Prostate Cancer Update: Screening, Active Surveillance, Imaging and Treatment

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DISCLOSURES

- Speakers Bureau.
  - Exelixis.
  - Sanofi.

- Some slides purchased from ASCO University (GU ASCO 2019).

OBJECTIVES

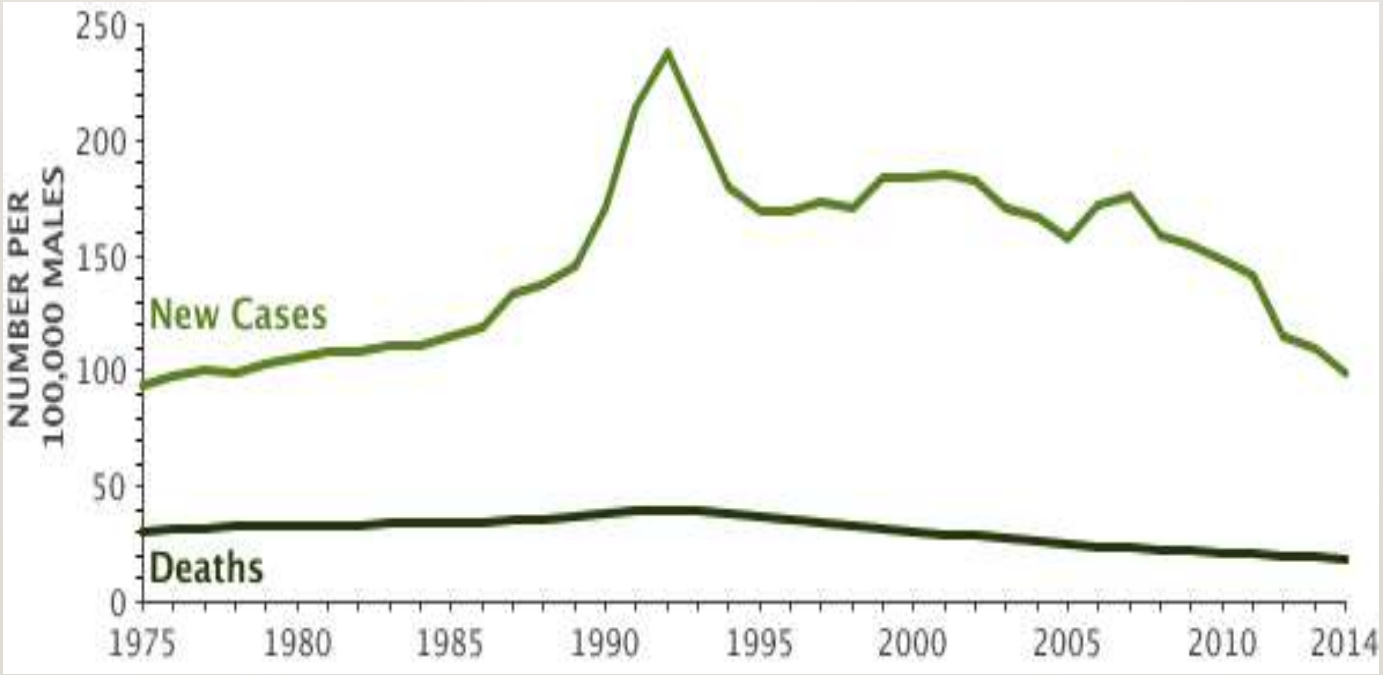
- Prostate Cancer Over Diagnosis and Over Treatment
- Active Surveillance
- Potential Preventative Approaches
  - Life Style Interventions(Diet, Exercise)
  - Chemoprevention
- Imaging
- Recent Therapeutic Advances

CHANGE IN PATIENT POPULATION AND NATURAL HISTORY

- Burden of prostate cancer in 2019*
  - 174,650 new cases
  - 31,620 deaths
- Stage migration of disease
  - Primarily due to PSA screening
  - Low risk disease predominates
- Number of diagnosed outweighs lethal cases (over detection)

*Siegel et al, CA Cancer J Clin, 2019

PROSTATE CANCER INCIDENCE OVER TIME



THE TREND IN US CANCER MORTALITY WITH ASSOCIATED APC(%) FOR CANCER OF THE PROSTATE BETWEEN 1975-2009, ALL RACES

SEER Data-Decreasing mortality correlates with onset of PSA screening.

Male

Trend	Period
0.9	1975-1987
3.1	1987-1991
-0.7	1991-1994
-3.9	1994-2004
-3.2	2004-2009

PROSTATE CANCER PREVALENCE AND MORTALITY

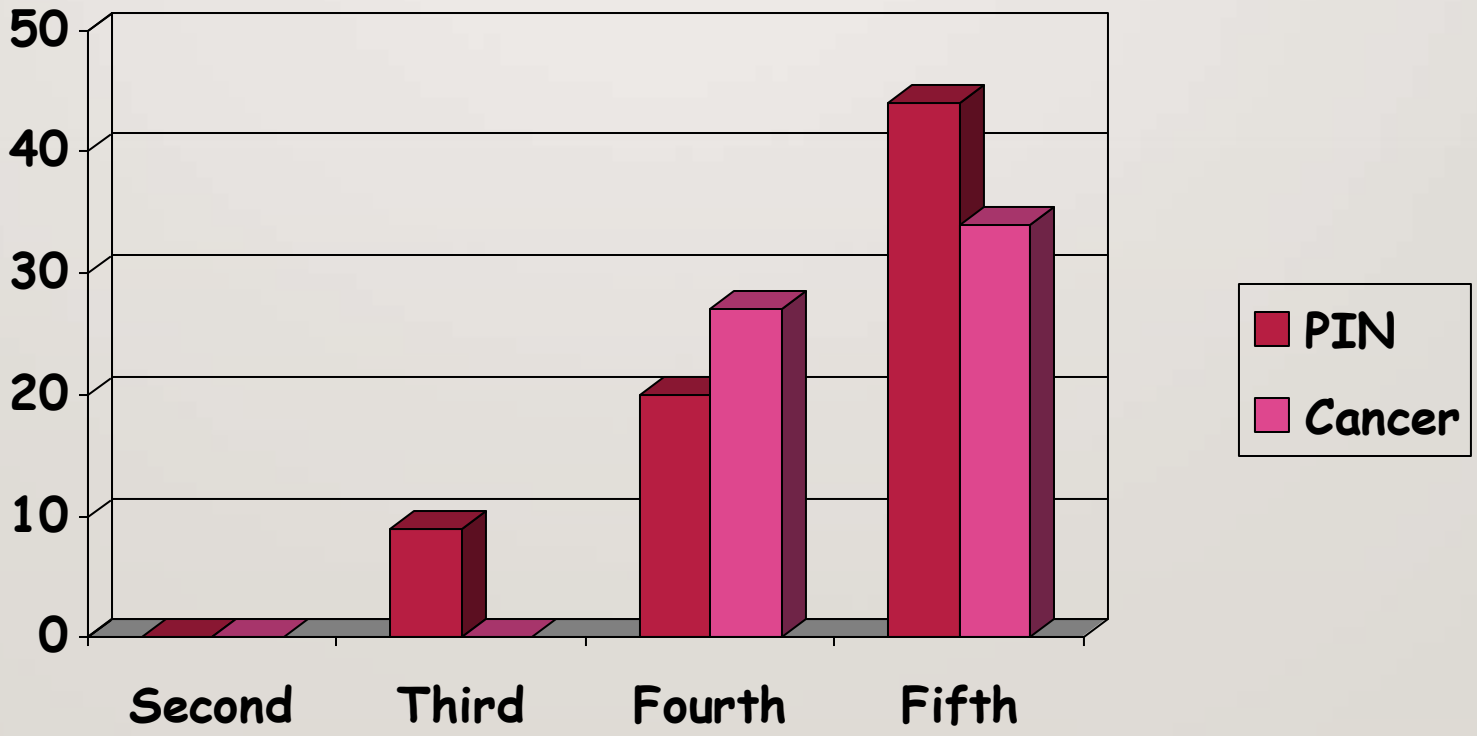
- US male has 16% lifetime risk of being diagnosed with prostate cancer – 1 new case every 3 minutes.
- 1/3 of men over age 60 and 1/2 of men over age 70 have prostate cancer.
- But lifetime risk of death from prostate cancer is only 3%.
- 2.5 million men in US with history of prostate cancer.

CARCINOMA AND PIN IN YOUNG MALES

- Examined152 prostate glands in patients age 10-49.
- 98 were AA and 54 were Caucasian.
- Preneoplastic and neoplastic changes starting in the third decade of life.
  - Majority of PIN was low grade.
  - Similar frequency in AA and Caucasian.
  - AA had more multifocal disease.

☐ WA Sakr, Journal of Urology, 150, 1993.

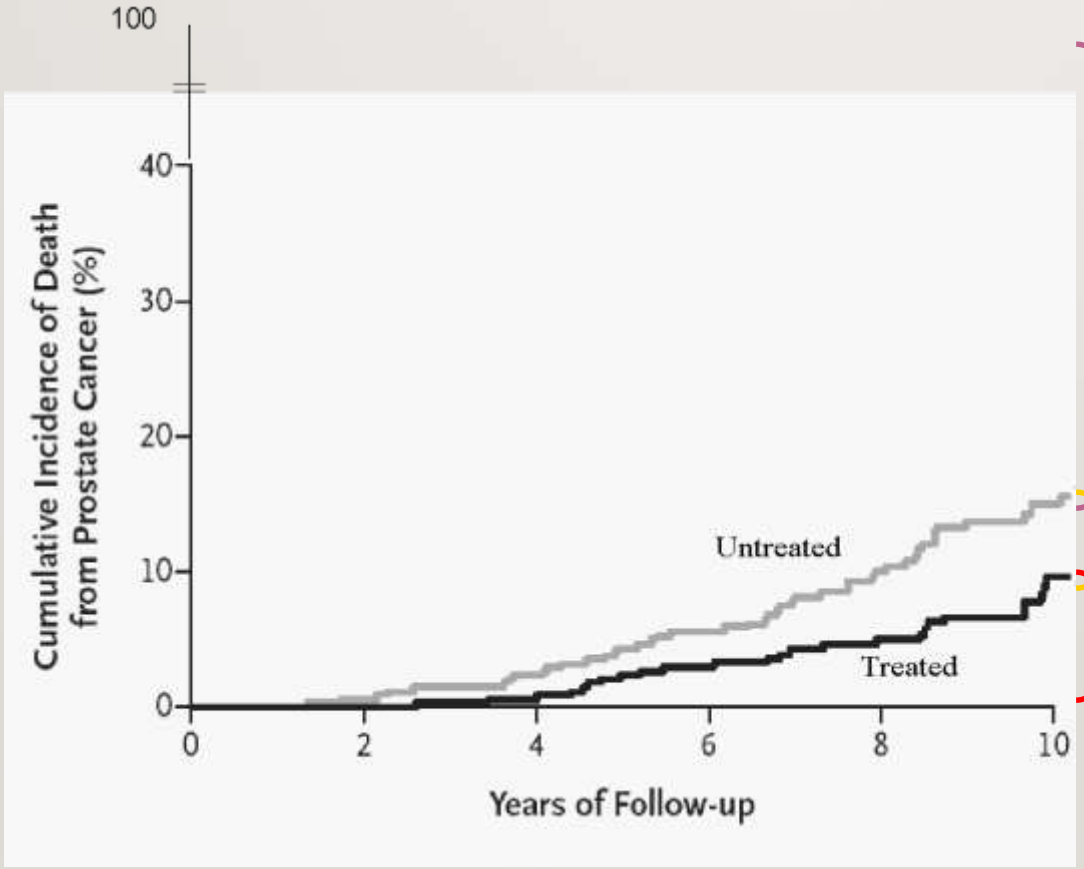
CARCINOMA AND PIN IN YOUNG MALES



WA Sakr, Journal of Urology, 150, 1993.

- Long Natural History
  - Opportunities for Intervention
    - Nutrition and Dietary
    - Exercise
- Large Survivorship Population
- Prostate Cancer Screening
  - The Controversy Continues

CHALLENGE IN MANAGING LOCALIZED PROSTATE CANCER



Natural history—Men who could avoid therapy (or avoid diagnosis)

Men who benefit from treatment

Men who die despite radical treatment

Bill-Axelson, Holmberg, et al, NEJM 2005

Prostate Cancer: Screening

Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO).

- 76,693 men randomized between no screening vs. screening showing no difference in mortality.
- Contamination bias?

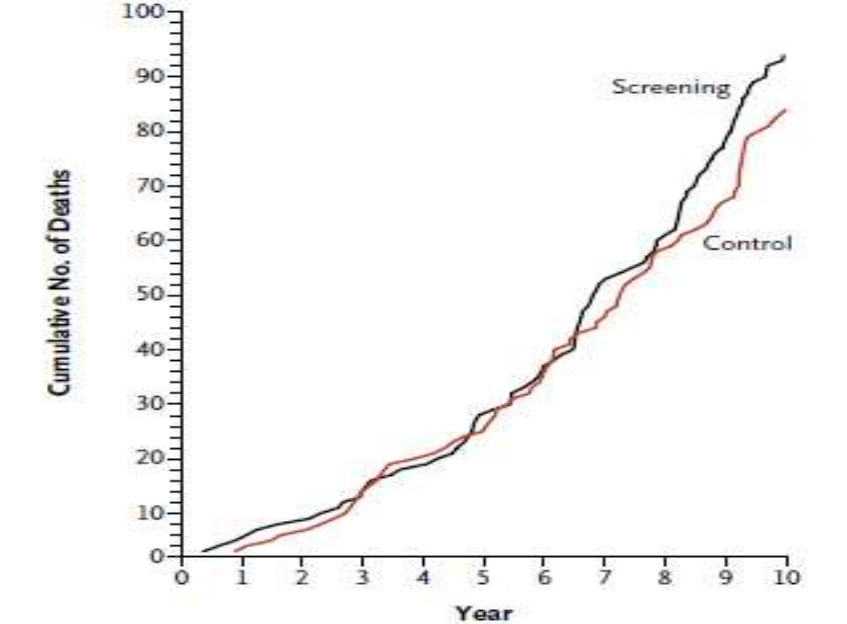
European Randomized Study of Screening for Prostate Cancer (ERSPC).

- 162,433 men randomized between screening and no screening showing an 8.2% vs. 4.8% incidence of PC with relative risk reduction of 20% at 10 years.

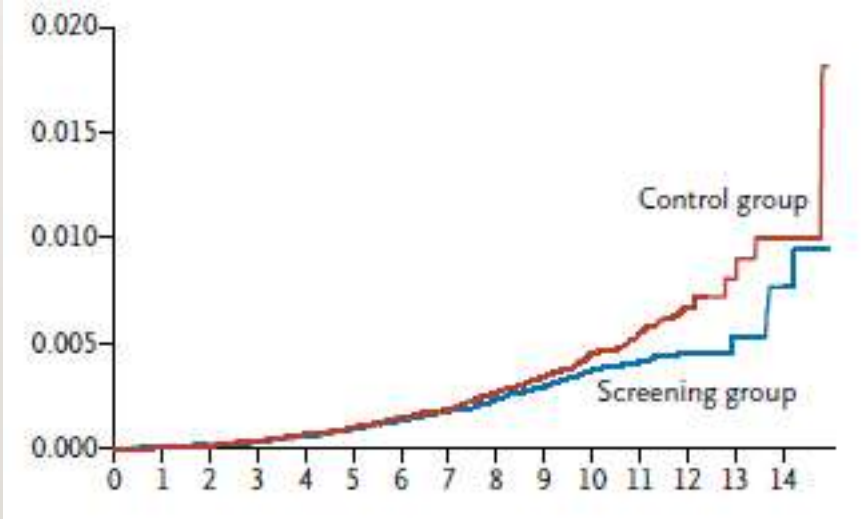
NEJM, 2010

Prostate Cancer Screening Trials

AMERICAN TRIAL



EUROPEAN TRIAL



Prostate Cancer: Screening

- U.S Preventive Services Task Force (October 2011)
  - Grade D recommendation suggesting no new benefit or harm outweighs benefit.

- NEJM, 2011

RECONCILING THE EFFECTS OF SCREENING ON PROSTATE CANCER MORTALITY IN ERSPC AND PLCO TRIALS

- Extended analysis evaluating increased incidence due to screening and diagnostic work-up in each group via mean lead times.
- Estimates of Reduction of Risk:
  - PLCO: 25-31% reduction
  - ERSPC: 27-32% reduction

    - Etzioni R, et al. Ann Intern Med, 2017.

Prostate Cancer: Screening

- U.S Preventive Services Task Force (April 2017)
  - Some men between 55 and 69 might well decide to get their PSA tested but discussion of pros/cons others might elected to skip the test.

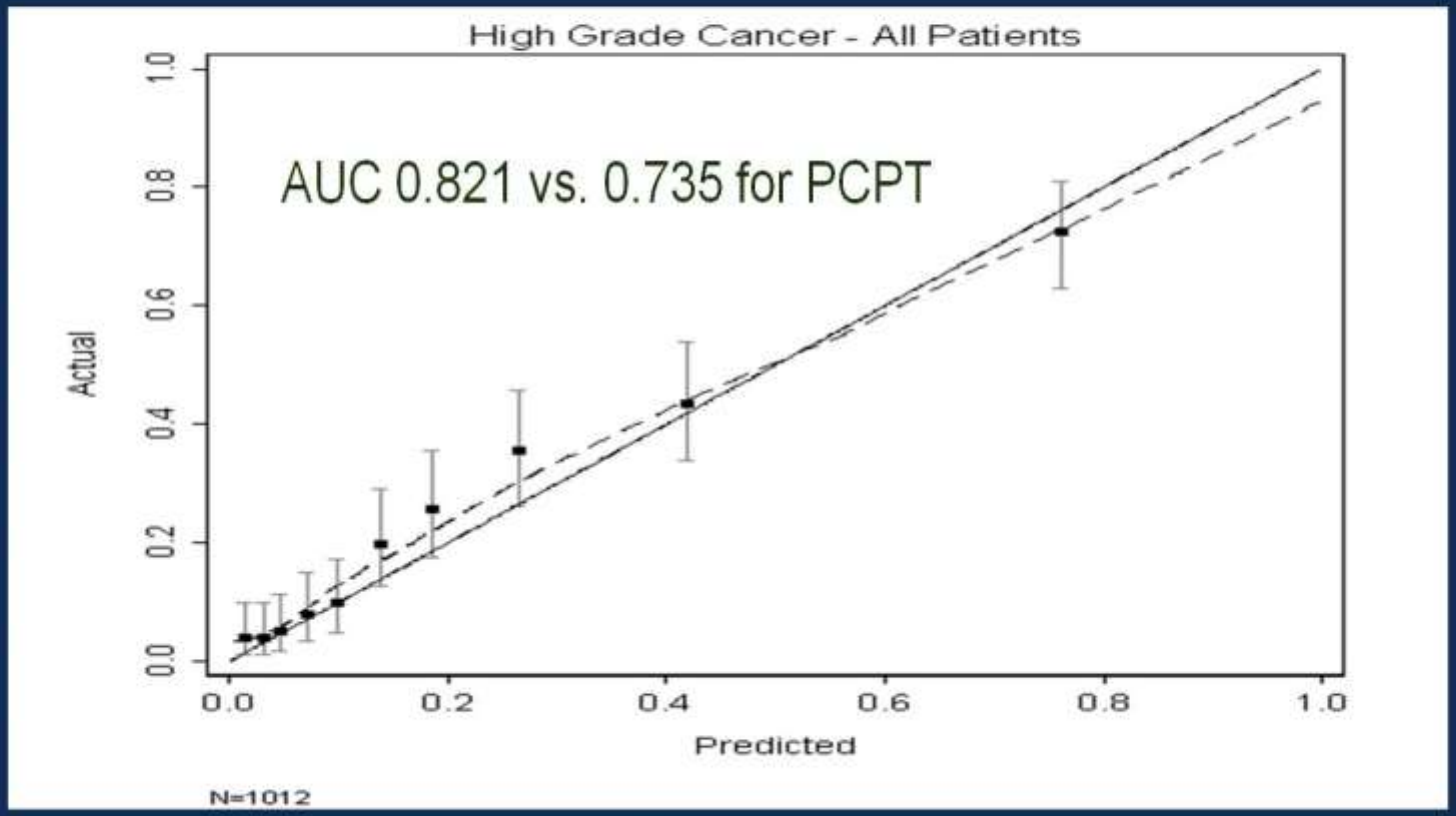
Which best represents your view on prostate cancer screening?

A. We should have PSA screening because it saves lives
B. PSA screening does not save lives
C. Patients should engage in shared decision-making about PSA screening based on personal preferences
D. Whether PSA screening does more good than harm depends on how you do it.

How to reduce overdiagnosis by 70% without really trying

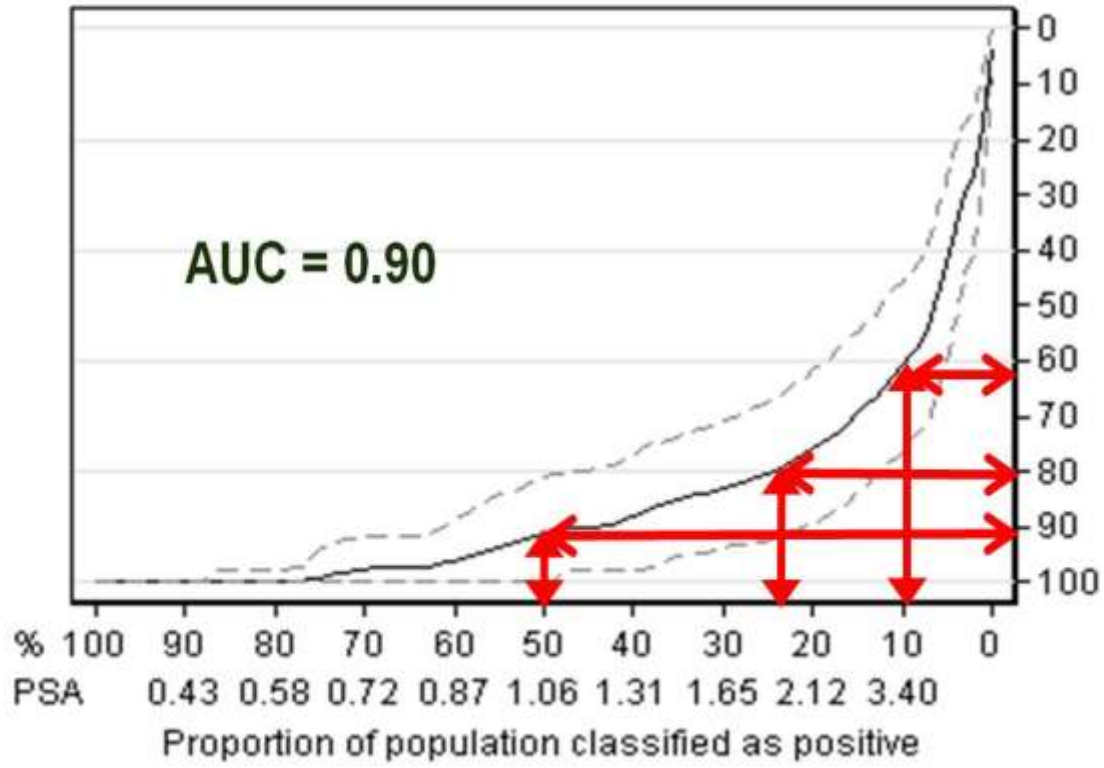
- No screening over 70
  - 40% reduction in overdiagnosis
- Use of reflex marker tests
  - ~50% reduction in overdiagnosis

US prospective study (n=1012) confirms value of 4Kscore



PSA at 60 highly predictive of cancer death by 85

Lorenz Curve: Mets within 25 years by PSA at 60



Prop. cases identified (%)	Cases identified per 1000	Cases missed per 1000
0	0	37
10	4	33
20	7	30
30	11	26
40	15	22
50	19	18
60	22	15
70	26	11
80	30	7
90	33	4
100	37	0

Presented By Andrew Vickers at 2019 Genitourinary Cancers Symposium

75% of the tests, 40% of the overdiagnosis, none of the benefit in low PSA

	Risk difference/10 000 men (95% CI)		
	Baseline total PSA level (ng/mL)		
Prostate cancer outcomes	0-0.99	1-1.99	≥2
Increase in diagnosis	171 (–32 to 374)	1462 (1101 to 1822)	2485 (1797 to 317[illegible])
Decrease in metastasis	–37 (–70 to 11)*	–70 (–182 to 42)	415 (30 to 799)
Decrease in death	–17 (–43 to 14)*	–85 (–138 to –2)*	453 (108 to 797)

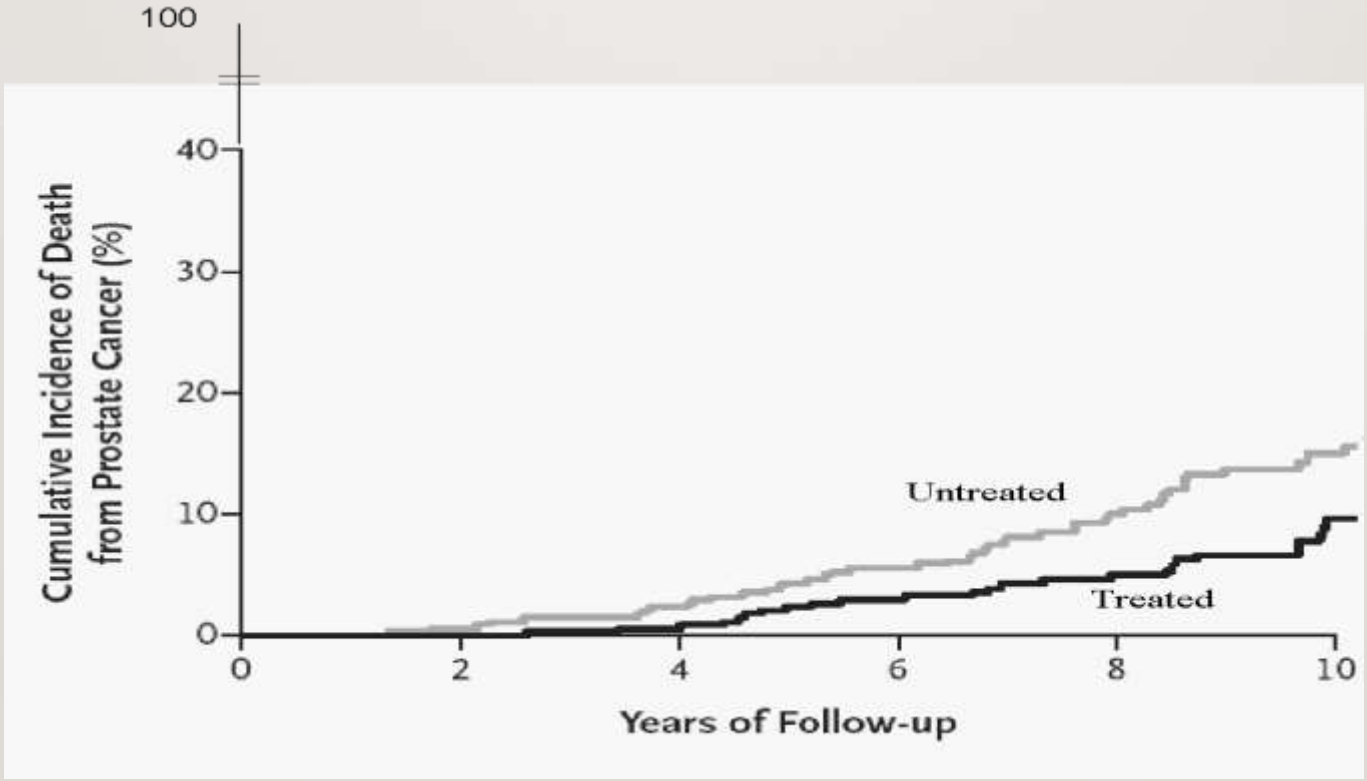
PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented By Andrew Vickers at 2019 Genitourinary Cancers Symposium

Conclusions: Screening

- Do not screen men greater than age 70?
- Stop screening at 60 based on PSA?
- Selective use of biopsy (biomarkers, MRI)?
- Active Surveillance for Gleason's 6 or less?

PROSTATE CANCER MORTALITY: RADICAL PROSTATECTOMY VS. WATCHFUL WAITING



Bill-Axelson, Holmberg, et al, NEJM 2005

RANDOMIZED TRIAL OF WATCHFUL WAITING VERSUS RADICAL PROSTATECTOMY

- Scandinavian randomized trial of 695 men with absolute risk reduction of 6.1% in prostate cancer deaths at 15 years in men undergoing radical prostatectomy versus watchful waiting.
  - Number needed to treat to prevent 1 prostate cancer death – 15
- Benefit more pronounced in men < 65 years of age.
  - Number needed to treat – 7
- Men in “low risk” group also benefited.
  - 4.2% reduction

Bill-Axelson, A, et al, Radical prostatectomy versus watchful waiting in early prostate cancer: NEJM 364:18 (1708-1717), 2011.

RANDOMIZED TRIAL OF WATCHFUL WAITING VERSUS RADICAL PROSTATECTOMY

- 23.2 years of follow-up: deaths from prostate cancer- 63 in surgery group and 99 in WW group.
- Absolute difference of 11%.
- Number needed to treat to prevent one death-8.

- *Bill-Axelson, A, et al, Radical prostatectomy versus watchful waiting in early prostate cancer: NEJM 370 (932-942), 2014.*

Prostatectomy/Watchful Waiting

- Benefit greatest in patients if age < 65 and intermediate risk prostate cancer.
- 25% reduction in the use of androgen deprivation in the surgery group.
- Significant percentage of the WW group have not required any therapy.

PIVOT RESULTS
(WILT ET AL, NEJM 2012/2017)

- Prostate Intervention Versus Observation Trial (PIVOT).
  - 731 patients randomized to RP or WW
    - > 50% with nonpalpable disease
  - 27 men in surgery group and 42 in observation group.
    - All patients: HR 0.84 (0.71-1.08), p=0.22
    - Low risk: HR 1.15 (0.86-1.53), p=0.45
    - Intermediate risk: HR 0.69 (0.49-0.98), p=0.04

ACTIVE SURVEILLANCE IN LOW RISK PROSTATE CANCER

- Management of early stage low risk disease
  - Active monitoring protocol to help differentiate between disease at risk of progression versus disease likely to progress to symptoms
- Active Surveillance provides an opportunity to limit treatment to those most likely to benefit

Wilt et al, NEJM, 2012
Sanda et al, NEJM, 2008
Dall'era et al, Cancer, 2008

ACTIVE SURVEILLANCE PROS AND CONS

Pros

- Screen-detected prostate cancers are both over diagnosed and over treated.
- Prostate cancer treatments are associated with significant morbidity.

Cons

- Potential for curability lost by disease progression during period of active surveillance.
- Patient anxiety (and provider) during active surveillance.
- Morbidity of repeat biopsies every 12-18 months.

NCCN GUIDELINES: ACTIVE SURVEILLANCE

- PSA no more than every 6 months.
- DRE no more than every 12 months.
- Repeat biopsy no more than every 12 months.
- Consider mpMRI if aggressive cancer suspected/biopsies negative.

Prostate Cancer Classification

Low risk (D'Amico, NCCN, AUA)

- Stage T1c/T2a
- PSA <10 ng/ml
- Gleason score ≤ 6

Very low risk (Epstein):

- Stage T1c
- PSAD < 0.15
- Gleason score ≤ 6
- < 3 cores with cancer
- ≤ 50% of any core involved

Active Surveillance

What Defines Progression

PSA

PSA kinetics not reliably related to progression or pathology.

Increase Grade

Interobserver variability in pathology evaluation and sample bias.

Increase in Volume

Lack of standardization of biopsy technique and blind biopsy.

Ross et al, J Clin Onc 28: 2810-15, 2010
Loblaw et al, J Urol , 184: 1942-6, 2010
McKenney et al, J Urol 186: 465-9, 2011

ACTIVE SURVEILLANCE - *SUMMARY OF STUDIES*

Institution (PI)	Most recent paper(s)	Total (*n*)	Strict* (n)	Median age	Median follow-up (months)	OS (%)	CSS (%)	TFS (%)
Royal Marsden (Parker)	2007[18,63]	326	326	67	22	98	100	73
Inclusion criteria	Gleason ≤3+4, PSA ≤15 ng/ml, cT stage ≤2a, ≤50% of cores positive							
ERSPC sites (Schröder)	2009[64,65]	988	616	66	52	91	99	68
Inclusion criteria	Gleason ≤3+3, PSA ≤10 ng/ml, PSAD ≤0.2 ng/ml/ml, cT stage 1c-2, ≤2 cores positive							
University of Miami (Soloway)	2010[66,67]	230	230	64	32	100	100	86
Inclusion criteria	Gleason ≤6, PSA ≤10 ng/ml, cT stage ≤2, ≤2 cores, ≤20% of any core positive							
Johns Hopkins (Carter)	2010[14,33]	618	506	65	35	98	100	59
Inclusion criteria	Gleason ≤3+3, PSAD ≤0.15 ng/ml/ml, cT stage 1, ≤2 cores positive, ≤50% of any core positive							
UCSF (Carroll)	2010[16,68]	640	376	62	47	97	100	68
Inclusion criteria	Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2, ≤33% of cores positive, ≤50% of any core positive							
University of Toronto (Klotz)	2010[13,69]	453	453	70	82	68 (10-yr)	97	70
Inclusion criteria	Gleason ≤6, PSA ≤10 ng/ml (until Jan 2000, for men >70: Gleason ≤3+4, PSA ≤15 ng/ml)							
Memorial-Sloan Kettering (Eastham)	2010[23,70]	238	238	64	22	n/a	n/a	n/a
Inclusion criteria	Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2a, ≤3 cores positive, ≤50% of any core positive							
TOTAL		3490	2733	67	43	90	99.7	64

Cooperberg, Carroll, Klotz. J Clin Oncol 29: 3669-75, 2011

ACTIVE SURVEILLANCE POTENTIAL TRIAL DESIGNS

- Lifestyle Chance
  - Dietary-MEAL Study
  - Exercise
- Surveillance intensity: Biopsy Frequency 2 versus 4 years
- Chemoprevention strategies
  - Enzalutamide
  - Complementary Medicine
  - 2-ME
- Role of imaging and focal therapy
- Impact on quality of life/social status/support
- Methods to assist patient decision-making

DIET AND LIFESTYLE AS A RISK FACTOR

- Prostate cancer risk among Asian immigrants increases with duration of exposure to Western lifestyle.
- High correlation between per capita consumption of fat, animal fat, red meat, diary products and the national prostate cancer incidence/mortality.

THE MEN'S EATING AND LIVING (MEAL) STUDY CALGB 70807

MEAL STUDY ELIGIBILITY

- Biopsy-proven adenocarcinoma, clinical stage < than or = to T2a diagnosed within past 24 months.
- Less than 25% positive cores.
- Less than 50% of any one cores positive.
- No prior treatment or 5-alpha reductase inhibitors within 90 days.
- Age 50-80 years.
- For men < 70, Gleason score 6 or less, for men >70, Gleason score 7 or less.

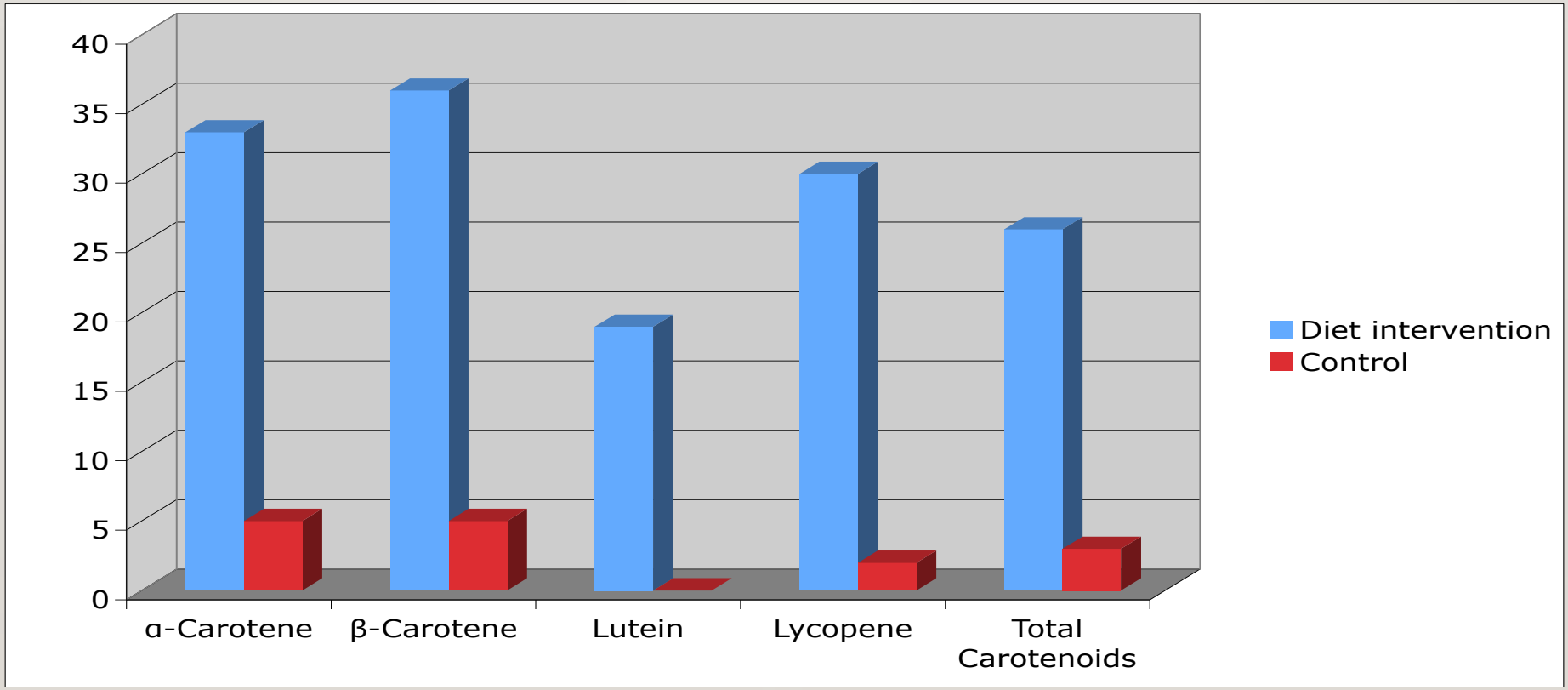
MEAL STUDY REGISTRATION/RANDOMIZATION

- Total of 464 patients (accrual completed 2015).
- Run in period with completion of three 24-hour dietary recalls.
- Randomization:
  - Arm A: Meal Program Intervention
    - Four phases of counseling calls over 24 month period.
  - Arm B: Prostate Cancer Foundation Booklet
- Quality of Life Measures:
  - Seven QOL measures.

MEAL STUDY OBJECTIVES

- Primary
  - To determine if a telephone-based dietary intervention compared to no intervention will decrease clinical progression in AS patients.
- Secondary
  - To compare incidence of active treatment.
  - To compare prostate cancer-related anxiety.
  - To compare health-related QOL.

MEAL PILOT STUDY
PLASMA CAROTENOIDS



Parsons et al. *BJU Int*, 2009

ACTIVE SURVEILLANCE IDENTIFICATION OF HIGH RISK DISEASE

- Imaging Approaches: Can we identify which cancer are most likely to progress.
  - Diffusion Weighted MRI.
  - PET/Metabolic imaging.
    - C11 choline.
    - Fluciclovine-18 (Axumin).
    - PSMA

PROMIS: Prostate MRI Imaging Study

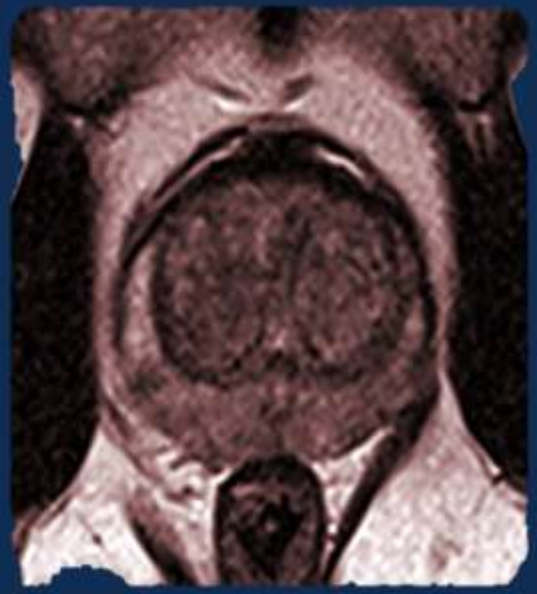
Presenter & Co-CI: Mr Hashim Ahmed

Chief Investigator: Prof Mark Emberton

Sponsored by University College London

Managed by MRC Clinical Trials Unit

Funded by UK NIHR HTA



PROMIS is funded by the UK Government Department of Health, National Institute of Health Research – Health Technology Assessment Programme, (Project number 09/22/67).

UK Department of Health Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the health technology assessment program, NIHR, NHS or the Department of Health.

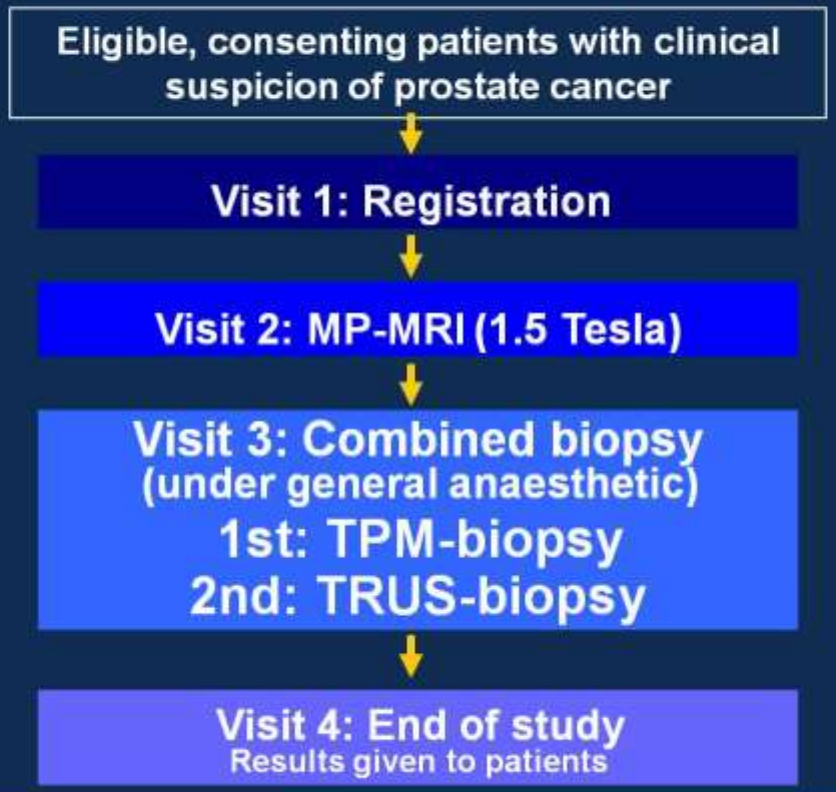
Presented By Hashim Ahmed at 2016 ASCO Annual Meeting

PROMIS Objectives

To assess the ability of Multi-Parametric prostate MRI prior to first biopsy to,

- Identify men who can safely avoid unnecessary biopsy
- Reduce over-diagnosis of clinically insignificant cancer
- Improve the detection of clinically significant cancer

Level 1b diagnostic study
Validating paired-cohort confirmatory study



El-Shater Bosaily A et al; PROMIS Group. Contemp Clin Trials. 2015;42:26-40.

Index Test – Multi-parametric MRI

- 1.5 Tesla, no endorectal coil
- Independent Quality Assurance and Quality Control of scans
- Compliant with international guidance

  T2W, Diffusion (ADC + b=1500), Dynamic gadolinium contrast
- LIKERT scoring 1 to 5:

  1=highly unlikely to harbour significant cancer

  …

  5=highly likely to harbour significant cancer
- Positive MP-MRI

  Score >/=3

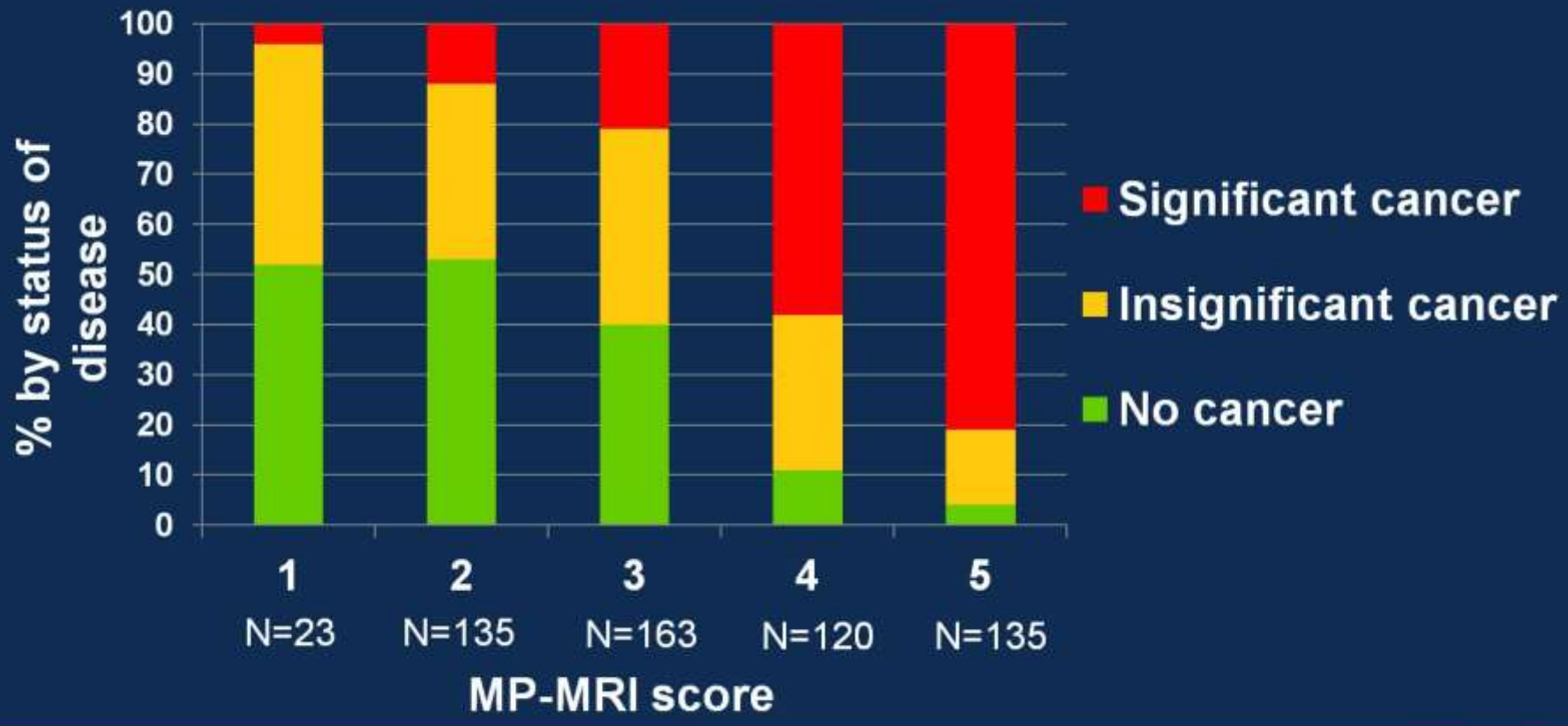
Histological definition of clinically significant cancer

Gleason >/=4+3 and/or

Cancer core length >/=6mm

Ahmed H. U. et al, J Urol. 2011;186(2):458-64

MP-MRI scores and disease severity



MP-MRI compared to TRUS-biopsy

Test attribute	TRUS-biopsy	MP-MRI	Odds ratio* [95% CI]	*p-value*
Sensitivity	**48%**	**93%**	0.06 [0.02-0.12]	*p<0.0001*
Specificity	**96%**	**41%**	0.02 [0.003-0.05]	*p<0.0001*
PPV	**90%**	**51%**	8.2 [4.7-14.3]	*p<0.0001*
NPV	**74%**	**89%**	0.34 [0.21-0.55]	*p<0.0001*

McNemar test to compare sensitivity and specificity; GEE logistic regression model to compare PPV and NPV

Clinically significant cancers missed by TRUS-biopsy and MP-MRI

		TRUS-biopsy Total = 119	MP-MRI Total = 17
Number and cancer core length (mm)	Gleason 3+3	**7** (6-11mm)	**1** (8mm)
	Gleason 3+4	**99** (6-14mm)	**16** (6-12mm)
	Gleason >/=4+3	**13** (3-16mm)	**0**

Conclusions

- TRUS-biopsy has poor attributes for a diagnostic test
- MP-MRI prior to TRUS-biopsy can identify at least one quarter of men presenting with an elevated PSA who might safely avoid prostate biopsies
- MP-MRI followed by biopsy can reduce the over-diagnosis of clinically insignificant prostate cancer
- MP-MRI can identify over 90% of men with clinically significant prostate cancers

Evolution of MRI in Urologic Practice

NYU Langone Health
Department of Urology

- Staging post positive biopsy
- Post-biopsy disease localization/staging
  - Previous negative biopsy
  - Active surveillance vs treatment
  - Treatment planning
- Pre-Biopsy disease localization
  - Better detection
  - Improved risk stratification
- Risk Stratification
  - Prediction of grade, stage, and clinical outcome
  - MRI as a Biomarker to determine the need for biopsy

Managing Patients with Low Risk MRI

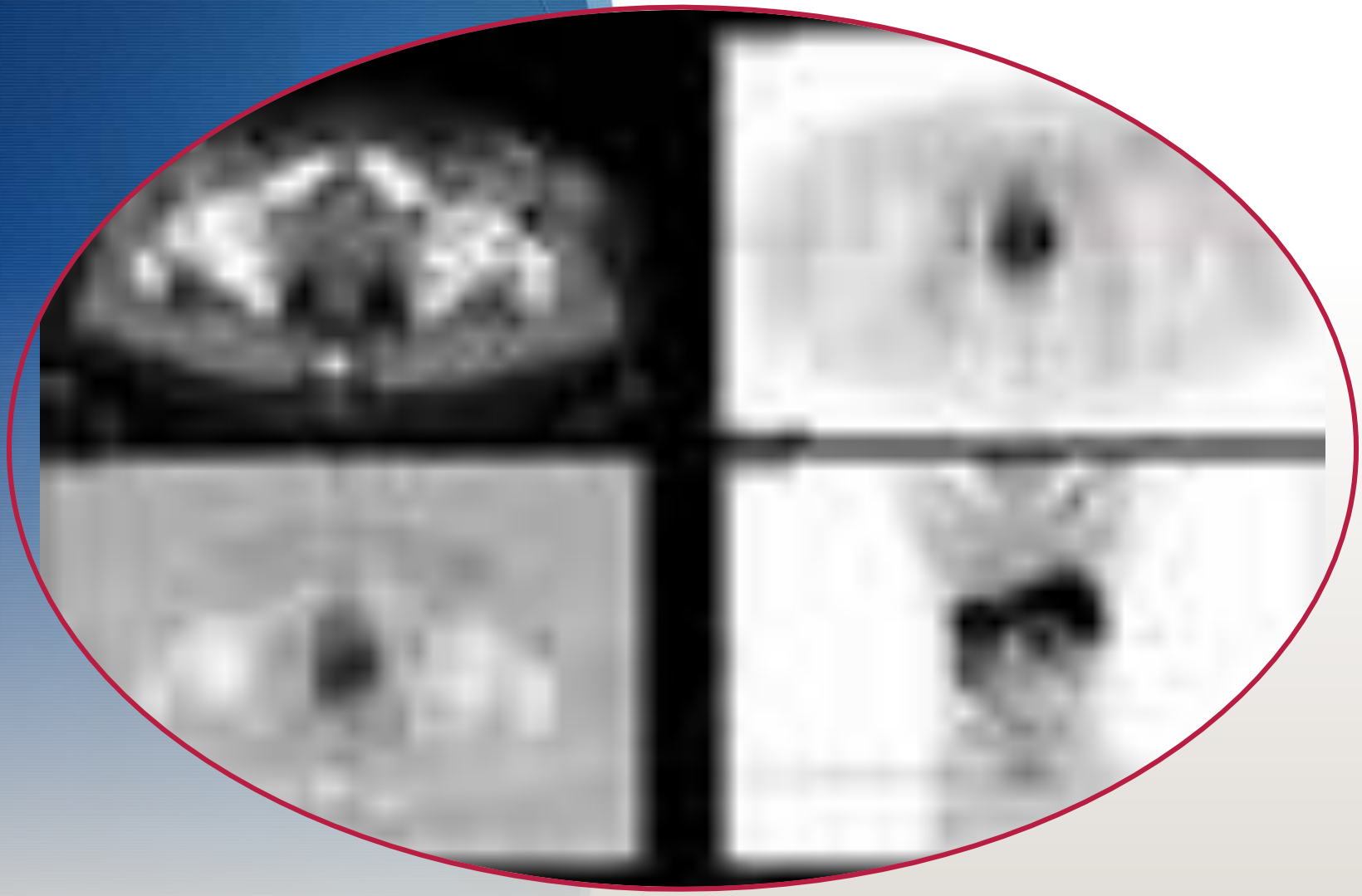
NYU Langone Health
Department of Urology

- Some need a biopsy
  - age/family history/genetic risk
  - markedly elevated PSA
- Some can have further risk stratification by
  - PSA Derivatives, Nomograms, Other Biomarkers (4k,PHI, Select MDx)
- Some can have deferral of biopsy
  - Monitor further PSA rise with serial measurement
  - Re-assess at one year
- Such an approach validated
  - 5% rate of CS Pca diagnosis at 48 months f/u

(Panebianco, et al, European Urology, 2018)

NOVEL IMAGING: IDENTIFICATION OF HIGH RISK DISEASE

- Imaging Approaches: Can we identify which cancer are most likely to progress.
  - C11 Acetate
  - C11 Choline
  - F-18 Fluciclovine
  - PSMA



What can we achieve with advanced imaging and molecular biomarkers?

Tailoring therapy through better:

- Detection of “occult” disease → **Imaging**
- Risk stratification (prognosis)
- Prediction of treatment response

} **Molecular Biomarkers**

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Presented by: Felix Feng, MD

The Advent of PET Imaging for Prostate Cancer

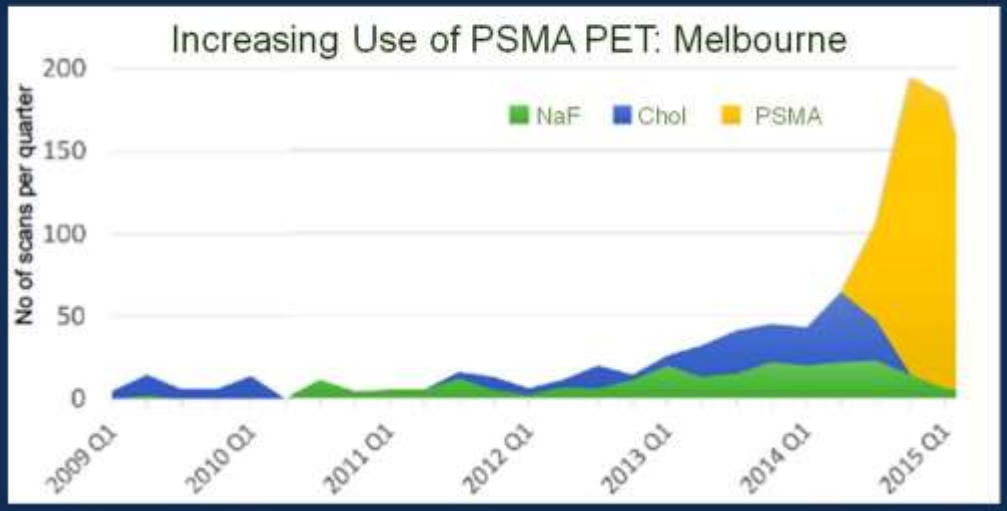


Figure courtesy of Michael Hofman, Peter MacCallum Cancer Center, Melbourne

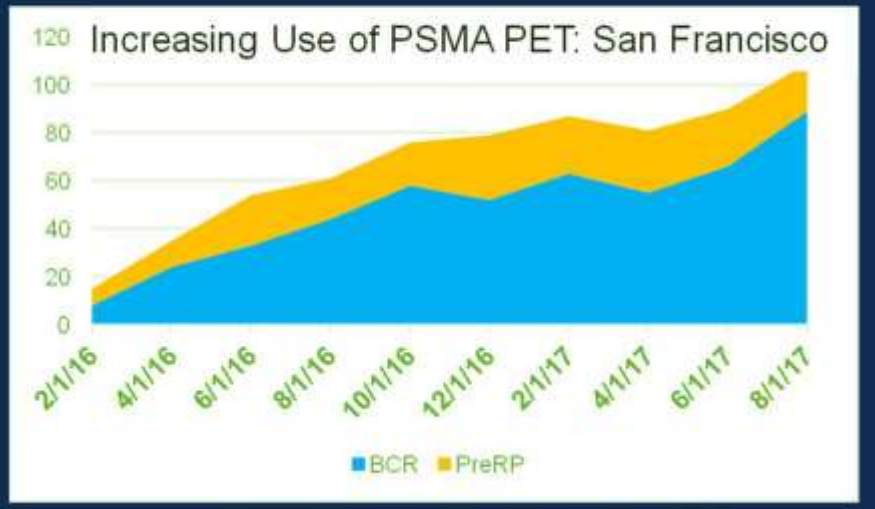


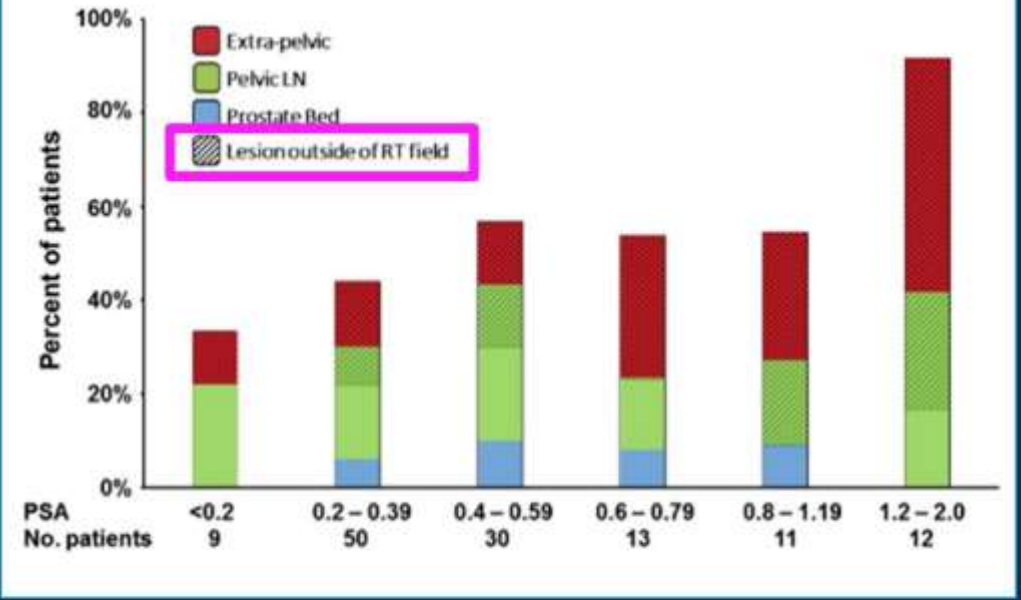
Figure courtesy of Thomas Hope, UC San Francisco

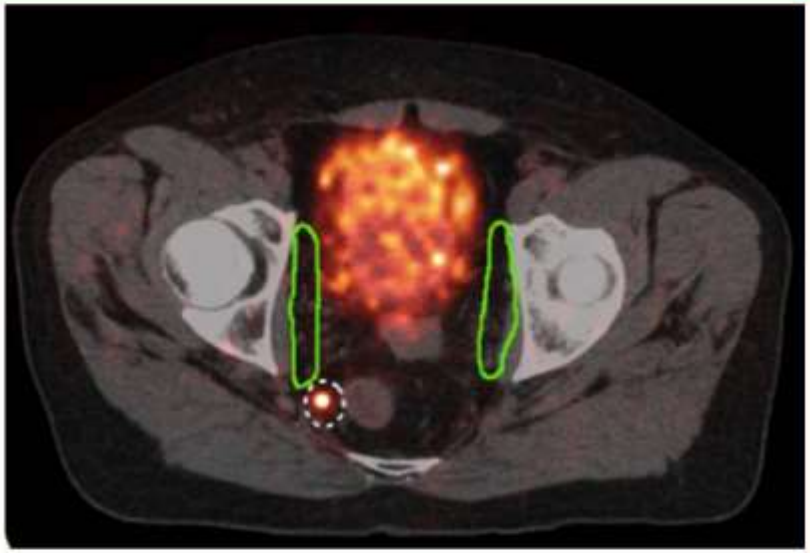
Axumin (fluciclovine F18) PET:

- Currently available at >800 imaging sites across the US
- FDA–approved for use in biochemical recurrence, reimbursed by Medicare and many private payers
- More than 28,000 patients have received Axumin PET imaging (P Gardiner, Blue Earth)

Presented by: Felix Feng, MD

Advanced PET Imaging Changes Clinical Decision-Making





Example of lymph node outside of radiation field

Boreta, Gadzinksi et al, *Urology*, in press

Presented by: Felix Feng, MD

Advanced PET Imaging: Achievements and Unanswered Questions

- Better detection of disease
- Changes in clinical management
- Definition of a "new" disease state – oligometastatic prostate cancer

- Does better detection of disease = improved outcomes?
- What is the clinical benefit of advanced PET imaging?
- What are the best approaches for treating oligometastatic disease?

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What Genomic Tests are Available Clinically?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations studied	Outcome Reported (Test independently predicts)	References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	Metastasis Prostate cancer-specific mortality		Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis Biochemical failure		
		Post RP, adjuvant or salvage radiotherapy	Metastasis		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	Metastasis		Not recommended
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
Oncotype DX	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non-organ-confined pT3 or Gleason grade 4 disease on RP		Cover post-biopsy for NCCN very-low- and low-risk prostate cancer at diagnosis with 10-20 years life expectancy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	Prostate cancer-specific mortality		Cover post-biopsy for NCCN very-low- and low-risk prostate cancer at diagnosis with at least 10 years life expectancy
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	Biochemical recurrence Metastasis		
		Biopsy, intermediate-risk treated with EBRT	Biochemical failure		
		RP, node-negative localized prostate cancer	Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non-organ-confined pT3 or Gleason pattern 4 disease on RP		Not reviewed
PTEN	Fluorescent in situ hybridization or IHC	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	Prostate cancer-specific mortality		Not recommended
		Biopsy, Gleason grade 3+3	Upgrading to Gleason pattern 4 at RP		
		RP, high risk localized disease	Biochemical recurrence		

→ Decipher primarily validated in post-operative or high-risk patients

→ Oncotype and Prolaris primarily validated in lower risk patients

All have been demonstrated to increase prognostic value when added to clinical features

CONCLUSION: IMAGING

- Can help define therapy in selected patients.
- Questions remain though on what the best approach is to the findings.
- Rapid evolution of the use of novel imaging with additional options in trials.

LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

Karim Fizazi,[1] NamPhuong Tran,[2] Luis Fein,[3] Nobuaki Matsubara,[4] Alfredo Rodriguez-Antolin,[5] Boris Y. Alekseev,[6] Mustafa Özgüroğlu,[7] Dingwei Ye,[8] Susan Feyerabend,[9] Andrew Protheroe,[10] Peter De Porre,[11] Thian Kheoh,[12] Youn C. Park,[13] Mary B. Todd,[14] Kim N. Chi,[15] on behalf of the LATITUDE Investigators

[1]Gustave Roussy, University of Paris Sud, Villejuif, France; [2]Janssen Research & Development, Los Angeles, CA; [3]Instituto de Oncologia de Rosário, Rosário, Argentina; [4]National Cancer Center Hospital East, Chiba, Japan; [5]12 de Octubre University Hospital, Madrid, Spain; [6]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; [7]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [8]Fudan University Shanghai Cancer Center, China; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [11]Janssen Research & Development, Beerse, Belgium; [12]Janssen Research & Development, San Diego, CA; [13]Janssen Research & Development, Raritan, NJ; [14]Janssen Global Services, Raritan, NJ; [15]BC Cancer Agency, Vancouver, BC, Canada

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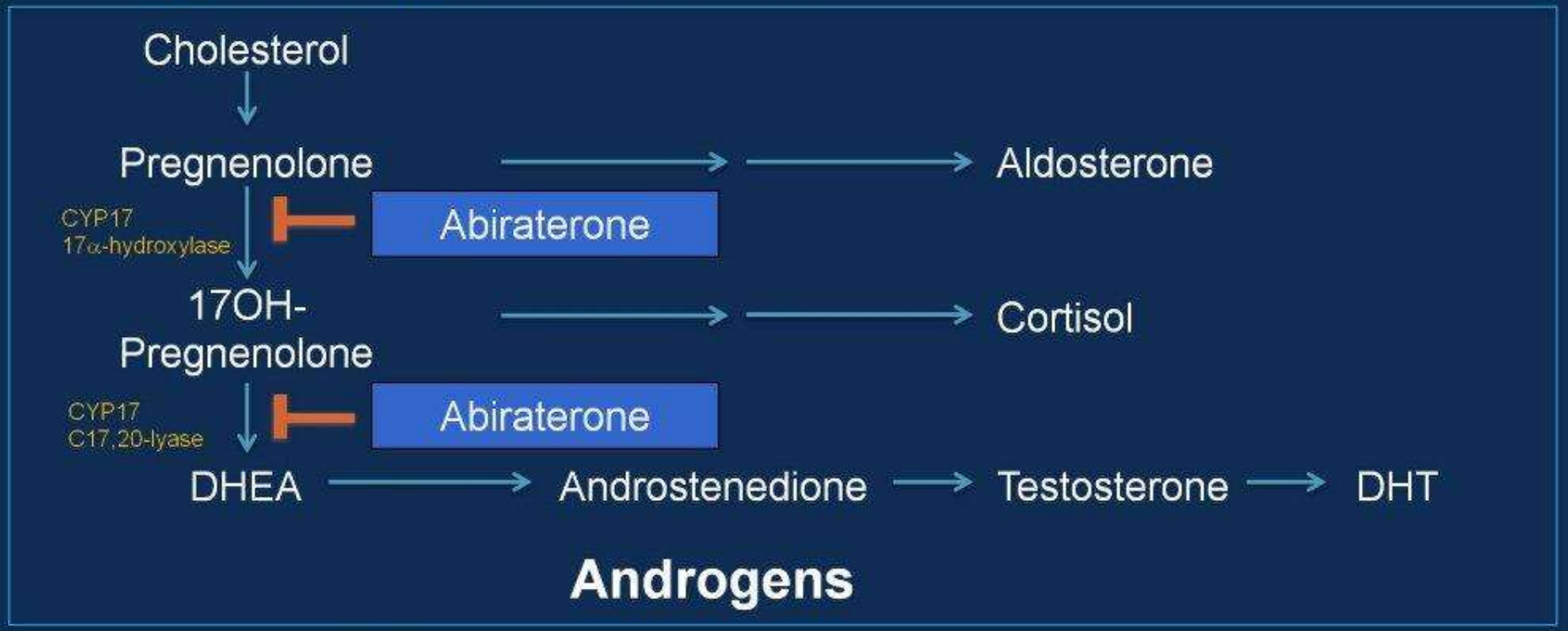
ADT + docetaxel: a new standard of care for men with mCNPC and high metastatic burden (2015)

Overall Survival	ADT + DOC	ADT		
	Median (mos)	Median (mos)	HR (95% CI)	*P* Value
GETUG-15[1]	62.1	48.6	0.88 (0.68-1.14)	0.3
CHAARTED[2]	57.6	47.2	0.73 (0.59-0.89)	0.0018
STAMPEDE[3]	60	45	0.76 (0.62-0.92)	0.005

1. Gravis G, et al. *Eur Urol*. 2016;70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-746; Sweeney C, et al. *Ann Oncol*. 2016;27(Suppl 6):243-265. 3. James N, et al. *Lancet*. 2016;387:1163-1177. and Vale C, et al. *Lancet Oncol* 2016;17:243-256.

Abiraterone mechanism of action: androgen biosynthesis inhibitor



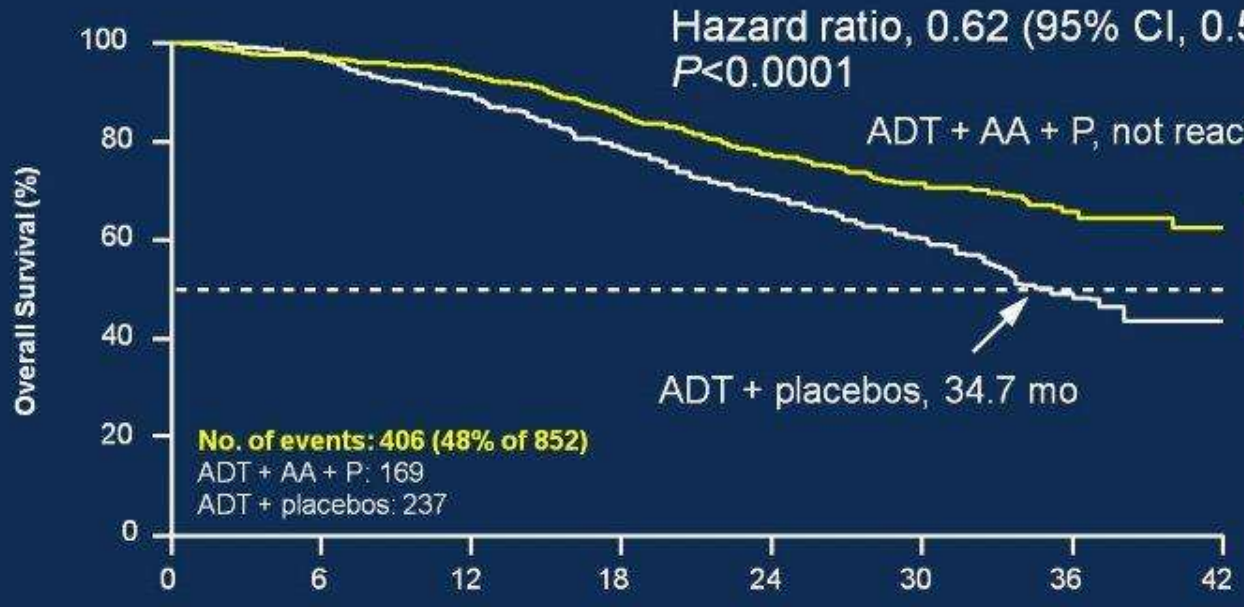
Rationale for AA + P added to ADT in mCNPC

- Mechanisms of resistance to ADT may develop early[1-3]
- ADT alone does not inhibit androgen synthesis by:
  - adrenal
  - prostatic cancer cells
- AA + P:
  - improves OS in mCRPC[4,5]
  - reduces tumor burden in high-risk, localized PC[6,7]

- These data suggest a potential role for inhibiting extragonadal androgen biosynthesis ***prior to the emergence of castration resistance***

1. Gravis G, et al. *Eur Urol*. 2018;70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-746. 3. James N, et al. *Lancet*. 2016;387:1163-1177. 4. de Bono JS, et al. *N Engl J Med*. 2011;364:1995-2005. 5. Ryan CJ, et al. *Lancet Oncol*. 2015;16:152-160. 6. Taplin ME, et al. *J Clin Oncol*. 2014;32:3705-3715. 7. Efstathiou E, et al. *J Clin Oncol*. 2015;33(suppl):15s. Abstract 5061

Statistically significant 38% risk reduction of death

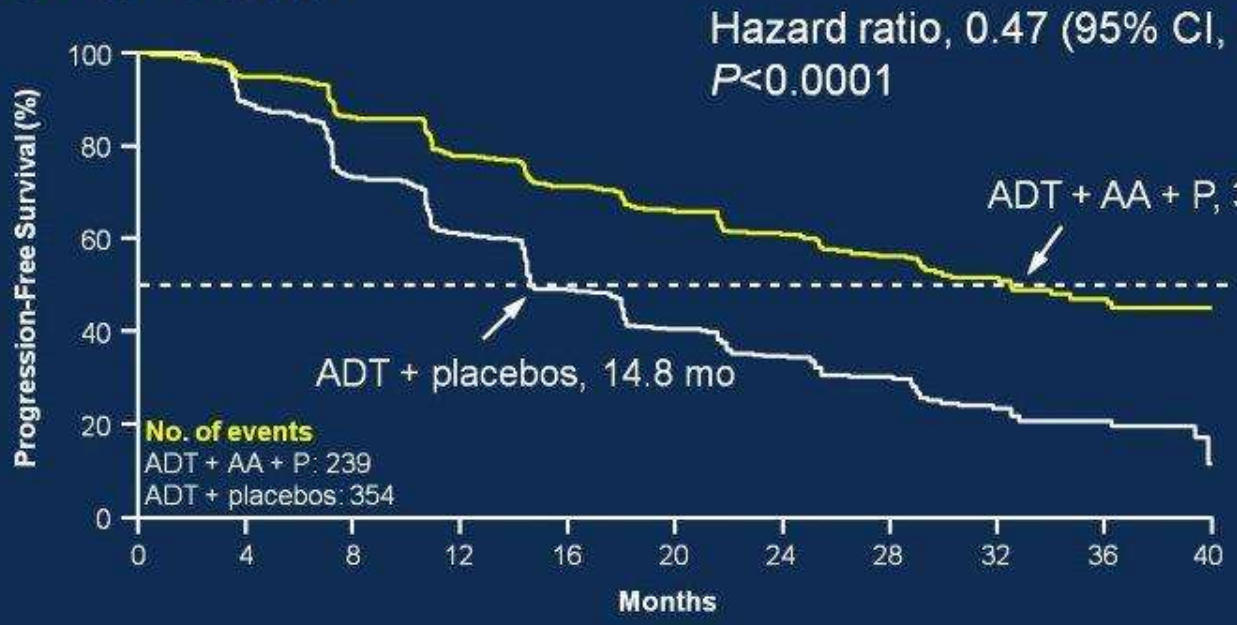


OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

Median follow-up: 30.4 months

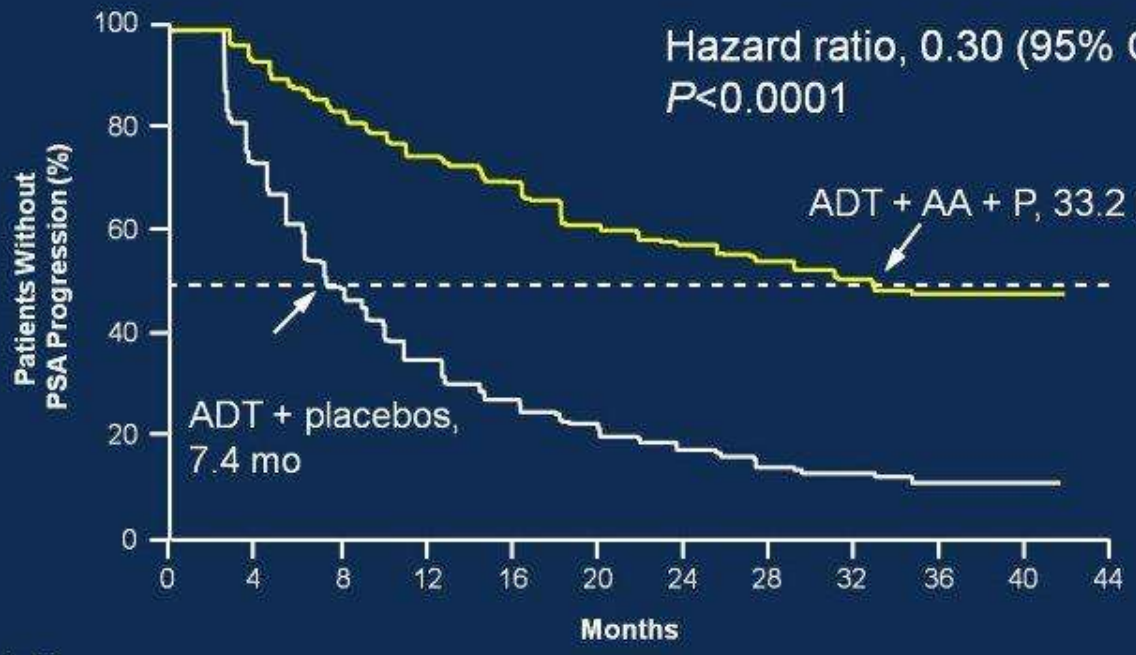
No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

Statistically significant 53% risk reduction of radiographic progression or death



No. at risk											
ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + placebos	602	488	367	289	214	168	127	81	41	17	7

Statistically significant 70% risk reduction of time to PSA progression



No. at risk												
ADT + AA + P	597	520	447	379	340	285	227	162	95	48	18	0
ADT + placebos	602	393	250	172	129	102	65	33	19	8	5	0

Subsequent life-prolonging therapy for prostate cancer

	ADT + AA + P (n = 597)	ADT + placebos (n = 602)
	n (%)	n (%)
Patients eligible*	n = 314 (53%)	n = 469 (78%)
Patients who received life-prolonging therapy	125 (40)	246 (52)
Docetaxel	106 (34)	187 (40)
Enzalutamide	30 (10)	76 (16)
AA-P	10 (3)	53 (11)
Cabazitaxel	11 (4)	30 (6)
Radium-223	11 (4)	27 (6)

*Patients who discontinued treatment and were eligible for subsequent therapy.

MRC Clinical Trials Unit

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UCL

Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

Nicholas James
University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

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Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

All patients

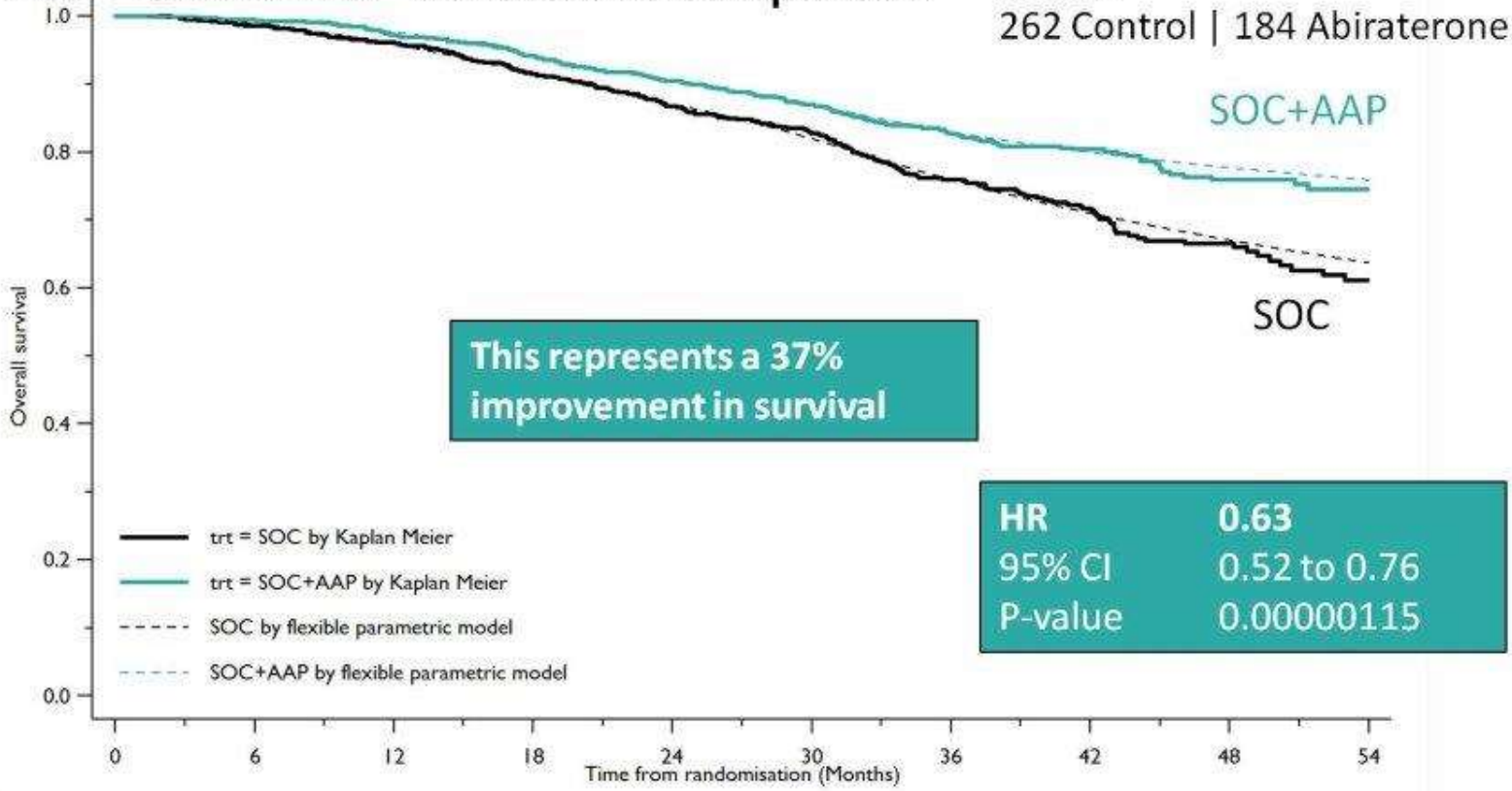
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

Overall Survival – STAMPEDE "abiraterone comparison"

Events
262 Control | 184 Abiraterone



This represents a 37% improvement in survival

HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.00000115

Number of patients (events)

SOC	957	(37)	909	(88)	806	(92)	491	(36)	123
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161

	SOC-only	SOC+AAP
Safety population		
Patients included in adverse event analysis	960	948
Grade 1-5 AE	950 (99%)	943 (99%)
Grade 3-5 AE	315 (33%)	443 (47%)
Grade 5 AE	3	9
Grade 3-5 AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	133 (14%)	129 (14%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):	41 (4%)	92 (10%)
Musculoskeletal disorder:	46 (5%)	68 (7%)
Gastrointestinal disorder:	40 (4%)	49 (5%)
Hepatic disorder (*incl. increased AST, increased ALT*):	12 (1%)	70 (7%)
General disorder (*incl. fatigue, oedema*):	29 (3%)	45 (5%)
Respiratory disorder (*incl. breathlessness*):	23 (2%)	44 (5%)
Lab abnormalities (*incl. hypokalaemia*):	21 (2%)	34 (4%)

Conclusions

- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  - Overall survival by 37%
  - Failure free survival by 71%
  - Symptomatic skeletal events by 55%
- **Treatment was well tolerated**
- Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy

Phase 3 study of androgen deprivation therapy with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer: the ARCHES trial

Andrew J. Armstrong,[1] Russell Szmulewitz,[2] Daniel Petrylak,[3] Arnauld Villers,[4] Arun Azad,[5,*] Antonio Alcaraz,[6] Boris Alekseev,[7] Taro Iguchi,[8] Neal D. Shore,[9] Brad Rosbrook,[10] Jennifer Sugg,[11] Benoit Baron,[12,†] Lucy Chen,[11] Arnulf Stenzl[13]

[1]Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC; [2]The University of Chicago, Chicago, IL; [3]Yale Cancer Center, New Haven, CT; [4]University Hospital Centre, Lille University, Lille, France; [5]Monash Health, Melbourne, Victoria, Australia; [6]Hospital Clinic de Barcelona, Barcelona, Spain; [7]Hertzen Moscow Cancer Research Institute, Moscow, Russia; [8]Osaka City University Graduate School of Medicine, Osaka, Japan; [9]Carolina Urologic Research Center, Myrtle Beach, SC; [10]Pfizer Inc., San Diego, CA; [11]Astellas Pharma Inc., Northbrook, IL; [12]Astellas Pharma Inc., Leiden, the Netherlands; [13]Department of Urology, University Hospital, Eberhard Karls University, Tübingen, Germany

*Current affiliation: Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
†Current affiliation: B-value, Leiden, the Netherlands

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Presented by: Andrew J. Armstrong, MD

Background

- Enzalutamide, a potent androgen receptor inhibitor, has demonstrated clinical benefit in men with metastatic and nonmetastatic CRPC[1-5]
- Here we report the results of the ARCHES* trial, which assessed the efficacy and safety of enzalutamide in combination with ADT in men with mHSPC
- ARCHES included patients with both low and high volume disease (CHAARTED criteria),[6] with and without prior docetaxel treatment

Hypothesis

- Enzalutamide, in combination with ADT, would prolong radiographic progression-free survival (rPFS) in men with mHSPC, compared to ADT alone

*Androgen Receptor Inhibition with CHemohormonal Therapy in Men with Metastatic Hormone-Sensitive Prostate Cancer (ARCHES)

1. Beer TM et al. N Engl J Med 2014;371:424–433; 2. Scher HI et al. N Engl J Med 2012;367:1187–1197; 3. Shore N et al. Lancet Oncol 2016;17:153–163; 4. Penson DF et al. J Clin Oncol 2016;34:2098–2106; 5. Hussain M et al. N Engl J Med 2018;378:2465–2474; 6. Sweeney CJ et al. N Engl J Med 2015;373:737–746

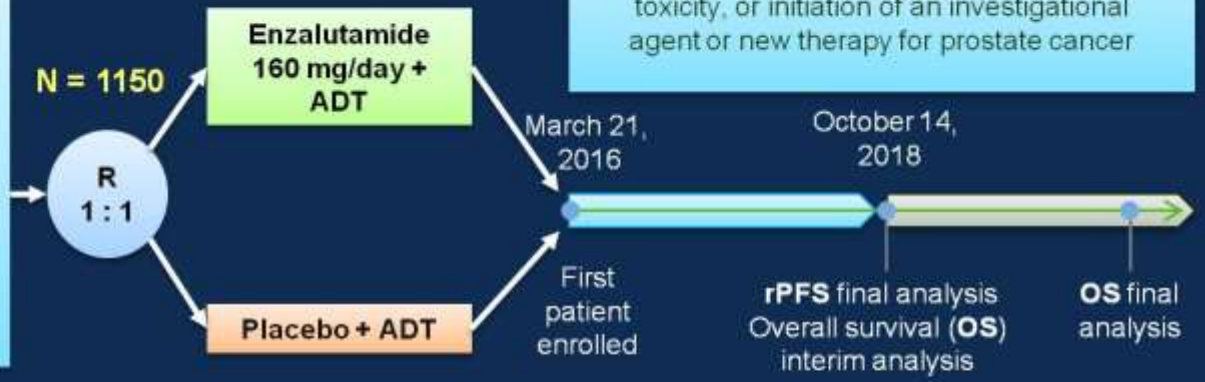
ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

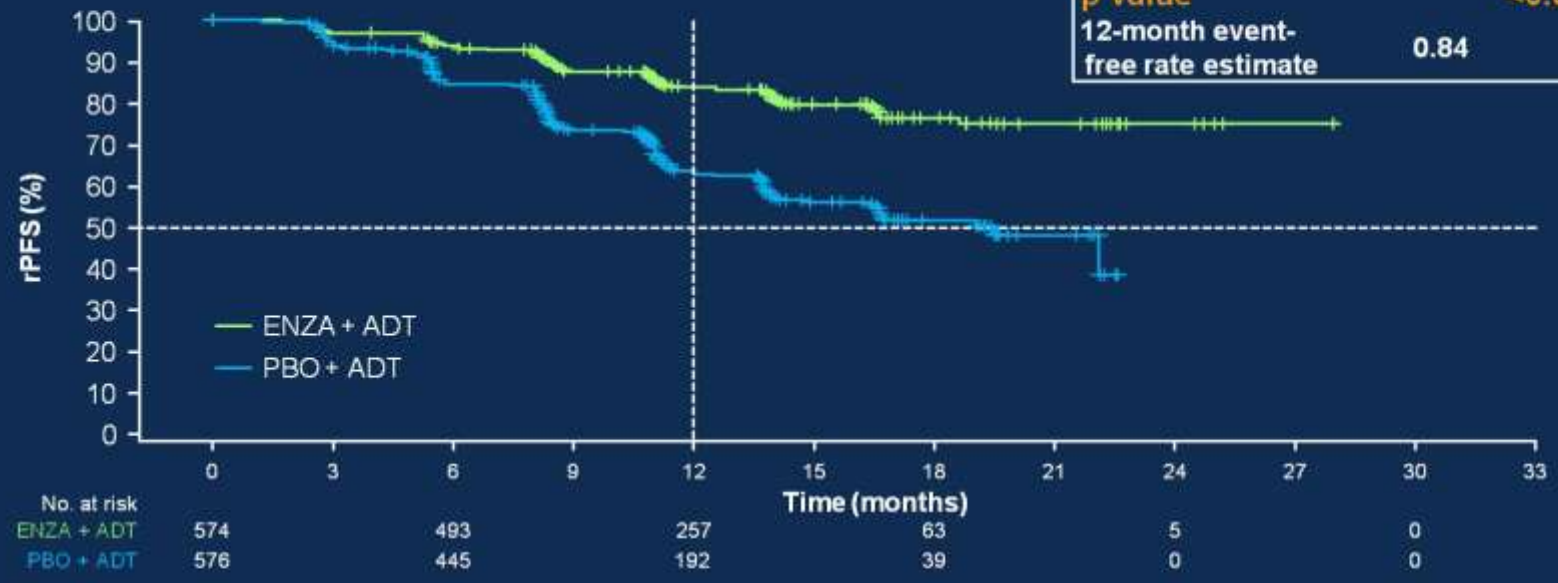
Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

Primary endpoint: rPFS

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64

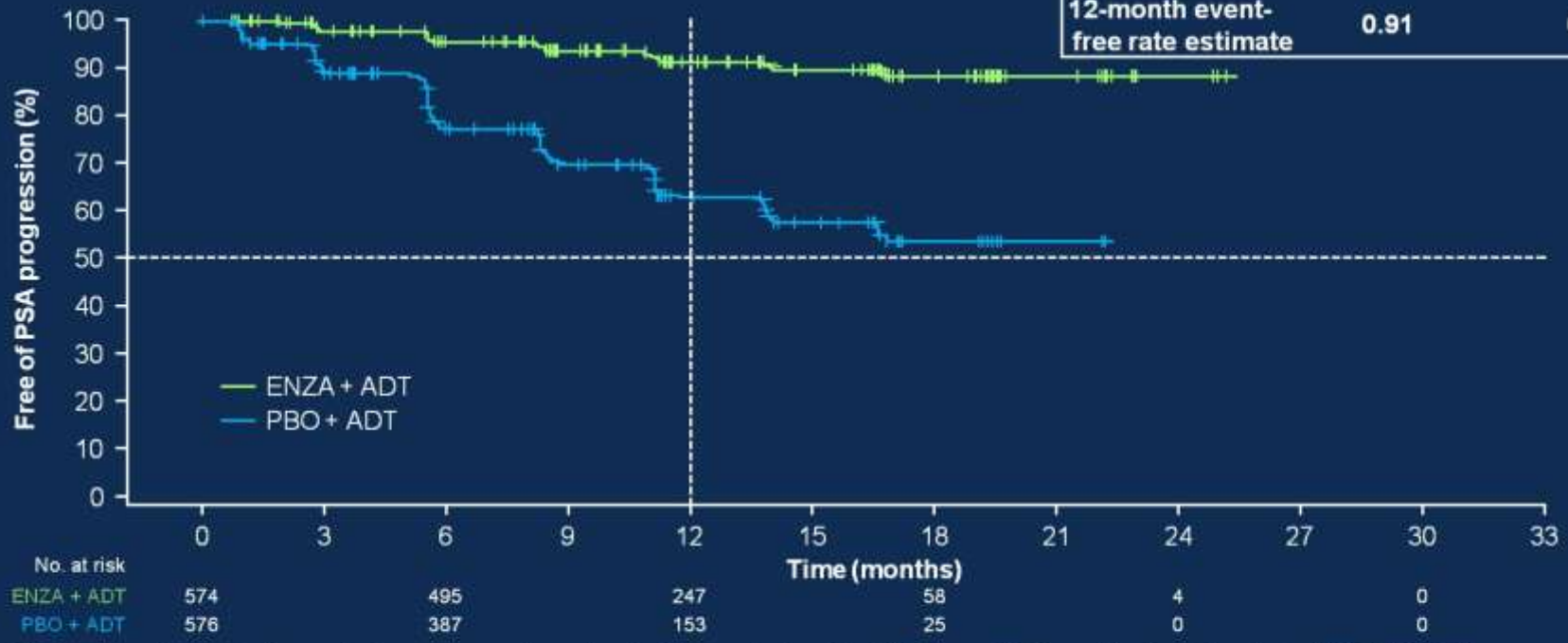


No. at risk						
ENZA + ADT	574	493	257	63	5	0
PBO + ADT	576	445	192	39	0	0

- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

Time to PSA progression

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	NR (16.59, NR)
HR (95% CI)	0.19 (0.13, 0.26)	
p value	<0.0001	
12-month event-free rate estimate	0.91	0.63



No. at risk						
ENZA + ADT	574	495	247	58	4	0
PBO + ADT	576	387	153	25	0	0

- Median time to castration resistance was not reached with enzalutamide + ADT, vs. 13.9 months for placebo + ADT (HR 0.28; 95% CI 0.22, 0.36; p<0.0001)

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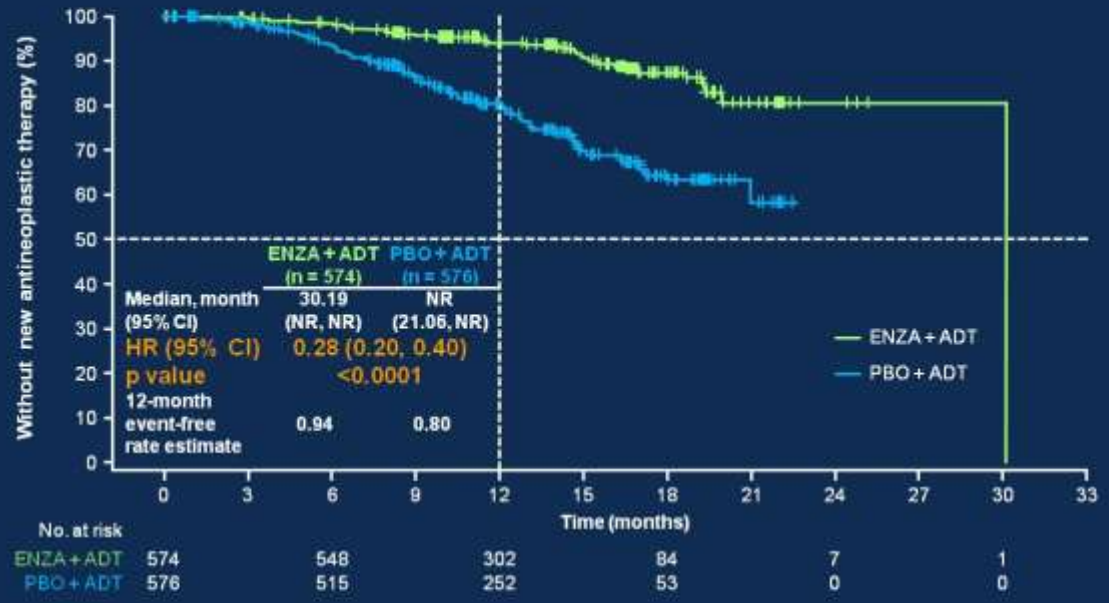
PSA undetectable rate and objective response rate

Event, n (%)	Enzalutamide + ADT	Placebo + ADT	Rate difference, % (95% CI)	p-value
PSA undetectable rate				
Detectable PSA at baseline, n	511	506		
Undetectable PSA (<0.2 ng/mL) rate, % (95% CI)	68.1 (63.9, 72.1)	17.6 (14.4, 21.2)	50.5 (45.3, 55.7)	<0.0001
Best overall response				
Measurable soft tissue disease at baseline, n	177	182		
Objective response rate,* % (95% CI)	83.1 (76.7, 88.3)	63.7 (56.3, 70.7)	19.3 (10.4, 28.2)	<0.0001
Complete response, %	36.7	23.1		
Partial response, %	46.3	40.7		

- Enzalutamide + ADT significantly increased the PSA undetectable rate and the objective response rate compared to placebo + ADT

*Complete or partial response using RECIST 1.1

Time to initiation of new antineoplastic therapy



First new antineoplastic prostate cancer therapy	Enzalutamide + ADT	Placebo + ADT
Overall, n	46	133
Docetaxel, n (%)	11 (24)	52 (39)
Abiraterone, n (%)	13 (28)	28 (21)
Enzalutamide, n (%)	4 (9)	28 (21)
Bicalutamide, n (%)	4 (9)	12 (9)
Other, n (%)	14 (30)	15 (11)

- Enzalutamide + ADT significantly reduced the risk of starting a new antineoplastic therapy by 72% compared to placebo + ADT; median for the enzalutamide + ADT group is not a reliable estimate as it resulted from an event observed in the only remaining patient at risk at approximately 30 months, leading to the vertical drop at the end of the Kaplan-Meier curve
- Docetaxel, followed by abiraterone, was the most common first new antineoplastic prostate cancer therapy

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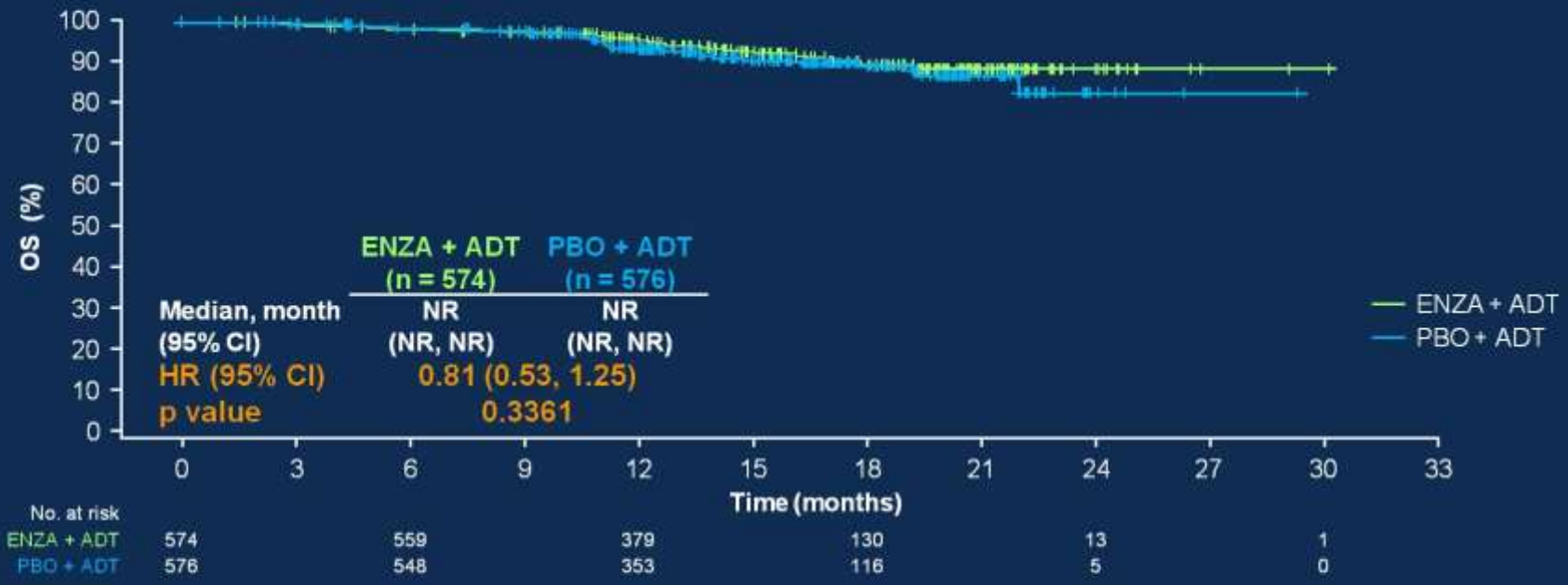
Overall survival: interim analysis (84 deaths)



- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo plus ADT, 45) and 19% reduction in risk of death that is not statistically significant
- Final OS analysis will be conducted with ~342 deaths at 4% significance level

Conclusions

- In men with mHSPC, the addition of enzalutamide to ADT significantly prolonged rPFS, with a 61% reduction in the risk of radiographic progression or death (HR 0.39; p<0.0001)
- Significant benefits in rPFS, ranging from 47–80% reduction, were seen across all pre-specified subgroups including:
  - Low and high disease volume
  - With or without prior docetaxel therapy
- Secondary endpoints (time to PSA progression, time to first use of new antineoplastic therapy, PSA undetectable rate, and objective response rate) were also significantly improved with enzalutamide + ADT compared with placebo + ADT, without significantly impacting time to deterioration in urinary symptoms and FACT-P total score

Updated Analysis of Progression-Free Survival With First Subsequent Therapy and Safety in the SPARTAN Study of Apalutamide in Patients With High-Risk Nonmetastatic Castration-Resistant Prostate Cancer

Eric J. Small,[1] Fred Saad,[2] Simon Chowdhury,[3] Stéphane Oudard,[4] Boris A. Hadaschik,[5] Julie N. Graff,[6] David Olmos,[7] Paul N. Mainwaring,[8] Ji Youl Lee,[9] Hiroji Uemura,[10] Angela Lopez-Gitlitz,[11] Byron M. Espina,[11] Youyi Shu,[12] Wayne R. Rackoff,[11] Brendan Rooney,[13] Anil Londhe,[14] Shinta Cheng,[15] Matthew R. Smith[16]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Québec, Canada; [3]Guy's, King's and St. Thomas' Hospitals, Great Maze Pond, London, UK; [4]Georges Pompidou Hospital, Paris, France; [5]University of Duisburg-Essen, Essen, Germany and Ruprecht-Karls-University, Heidelberg, Germany; [6]VA Portland Health Care System, Portland and Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [7]Spanish National Cancer Research Centre (CNIO), Madrid and Hospitales Universitarios Virgen de la Victoria y Regional de Málaga, Málaga, Spain; [8]Centre for Personalized Nanomedicine, University of Queensland, Brisbane, Australia; [9]St. Mary's Hospital of Catholic University, Seoul, South Korea; [10]Yokohama City University Medical Center, Yokohama, Japan; [11]Janssen Research & Development, Los Angeles, CA; [12]Janssen Research & Development, Spring House, PA; [13]Janssen Research & Development, High Wycombe, UK; [14]Janssen Research & Development, Yardley, PA; [15]Janssen Research & Development, Raritan, NJ; [16]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

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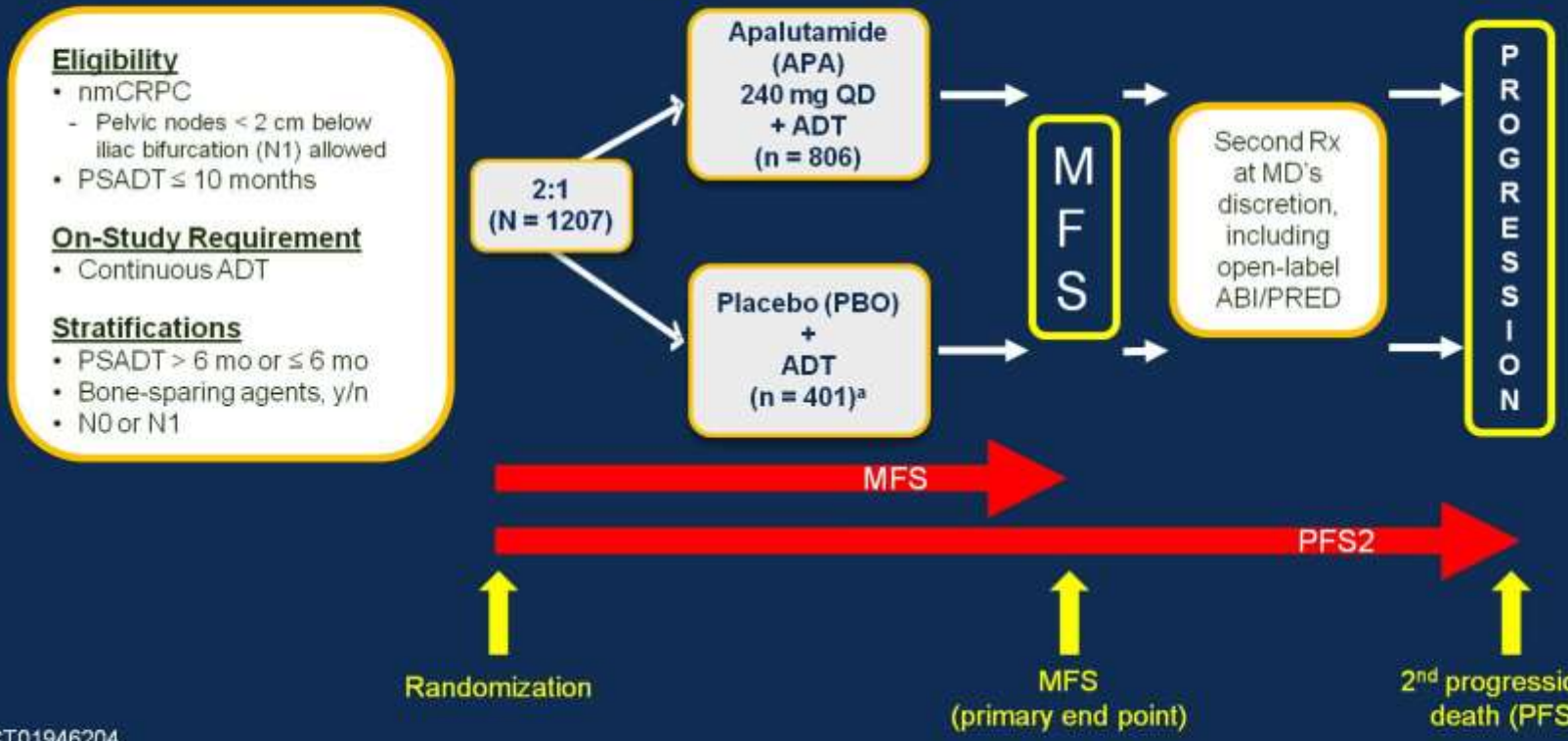
SPARTAN – Randomized, Phase 3, Placebo-Controlled Trial



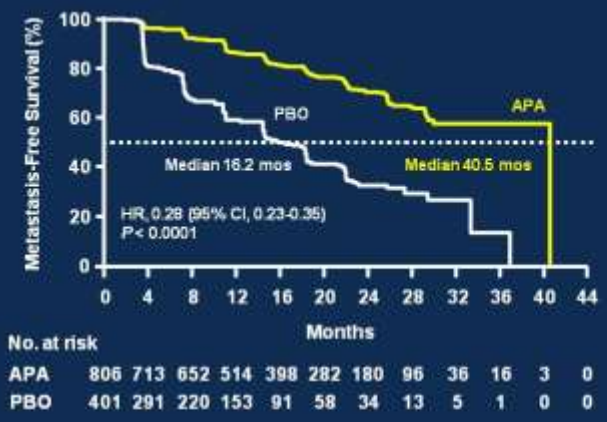
NCT01946204

ABI/PRED, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSADT prostate-specific antigen doubling time; Rx, treatment; QD, daily.

[a]Patients from the PBO group who did not have disease progression at the time of unblinding were allowed to cross over to APA treatment.

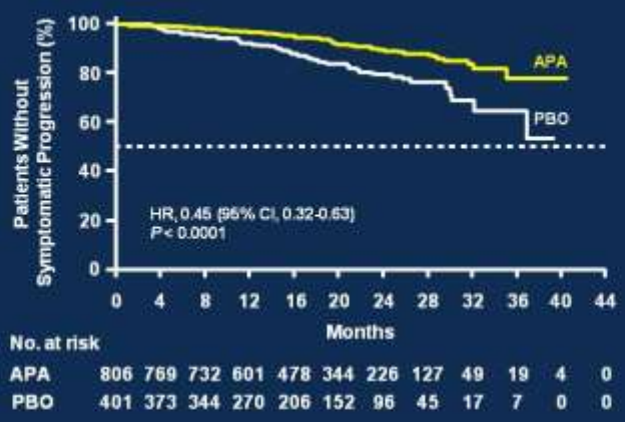
Background: Significant Improvement With APA vs PBO

Primary End Point: Metastasis-Free Survival



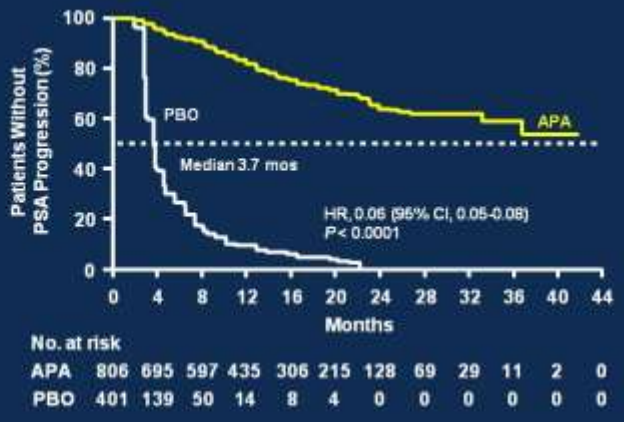
No. at risk												
APA	806	713	652	514	398	282	180	96	36	16	3	0
PBO	401	291	220	153	91	58	34	13	5	1	0	0

Secondary End Point: Time to Symptomatic Progression



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

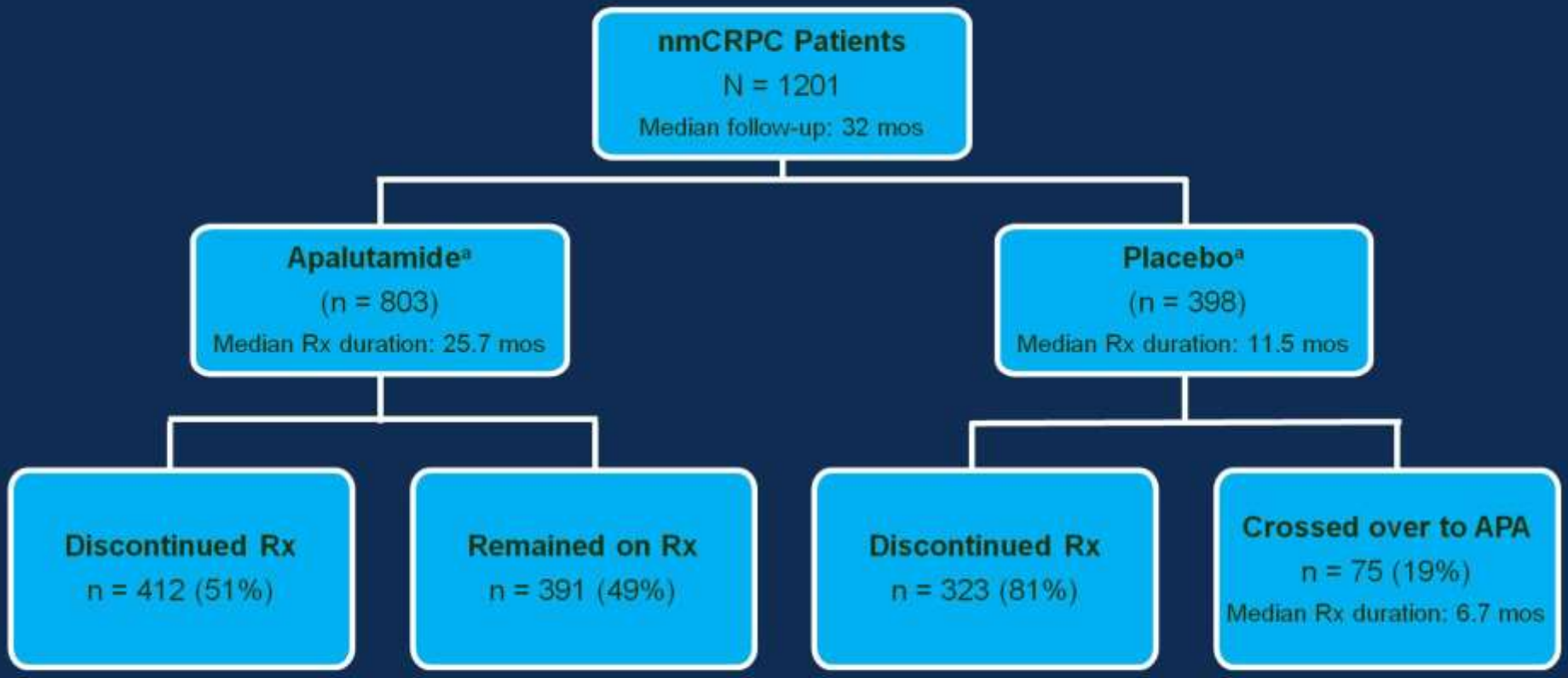
Exploratory End Point: Time to PSA Progression



No. at risk												
APA	806	695	597	435	306	215	128	69	29	11	2	0
PBO	401	139	50	14	8	4	0	0	0	0	0	0

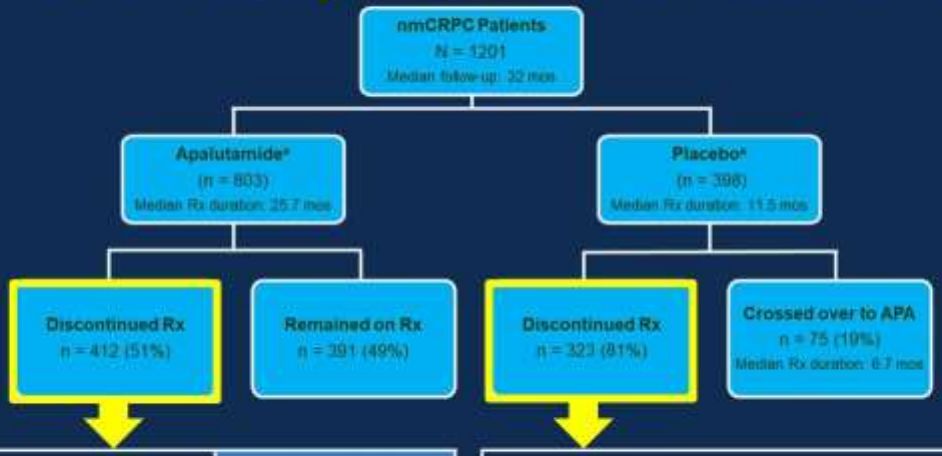
CI, confidence interval; HR, hazard ratio.

Results: Patient Disposition (1 Year Later – Clinical Cutoff, May 17, 2018)



[a]All patients received ADT during treatment.

Results: Reasons for Study Treatment Discontinuation



Discontinued APA	n = 412
Progressive disease	219 (53%)
Adverse event	102 (25%)
Withdrawal by patient	66 (16%)
Other[b]	25 (6.1%)

Discontinued PBO	n = 323
Progressive disease	237 (73%)
Adverse event	27 (8.4%)
Withdrawal by patient	49 (15%)
Other[b]	7 (2.2%)
Lost to follow-up	2 (0.6%)

[a]All patients received ADT during treatment. [b]Other includes protocol violations.

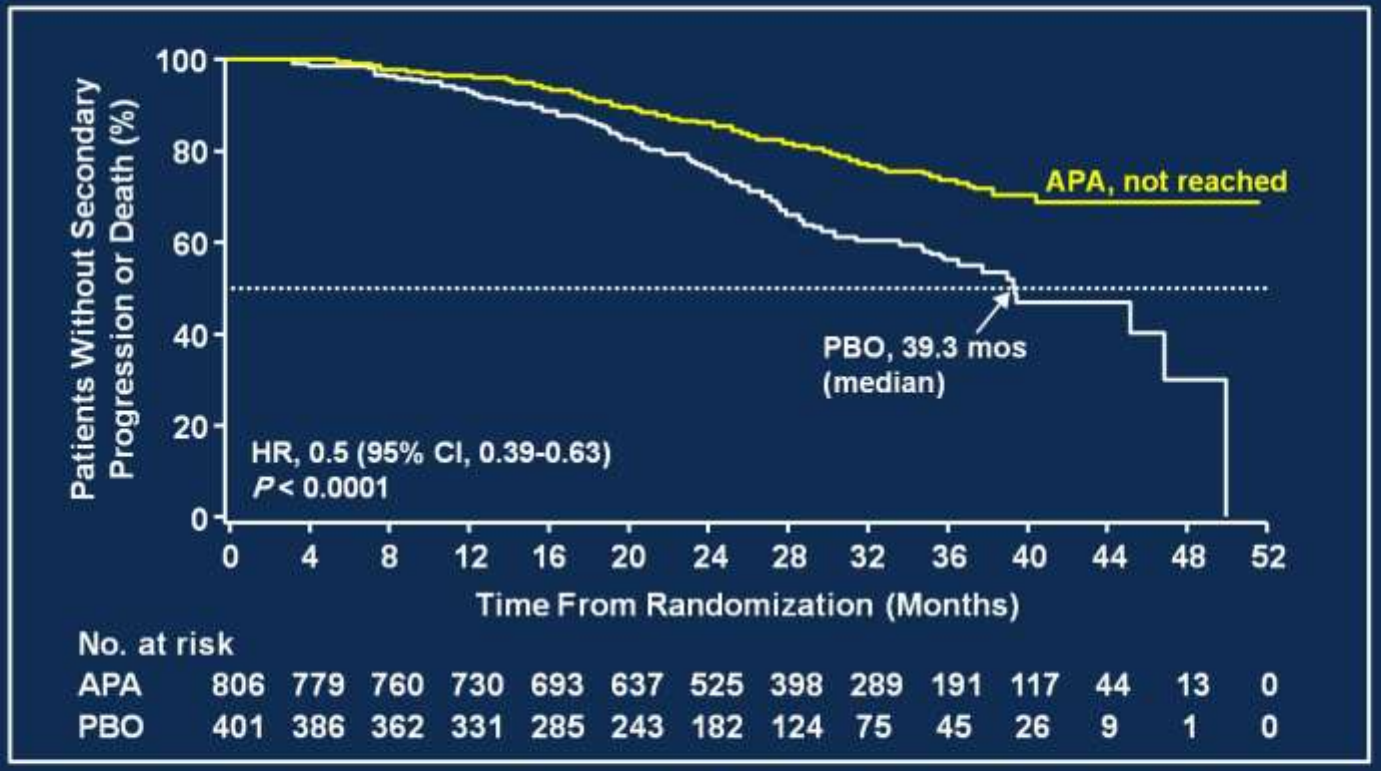
Results: Subsequent Treatment

Patients, n (%)	APA (n = 803)	PBO (n = 398)
Discontinued study treatment	412 (51)	323 (81)
Received systemic therapy for prostate cancer	249 (60)[a]	255 (79)
First subsequent treatment		
Abiraterone acetate plus prednisone	183 (44)	188 (58)
Enzalutamide	27 (6.6)	33 (10)
Docetaxel	20 (4.9)	18 (5.6)
Cabazitaxel	0	1 (0.3)
Sipuleucel-T	6 (1.5)	9 (2.8)
Radium-223	1 (0.2)	0

- 249/412 (60%) of APA patients and 255/323 (79%) of PBO patients who discontinued received FDA-approved treatment for mCRPC

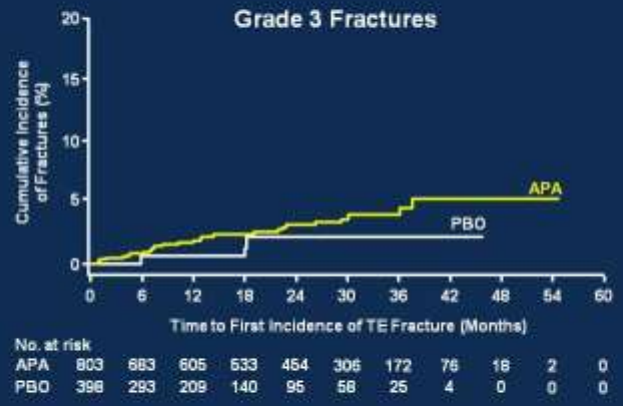
[a]One patient who discontinued APA treatment received an investigational drug.

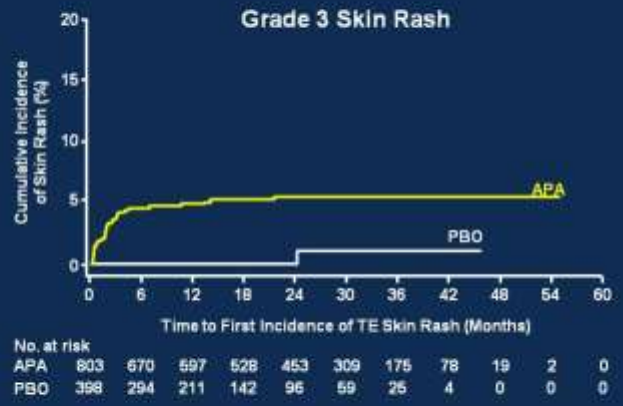
Results: APA Continues to Result in PFS2 Improvement

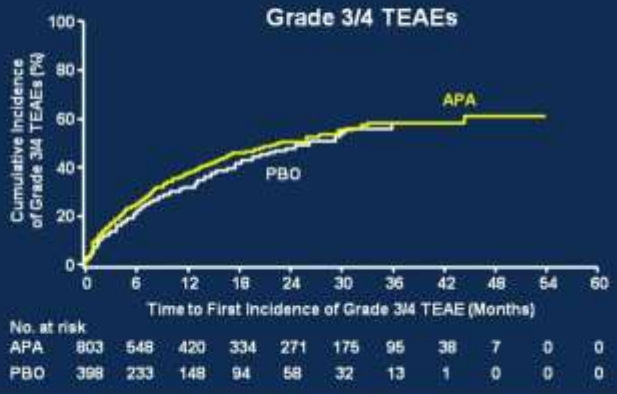


Median time to PFS2 was not reached (APA) vs 39.3 months (PBO); $P < 0.0001$

Results: Cumulative Incidence Plots







Conclusions

With 1 year of additional follow-up on SPARTAN:

- The median treatment duration for patients randomized to APA was 25.7 months, with nearly half (49%) remaining on treatment
- The majority of patients received FDA-approved therapy for mCRPC upon development of metastatic disease
- Treatment with APA prior to the development of metastases continues to result in an improvement in PFS2, with a 50% reduction in risk of secondary progression or death, suggesting that initiating therapy early may be more effective than waiting until metastases develop
- The safety profile of APA remains unchanged, with no increase in cumulative toxicity
- Patients continue to be followed for overall survival

KEYNOTE-365 Cohort A: Pembrolizumab Plus Olaparib in Docetaxel-Pretreated Patients With Metastatic Castrate-Resistant Prostate Cancer

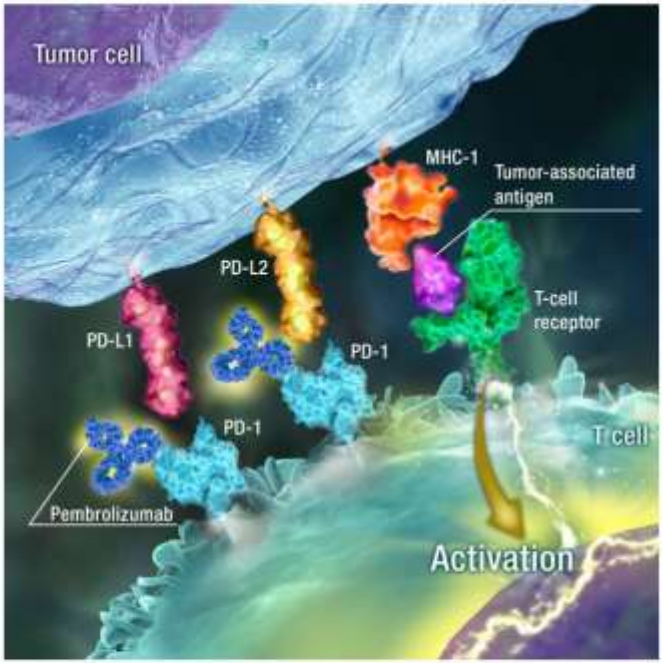
E. Y. Yu[1]; C. Massard[2]; M. Retz[3]; A. Tafreshi[4]; J. Carles[5]; P. Hammerer[6]; P. Fong[7]; N. Shore[8]; A. Joshua[9]; M. Linch[10]; H. Gurney[11]; E. Romano[12]; M. Augustin[13]; J. Piulats[14]; H. Wu[15]; C. Schloss[15]; C. Poehlein[15]; J. De Bono[16]

[1]University of Washington, Seattle, WA; [2]Gustave Roussy Cancer Campus and Université Paris-Sud, Villejuif, France; [3]Rechts der Isar University Hospital, Technical University of Munich, Munich, Germany; [4]University of Wollongong, Wollongong, NSW, Australia; [5]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Academic Hospital Braunschweig, Braunschweig, Germany; [7]Auckland City Hospital, Auckland, New Zealand; [8]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [9]Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; [10]University College London Cancer Institute, London, United Kingdom; [11]Macquarie University Hospital, Sydney, NSW, Australia; [12]Institut Curie, Paris, France; [13]Klinikum Nürnberg, Nürnberg, Germany; [14]Catalan Cancer Institute, Barcelona, Spain; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]The Royal Marsden, London, United Kingdom

Presented By Evan Yu at 2019 Genitourinary Cancers Symposium

Pembrolizumab and Olaparib in Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

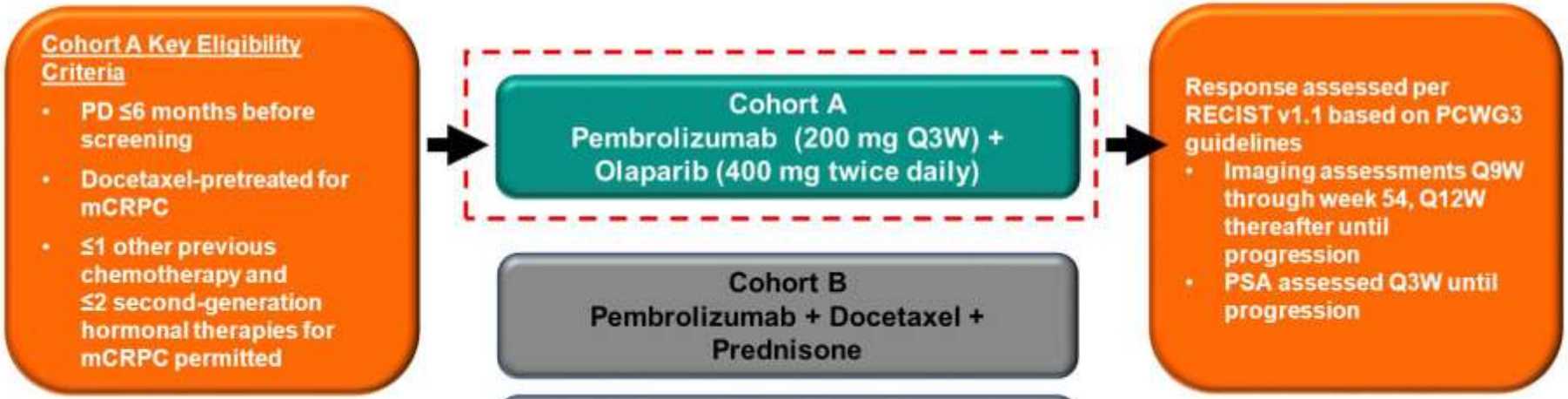
- Pembrolizumab, a PD-1 inhibitor, has shown activity in docetaxel-resistant mCRPC and in heavily pretreated, PD-L1–positive advanced prostate cancer[1-3]
- KEYNOTE-199
  - Assessed single-agent pembrolizumab in mCRPC with previous docetaxel-based chemotherapy
  - Objective responses observed in a heavily pretreated population; DCR ≥6 months, 11%[2]
- Olaparib was found to have antitumor activity as monotherapy in previously treated mCRPC[4]
  - 14/16 (88%) HRD patients responded
  - 2/33 (6%) HRP patients responded
- KEYNOTE-365
  - Assessed pembrolizumab combination therapies in mCRPC



HRD, homologous recombination deficient; HRP, homologous recombination proficient.

1. Merck Sharp & Dohme Corp., KEYTRUDA® (pembrolizumab) injection, for intravenous use. Whitehouse Station, NJ USA; 11/2018. 2. De Bono et al. *J Clin Oncol*. 2018;36:5007. 3. Hansen AR et al. *Ann Oncol*. 2018;29:1807-1813. 4. Mateo J et al. *N Engl J Med*. 2015;373:1697-1708.

KEYNOTE-365 Study Design (NCT02861573)



End Points

- **Primary:** Safety and PSA response rate (confirmed PSA decrease ≥50%)
- **Secondary:** Time to PSA progression, ORR, DCR, CRR, rPFS, and OS

Database cutoff: July 27, 2018.

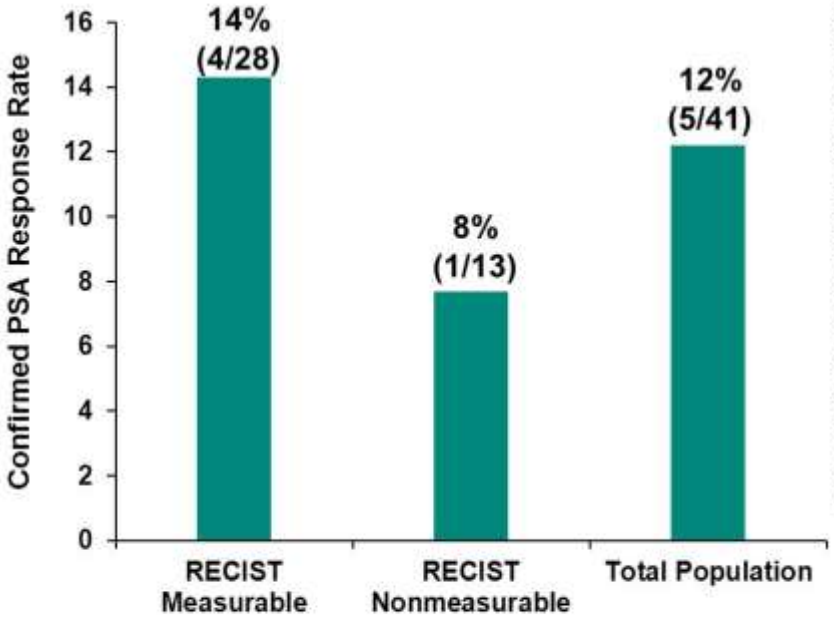
Exploratory HRD Analysis

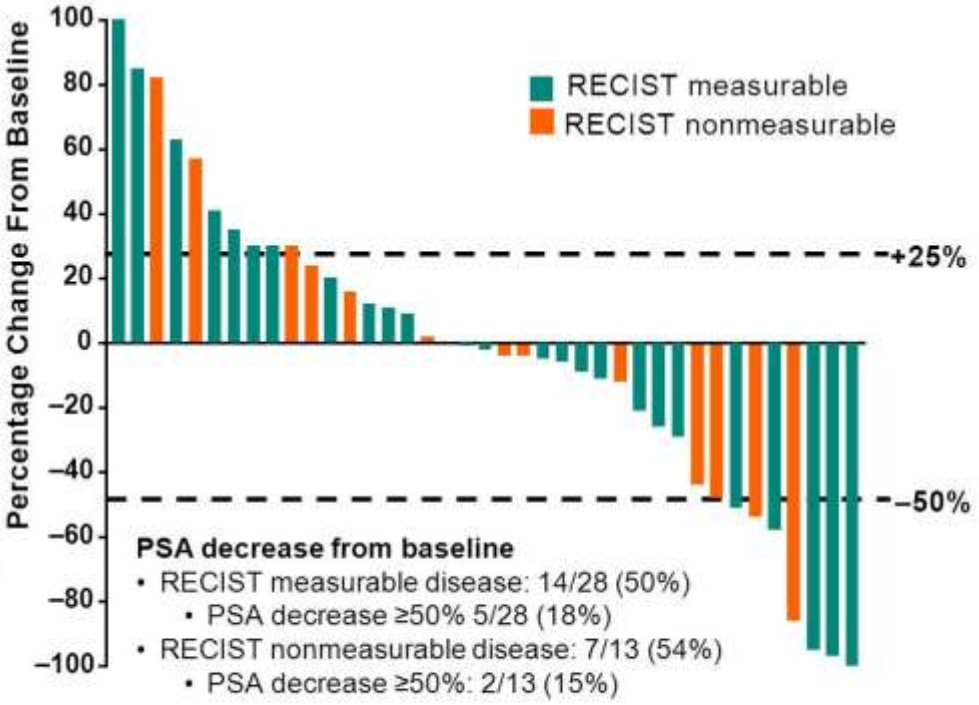
- Conducted for baseline samples of all patients, using Guardant360 ctDNA panel
  - Includes *BRCA1/2* and partial *ATM* genes
- Formalin-fixed, paraffin-embedded tissue was analyzed with WES[a]
  - Genes evaluated: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*

	Pembrolizumab + Olaparib N = 41
Guardant360 ctDNA panel, n	
Patients with detectable ctDNA	37
HRP	36
ATM R3008H mutation[b]	1
WES analysis, n	
Soft tissue available for analysis	17
Qualified WES results	12
HRP	11
BRIP1 frameshift mutation[c]	1

[a]WES depth: ~100-150X. Results not validated for copy number estimation and data presented only reflects somatic mutations.
[b]Very low AF (0.16%), suggesting possible false-positive, somatic mutation. However, WES data were not available to confirm.
[c]Biallelic status not determined.

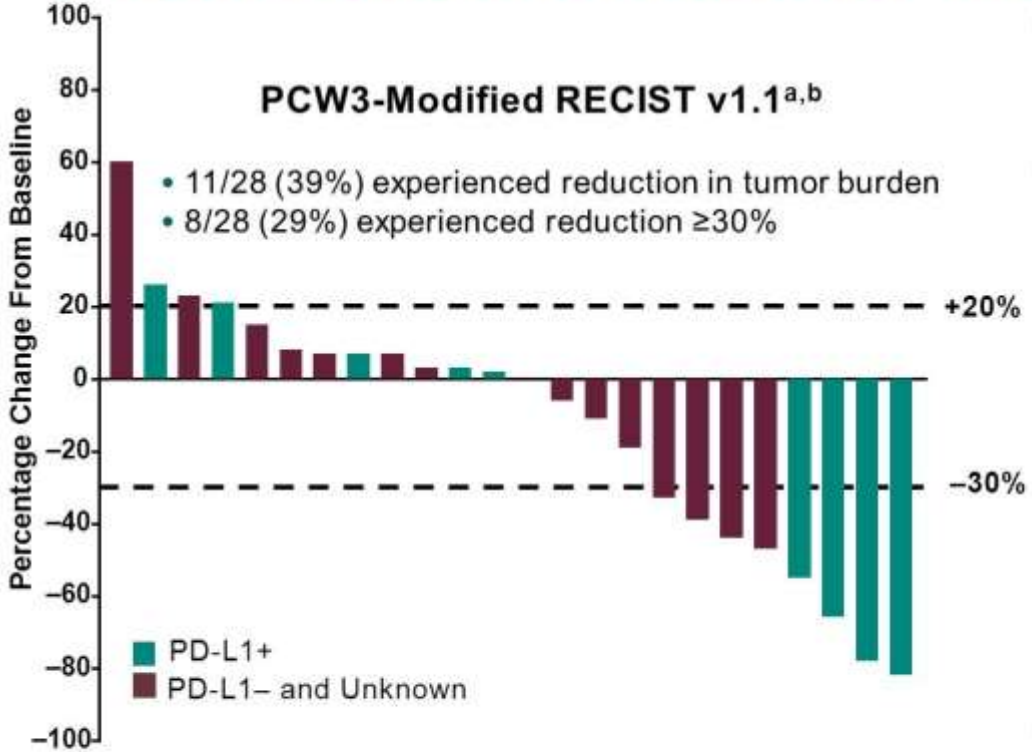
Confirmed PSA Response Rate and Percentage Change From Baseline[a]





[a]Patients who had a baseline and postbaseline PSA assessment (n = 39). Includes confirmed and unconfirmed PSA decreases from baseline.
Database cutoff: July 27, 2018.

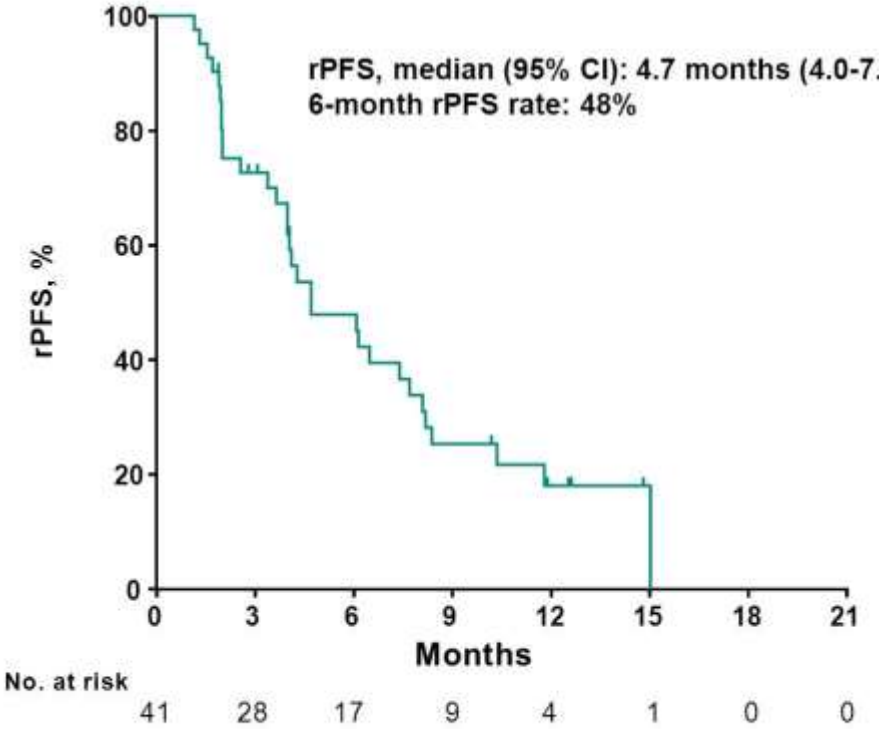
Best Response and Target Lesion Change From Baseline: RECIST-Measurable Disease

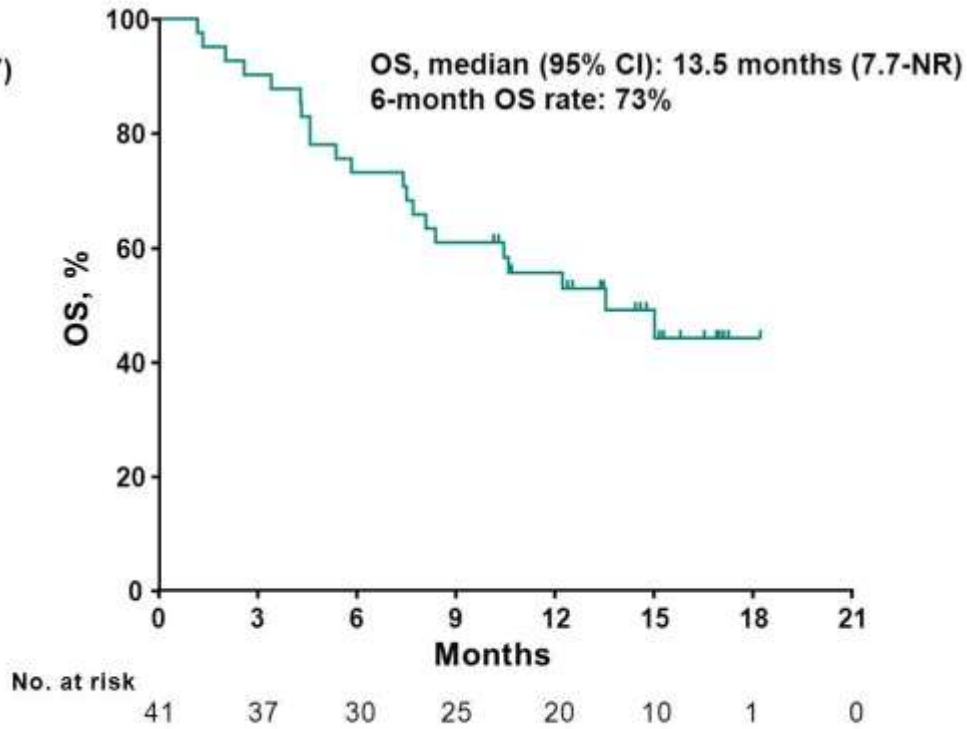


Confirmed Response	RECIST-Measurable Disease n = 28
ORR, % (95% CI)	7 (1-23)
DCR ≥6 mo, % (95% CI)	32 (16-52)
Best response, n (%)	
CR	0
PR	2 (7)
SD of any duration	13 (46)
PD	9 (32)
Not evaluable[c]	0
No assessment[d]	4 (14)

[a]Based on investigator assessment. Includes confirmed and unconfirmed responses. [b]Patients who received ≥1 dose of study drug and had a baseline scan and a postbaseline assessment (n = 24). [c]Includes patients who discontinued or died before first postbaseline scan. [d]Includes patients with insufficient data for response assessment.
Database cutoff: July 27, 2018.

Kaplan-Meier Estimates of rPFS[a] and OS





[a]Based on investigator assessment per PCWG3-modified RECIST v1.1.
Database cutoff: July 27, 2018.

Summary and Conclusions

- Pembrolizumab plus olaparib is generally well tolerated and has promising activity in a molecularly unselected population of mCRPC patients previously treated with chemotherapy and second-generation hormonal therapies
  - Safety/tolerability profile of the combination is consistent with profiles of each agent
    - Most common treatment-related AE, anemia (37%)
    - All immune-mediated AEs grade 1 or 2; most common, hypothyroidism (5%)
  - Confirmed PSA response rate: Total population, 12%; RECIST-measurable disease, 14%
  - Tumor burden reduction from baseline: RECIST-measurable disease, 39%
  - In the total population
    - Median rPFS, 4.7 months; median OS, 13.5 months
- Results support further evaluation of pembrolizumab and olaparib in this patient population
  - Enrollment to cohort A of KEYNOTE-365 to increase to 100 patients
  - Randomized phase 3 study of olaparib with pembrolizumab in patients with molecularly unselected mCRPC who were enzalutamide or abiraterone pretreated and progressed on chemotherapy currently open to enrollment (KEYLYNK-010, NCT03834519)