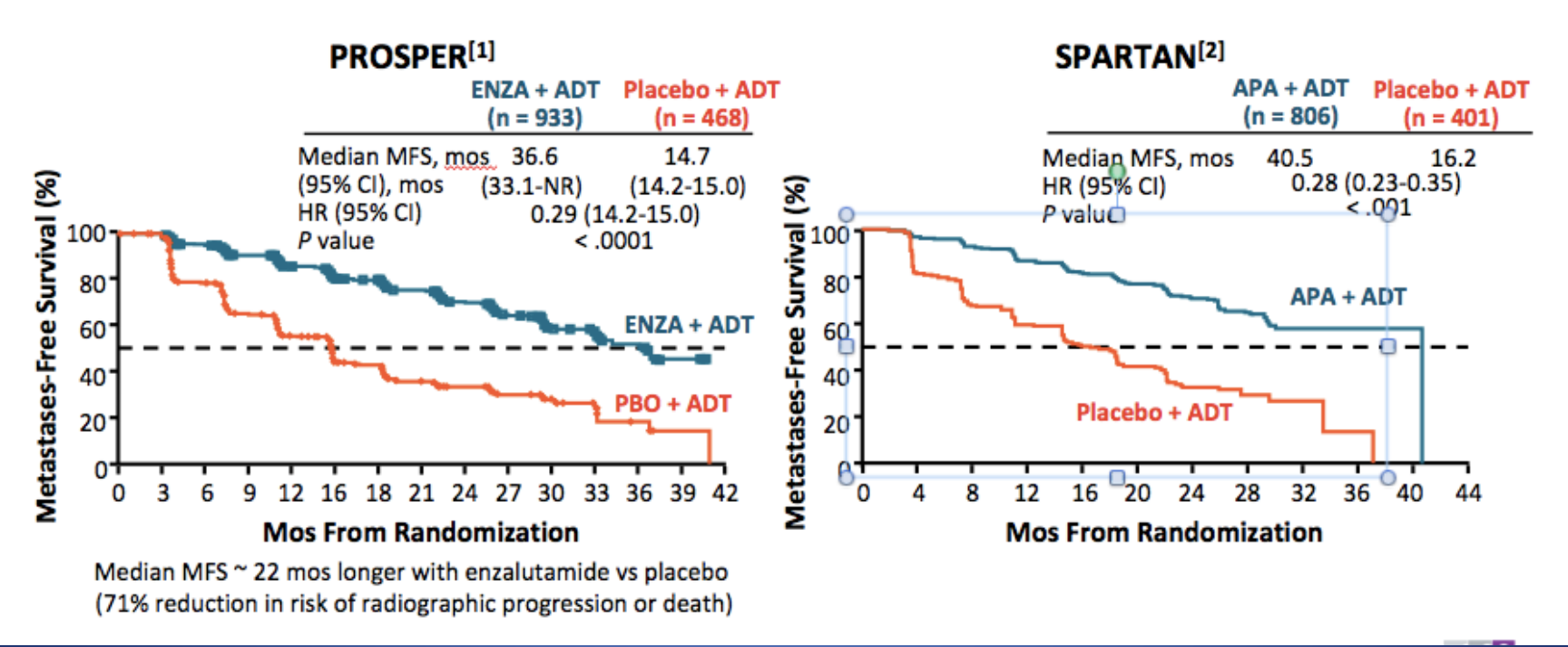
Enzalutamide vs Placebo in Nonmetastatic CRPC (PROSPER): Phase III Study Design



- Primary endpoint: metastasis-free survival
- Secondary endpoints including: safety, time to PSA progression, time to next therapy, OS, PSA response, QoL

Hussain M, et al. ASCO GU 2018. Abstract 3.

PROSPER and SPARTAN: FFS primary endpoint



M0 CRPC

- What is M0 CRPC anyway?

- These studies did not use PET-PSMA/WBMRI

- Will there be a survival advantage to starting secondary hormonal therapy earlier in disease course – need longer F/U

- Will this be cost-effective?

Treatment for castration-resistant prostate cancer

Androgen-biosynthesis inhibitors:

Abiraterone

Chemotherapy:

Docetaxel

Cabazitaxel

Supportive care:

Palliative radiation

Bone-targeting agents

Anti-androgens:

Enzalutamide

Apalutamide (M0)

Radionuclide therapy:

Radium-223

Lutetium-PSMA

Hot topic in advanced prostate cancer

- Treatment of oligometastatic disease
- Sequencing of therapy
- Precision medicine – somatic/germline mutations predicting response to treatment
- Circulating biomarkers
- Emergence of neuro-endocrine phenotype

Mutational landscape of CRPC

Table 2. Selected Gene Aberrations in Patients with Metastatic Prostate Cancer.*

Gene	% of Patients with Aberrant Gene	Pathway	Common Aberrations†
AR gene	62.7	Androgen signaling	Amplification, splice variants, mutation
TP53	53.3	Cell cycle or tumor suppressor	Mutation, copy loss
PTEN	40.7	PI3K–AKT regulator	Copy loss, mutation
ETS	56.7	Transcriptional regulator	Gene fusions
BRCA2	13.3	DNA repair	Copy loss, mutation
KMT2C	12.7	Chromatin modifier	Mutation
FOXA1	12.0	AR-associated	Mutation
ZBTB16	10.0	AR-associated	Copy loss
RB1	9.3	Cell cycle	Copy loss
APC	8.7	Wnt pathway	Copy loss, mutation
CHD1	8.0	Chromatin modifier	Copy loss, mutation
SPOP	8.0	Androgen signaling	Mutation
ATM	7.3	DNA repair	Copy loss, mutation

* Data are from Robinson et al.[34] AR denotes androgen receptor.
† Aberrations are listed in descending order of predominance (e.g., for *TP53*, mutation is the predominant gene alteration, and for *PTEN*, copy loss is predominant).

Sartor NEJM 2018
Robinson Cell 2015

12% of patients with advanced CRPC have germline mutations in DNA-repair genes

Table 3. Selected Common Germline DNA-Repair Mutations in Patients with Metastatic Prostate Cancer.*

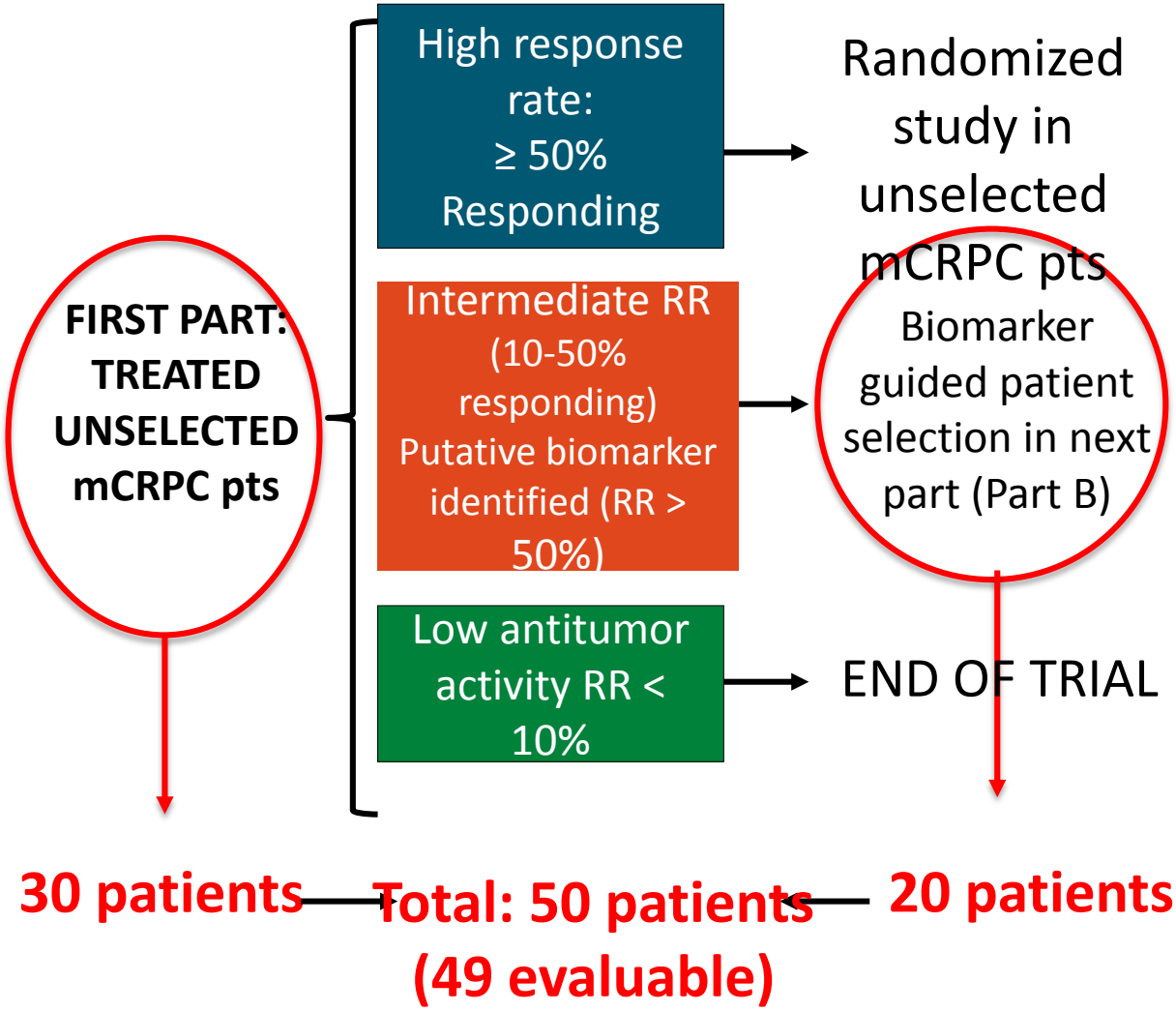
Gene	% of Patients with Mutation	Relative Risk of Metastases†
BRCA2	5.35	18.6
CHEK2	1.87	3.1
ATM	1.59	6.3
BRCA1	0.87	3.9
GEN1	0.46	5.8
RAD51D	0.43	5.7
PALB2	0.43	3.5

* Data are from Pritchard et al.[37]
† Relative risks are for the comparison with men who do not have known prostate cancer.

Sartor NEJM 2018
Pritchard NEJM 2016

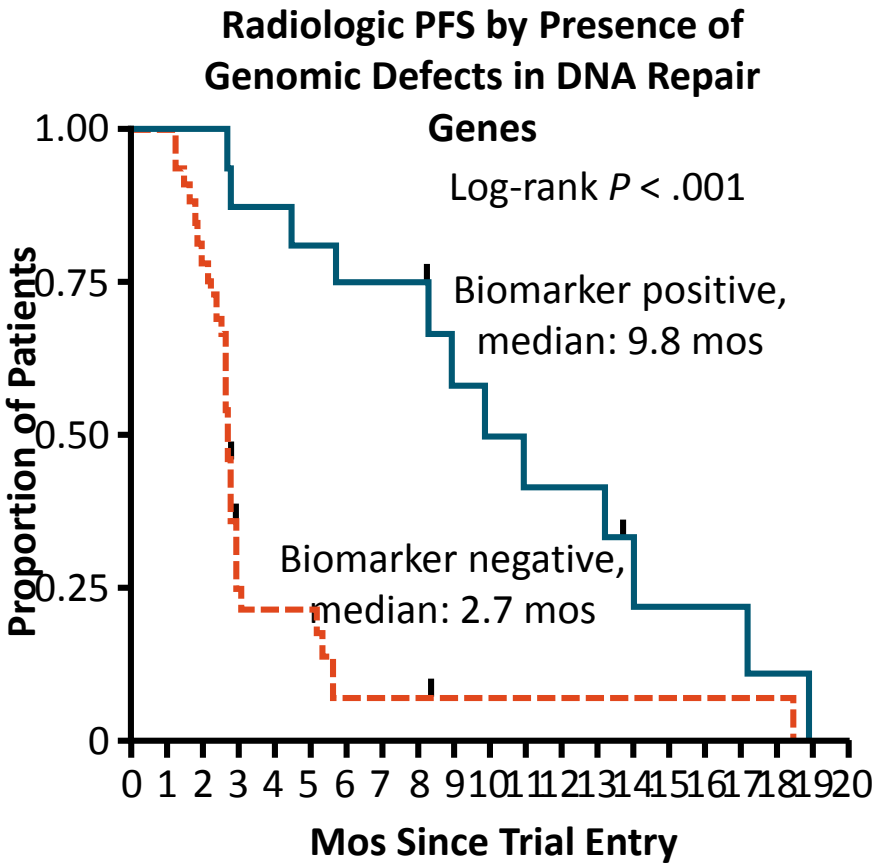
TOPARP: Trial of Olaparib in mCRPC

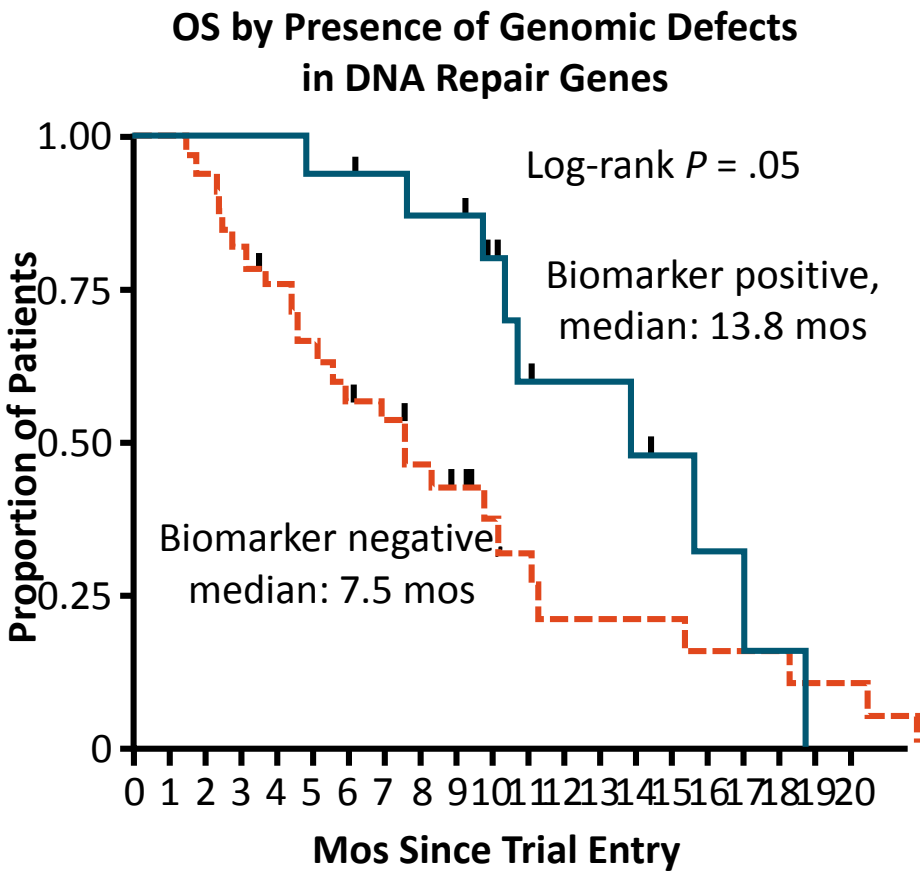
Eligibility: Histologically confirmed metastatic CRPC, ECOG 0-2, no previous PARPi or platinum



Mateo J, et al. N Engl J Med. 2015;373:1697-1708.

TOPARP-A: PFS and OS by Presence of DNA Repair Defects





- All patients (N = 50) treated with olaparib 400 mg PO BID

Mateo J, et al. N Engl J Med. 2015;373:1697-1708.

Prostate cancer from PSA elevation to late stage: therapeutic algorithm

- PSA screening recommended again by USPTF (55-69)
- MRI recommended prior to prostate biopsy
- For de-novo hormone-sensitive metastatic disease – addition of docetaxel or abiraterone to ADT
- Consider radiation to primary in low-volume metastatic disease

Prostate cancer from PSA elevation to late stage: therapeutic algorithm

- New approvals for enzalutamide/apalutamide in M0 CRPC (improved FFS/OS immature)
- Abiraterone/enzalutamide/doctaxel/ cabazitaxel and radium-223 improve survival in mCRPC
- On-going studies for PSMA-based radionuclide therapy, PARP-inhibitors for patients with DNA-repair defects, immunotherapy if MSI-high

Thank you

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