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.

<table>
<thead>
<tr>
<th>Male Trend</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1975-1987</td>
</tr>
<tr>
<td>3.1</td>
<td>1987-1991</td>
</tr>
<tr>
<td>-0.7</td>
<td>1991-1994</td>
</tr>
<tr>
<td>-3.9</td>
<td>1994-2004</td>
</tr>
<tr>
<td>-3.2</td>
<td>2004-2009</td>
</tr>
</tbody>
</table>
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

- Examined 152 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.

CARCINOMA AND PIN IN YOUNG MALES

• 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

Men who die despite radical treatment

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

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

AUC 0.821 vs. 0.735 for PCPT
PSA at 60 highly predictive of cancer death by 85

Lorenz Curve: Mets within 25 years by PSA at 60

AUC = 0.90
75% of the tests, 40% of the overdiagnosis, none of the benefit in low PSA

<table>
<thead>
<tr>
<th>Prostate cancer outcomes</th>
<th>0-0.99</th>
<th>1-1.99</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in diagnosis</td>
<td>171 (−32 to 374)</td>
<td>1462 (1101 to 1822)</td>
<td><strong>2485 (1797 to 3171)</strong></td>
</tr>
<tr>
<td>Decrease in metastasis</td>
<td>−37 (−70 to 11)*</td>
<td>−70 (−182 to 42)</td>
<td><strong>415 (30 to 799)</strong></td>
</tr>
<tr>
<td>Decrease in death</td>
<td>−17 (−43 to 14)*</td>
<td>−85 (−138 to −2)*</td>
<td><strong>453 (108 to 797)</strong></td>
</tr>
</tbody>
</table>
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

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.

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.
• 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.

Loblaw et al, J Urol, 184: 1942-6, 2010
## Active Surveillance - Summary of Studies


<table>
<thead>
<tr>
<th>Institution (PI)</th>
<th>Most recent paper(s)</th>
<th>Total (n)</th>
<th>Strict* (n)</th>
<th>Median age</th>
<th>Median follow-up (months)</th>
<th>OS (%)</th>
<th>CSS (%)</th>
<th>TFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden (Parker)</td>
<td>2007&lt;sup&gt;18,63&lt;/sup&gt;</td>
<td>326</td>
<td>326</td>
<td>67</td>
<td>22</td>
<td>98</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤3+4, PSA ≤15 ng/ml, cT stage ≤2a, ≤50% of cores positive</td>
<td></td>
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<tr>
<td>ERSPC sites (Schröder)</td>
<td>2009&lt;sup&gt;64,65&lt;/sup&gt;</td>
<td>988</td>
<td>616</td>
<td>66</td>
<td>52</td>
<td>91</td>
<td>99</td>
<td>68</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, PSAD ≤0.2 ng/ml/ml, cT stage 1c-2 ≤2 cores positive</td>
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<tr>
<td>University of Miami (Soloway)</td>
<td>2010&lt;sup&gt;66,67&lt;/sup&gt;</td>
<td>230</td>
<td>230</td>
<td>64</td>
<td>32</td>
<td>100</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤6, PSA ≤10 ng/ml, cT stage ≤2, ≤2 cores, ≤20% of any core positive</td>
<td></td>
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<tr>
<td>Johns Hopkins (Carter)</td>
<td>2010&lt;sup&gt;14,33&lt;/sup&gt;</td>
<td>618</td>
<td>506</td>
<td>65</td>
<td>35</td>
<td>98</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤3+3, PSAD ≤0.15 ng/ml/ml, cT stage 1, ≤2 cores positive, ≤50% of any core positive</td>
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<tr>
<td>UCSF (Carroll)</td>
<td>2010&lt;sup&gt;16,68&lt;/sup&gt;</td>
<td>640</td>
<td>376</td>
<td>62</td>
<td>47</td>
<td>97</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2, ≤33% of cores positive, ≤60% of any core positive</td>
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<tr>
<td>University of Toronto (Klotz)</td>
<td>2010&lt;sup&gt;13,69&lt;/sup&gt;</td>
<td>453</td>
<td>453</td>
<td>70</td>
<td>82 (10-yr)</td>
<td>68</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤6, PSA ≤10 ng/ml (until Jan 2000, for men &gt;70: Gleason ≤3+4, PSA ≤15 ng/ml)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Memorial-Sloan Kettering (Eastham)</td>
<td>2010&lt;sup&gt;23,70&lt;/sup&gt;</td>
<td>238</td>
<td>238</td>
<td>64</td>
<td>22</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2a, ≤3 cores positive, ≤50% of any core positive</td>
<td></td>
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</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>3490</strong></td>
<td><strong>2733</strong></td>
<td><strong>67</strong></td>
<td><strong>43</strong></td>
<td><strong>90</strong></td>
<td><strong>99.7</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>
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.
MEAL STUDY
ELIGIBILITY

- Biopsy-proven adenocarcinoma, clinical stage ≤ 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.
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

Eligible, consenting patients with clinical suspicion of prostate cancer

Visit 1: Registration

Visit 2: MP-MRI (1.5 Tesla)

Visit 3: Combined biopsy (under general anaesthetic)
1st: TPM-biopsy
2nd: TRUS-biopsy

Visit 4: End of study
Results given to patients

Index Test – Multi-parametric MRI

- 1.5 Tesla, no endorectal coil
- Independent Quality Assurance and Quality Control of scans
- Compliant with international guidance
  \[ T2W, \text{Diffusion} \ (ADC + b=1500), \text{Dynamic gadolinium contrast} \]
- LIKERT scoring 1 to 5:
  \[ 1=\text{highly unlikely to harbour significant cancer} \]
  \[ \ldots \]
  \[ 5=\text{highly likely to harbour significant cancer} \]
- Positive MP-MRI
  \[ \text{Score } \geq 3 \]
Histological definition of clinically significant cancer

Gleason $\geq 4+3$ and/or

Cancer core length $\geq 6\text{mm}$

MP-MRI scores and disease severity

% by status of disease

Significant cancer
Insignificant cancer
No cancer

MP-MRI score

N=23  N=135  N=163  N=120  N=135

Presented By Hashim Ahmed at 2016 ASCO Annual Meeting
## MP-MRI compared to TRUS-biopsy

<table>
<thead>
<tr>
<th>Test attribute</th>
<th>TRUS-biopsy</th>
<th>MP-MRI</th>
<th>Odds ratio* [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>48%</td>
<td>93%</td>
<td>0.06 [0.02-0.12]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>96%</td>
<td>41%</td>
<td>0.02 [0.003-0.05]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PPV</td>
<td>90%</td>
<td>51%</td>
<td>8.2 [4.7-14.3]</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>NPV</td>
<td>74%</td>
<td>89%</td>
<td>0.34 [0.21-0.55]</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Number and cancer core length (mm)</th>
<th>TRUS-biopsy Total = 119</th>
<th>MP-MRI Total = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason 3+3</td>
<td>7 (6-11mm)</td>
<td>1 (8mm)</td>
</tr>
<tr>
<td>Gleason 3+4</td>
<td>99 (6-14mm)</td>
<td>16 (6-12mm)</td>
</tr>
<tr>
<td>Gleason &gt;/=4+3</td>
<td>13 (3-16mm)</td>
<td>0</td>
</tr>
</tbody>
</table>
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

- 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

- 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
ACTIVE SURVEILLANCE: NOVEL IMAGING C11 Acetate PET scanning in patient with localized prostate cancer.
What can we achieve with advanced imaging and molecular biomarkers?

Tailoring therapy through better:

• Detection of “occult” disease
• Risk stratification (prognosis)
• Prediction of treatment response
The Advent of PET Imaging for Prostate Cancer

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)

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

Figure courtesy of Thomas Hope, UC San Francisco
Advanced PET Imaging Changes Clinical Decision-Making

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

Presented by Felix Feng, MD

2019 Genitourinary Cancers Symposium | #GU19

Presented By Felix Feng at 2019 Genitourinary Cancers Symposium
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?
## What Genomic Tests are Available Clinically?

### NCCN Guidelines Version 2.2018
#### Prostate Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Populations studied</th>
<th>Outcome Reported (Test independently predicts)</th>
<th>References</th>
<th>Molecular Diagnostic Services Program (MDS) Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decipher</td>
<td>Whole-transcriptome 1.6M RNA sequencing (44,000 genes) oligonucleotide array optimized for FFPE tissue</td>
<td>Prostate cancer risk genotypes, high-risk features, post RP, biochemical recurrence, post RP, adjusted or salvage radiotherapy</td>
<td>Metastasis, Prostate-specific mortality, Metastasis, Biochemical failure</td>
<td>2018-01-31</td>
<td>Cover post-RP for 1) pT3, 2) any of T3 disease, 3) rising PSA (above 10 ng/mL)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>IHC</td>
<td>Biopsy, intermediate to high risk treated with IMRT</td>
<td>Metastasis, Prostate-specific mortality</td>
<td>2017-12-22</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls</td>
<td>Biopsy, low to intermediate risk treated with RP</td>
<td>Non-organ-confined T3 or Gleason grade 4 disease on RP</td>
<td>2019-07-08</td>
<td>Cover post-biopsy for NCCN very low and low-risk prostate cancer at diagnosis with &gt; 20 years life expectancy</td>
</tr>
<tr>
<td>ProMark</td>
<td>Quantitative RT-PCR for 21 cell cycle-related genes and 15 housekeeping controls</td>
<td>Prostate cancer-related genes</td>
<td>Prostate-specific mortality, Prostate cancer-specific mortality</td>
<td>2017-12-22</td>
<td>Cover post-biopsy for NCCN very low and low-risk prostate cancer at diagnosis with &gt; 10 years life expectancy</td>
</tr>
<tr>
<td>PTEN</td>
<td>FISH or IHC</td>
<td>Biopsy, Gleason grade 3-4 or Gleason pattern 4 disease on RP</td>
<td>Prostate-specific mortality</td>
<td>2018-01-31</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

### 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

**Presented at:** 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Felix Feng, MD
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

¹Gustave Roussy, University of Paris Sud, Villejuif, France; ²Janssen Research & Development, Los Angeles, CA; ³Instituto de Oncologia de Rosário, Rosário, Argentina; ⁴National Cancer Center Hospital East, Chiba, Japan; ⁵12 de Octubre University Hospital, Madrid, Spain; ⁶P. A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; ⁷Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; ⁸Fudan University Shanghai Cancer Center, China; ⁹Studienpraxis Urologie, Nürtingen, Germany; ¹⁰Oxford University Hospitals Foundation NHS Trust, Oxford, UK; ¹¹Janssen Research & Development, Beerse, Belgium; ¹²Janssen Research & Development, San Diego, CA; ¹³Janssen Research & Development, Raritan, NJ; ¹⁴Janssen Global Services, Raritan, NJ; ¹⁵BC Cancer Agency, Vancouver, BC, Canada
ADT + docetaxel: a new standard of care for men with mCNPC and high metastatic burden (2015)

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>ADT + DOC</th>
<th>ADT</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (mos)</td>
<td>Median (mos)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GETUG-15¹</td>
<td>62.1</td>
<td>48.6</td>
<td>0.88 (0.68-1.14)</td>
<td>0.3</td>
</tr>
<tr>
<td>CHAARTED²</td>
<td>57.6</td>
<td>47.2</td>
<td>0.73 (0.59-0.89)</td>
<td>0.0018</td>
</tr>
<tr>
<td>STAMPEDE³</td>
<td>60</td>
<td>45</td>
<td>0.76 (0.62-0.92)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Abiraterone mechanism of action: androgen biosynthesis inhibitor

- Cholesterol
  - Pregnenolone
    - 17α-hydroxylase
      - 17OH-Pregnenolone
        - CYP17, C17,20-lyase
          - DHEA
            - Abiraterone
              - Androstenedione
                - Testosterone
                  - DHT
                - Cortisol
                  - Aldosterone

Androgens
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*
Statistically significant 38% risk reduction of death

Hazard ratio, 0.62 (95% CI, 0.51-0.76)

$P < 0.0001$

ADT + AA + P, not reached

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

No. of events: 406 (48% of 852)
ADT + AA + P: 169
ADT + placebos: 237

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

Median follow-up: 30.4 months
Statistically significant 53% risk reduction of radiographic progression or death

Hazard ratio, 0.47 (95% CI, 0.39-0.55)  
\( P<0.0001 \)

- ADT + AA + P, 33.0 mo
- ADT + placebos, 14.8 mo

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

Hazard ratio, 0.30 (95% CI, 0.26-0.35)
P<0.0001

ADT + AA + P, 33.2 mo
ADT + placebo, 7.4 mo

No. at risk
ADT + AA + P 597 520 447 379 340 285 227 162 95 48 18 0
ADT + placebo 602 393 250 172 129 102 65 33 19 8 5 0
Subsequent life-prolonging therapy for prostate cancer

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

*Patients who discontinued treatment and were eligible for subsequent therapy.
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
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.stampdetrtrial.org
Overall Survival – STAMPEDE “abiraterone comparison”

Events
262 Control | 184 Abiraterone

SOC + AAP
SOC

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

trt = SOC by Kaplan-Meier
trt = SOC + AAP by Kaplan-Meier
SOC by flexible parametric model
SOC + AAP by flexible parametric model
<table>
<thead>
<tr>
<th>Safety population</th>
<th>SOC-only</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in adverse event analysis</td>
<td>960</td>
<td>948</td>
</tr>
<tr>
<td>Grade 1-5 AE</td>
<td>950 (99%)</td>
<td>943 (99%)</td>
</tr>
<tr>
<td>Grade 3-5 AE</td>
<td>315 (33%)</td>
<td>443 (47%)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3-5 AEs by category (incl. expected AEs)</th>
<th>SOC-only</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorder (incl. hot flashes, impotence)</td>
<td>133 (14%)</td>
<td>129 (14%)</td>
</tr>
<tr>
<td><strong>Cardiovascular disorder (incl. hypertension, MI, cardiac dysrhythmia):</strong></td>
<td>41 (4%)</td>
<td>92 (10%)</td>
</tr>
<tr>
<td>Musculoskeletal disorder:</td>
<td>46 (5%)</td>
<td>68 (7%)</td>
</tr>
<tr>
<td>Gastrointestinal disorder:</td>
<td>40 (4%)</td>
<td>49 (5%)</td>
</tr>
<tr>
<td>Hepatic disorder (incl. increased AST, increased ALT):</td>
<td>12 (1%)</td>
<td>70 (7%)</td>
</tr>
<tr>
<td>General disorder (incl. fatigue, oedema):</td>
<td>29 (3%)</td>
<td>45 (5%)</td>
</tr>
<tr>
<td>Respiratory disorder (incl. breathlessness):</td>
<td>23 (2%)</td>
<td>44 (5%)</td>
</tr>
<tr>
<td>Lab abnormalities (incl. hypokalaemia):</td>
<td>21 (2%)</td>
<td>34 (4%)</td>
</tr>
</tbody>
</table>
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 Stenzl13

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

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Andrew J. Armstrong, MD

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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 Chemical Hormonal Therapy in Men with Metastatic Hormone-Sensitive Prostate Cancer (ARCHES)

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)

N = 1150
R 1:1

Enzalutamide 160 mg/day + ADT
March 21, 2016
First patient enrolled

Placebo + ADT

Key discontinuation criteria
Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer
October 14, 2018

rPFS final analysis
Overall survival (OS) interim analysis
OS final analysis

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

Presented by: Andrew J. Armstrong, MD
Primary endpoint: rPFS

- 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

![Graph showing the time to PSA progression for ENZA + ADT and PBO + ADT. The graph includes a Kaplan-Meier curve and a table with statistical information.]

- 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)

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>ENZA + ADT (n = 574)</th>
<th>PBO + ADT (n = 576)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, month</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(NR, NR)</td>
<td>(16.59, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.19 (0.13, 0.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p value</td>
<td>0.91</td>
<td>0.63</td>
</tr>
<tr>
<td>12-month event-free rate estimate</td>
<td>0.91</td>
<td>0.63</td>
</tr>
</tbody>
</table>

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### PSA undetectable rate and objective response rate

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

- 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

- 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

Presented By Eric Small at 2019 Genitourinary Cancers Symposium

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

**Eligibility**
- nmCRPC
  - 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

**Schematic Diagram**
1. **Randomization**
2. **MFS** (primary end point)
3. **2nd progression or death (PFS2)**

**Eligibility Criteria**
- Apalutamide (APA) 240 mg QD + ADT (n = 806)
- Placebo (PBO) + ADT (n = 401)\

**Progression Criteria**
- MFS
- Second Rx at MD’s discretion, including open-label ABI/PRED

---

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.

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

Presented by: Eric Small, MD, FASCO

---

Presented By Eric Small at 2019 Genitourinary Cancers Symposium
Background: Significant Improvement With APA vs PBO

Primary End Point: Metastasis-Free Survival

Secondary End Point: Time to Symptomatic Progression

Exploratory End Point: Time to PSA Progression

Ci, confidence interval; HR, hazard ratio.

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Presented by: Eric Small, MD, FASCO

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

nmCRPC Patients
N = 1201
Median follow-up: 32 mos

- Apalutamide\(^a\)
  (n = 803)
  Median Rx duration: 25.7 mos
  - Discontinued Rx
    n = 412 (51%)
  - Remained on Rx
    n = 391 (49%)

- Placebo\(^a\)
  (n = 398)
  Median Rx duration: 11.5 mos
  - Discontinued Rx
    n = 323 (81%)
  - Crossed over to APA
    n = 75 (19%)
    Median Rx duration: 6.7 mos

\(^a\)All patients received ADT during treatment.
Results: Reasons for Study Treatment Discontinuation

nmCRPC Patients
N = 1201
Median follow-up: 32 mos

Apalectamide*
(n = 803)
Median Rx duration: 25.7 mos

Discontinued Rx
n = 412 (51%)

Remained on Rx
n = 391 (49%)

Placebo*
(n = 398)
Median Rx duration: 11.6 mos

Discontinued Rx
n = 323 (81%)

Crossed over to APA
n = 75 (19%)
Median Rx duration: 6.7 mos

Discontinued APA

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>219 (53%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>102 (25%)</td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>66 (16%)</td>
</tr>
<tr>
<td>Other(^b)</td>
<td>25 (6.1%)</td>
</tr>
</tbody>
</table>

Discontinued PBO

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>237 (73%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>27 (8.4%)</td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>49 (15%)</td>
</tr>
<tr>
<td>Other(^b)</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (0.6%)</td>
</tr>
</tbody>
</table>

\(^a\) All patients received ADT during treatment. \(^b\) Other includes protocol violations.
# Results: Subsequent Treatment

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>APA (n = 803)</th>
<th>PBO (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued study treatment</td>
<td>412 (51)</td>
<td>323 (81)</td>
</tr>
<tr>
<td>Received systemic therapy for prostate cancer</td>
<td><strong>249 (60)(^a)</strong></td>
<td><strong>255 (79)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First subsequent treatment</th>
<th>APA (n = 803)</th>
<th>PBO (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate plus prednisone</td>
<td>183 (44)</td>
<td>188 (58)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>27 (6.6)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>20 (4.9)</td>
<td>18 (5.6)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>6 (1.5)</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 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

Grade 3 Falls

Grade 3 Fractures

Grade 3 Skin Rash

Grade 3/4 TEAEs

SAEs
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

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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.

Presented By Evan Yu at 2019 Genitourinary Cancers Symposium
KEYNOTE-365 Study Design (NCT02861573)

Cohort A Key Eligibility Criteria
- PD ≤6 months before screening
- Docetaxel-pretreated for mCRPC
- ≤1 other previous chemotherapy and ≤2 second-generation hormonal therapies for mCRPC permitted

Cohort A
- Pembrolizumab (200 mg Q3W) + Olaparib (400 mg twice daily)

Response assessed per RECIST v1.1 based on PCWG3 guidelines
- Imaging assessments Q9W through week 54, Q12W thereafter until progression
- PSA assessed Q3W until progression

Cohort B
- Pembrolizumab + Docetaxel + Prednisone

Cohort C
- Pembrolizumab + Enzalutamide

Cohort D
- Pembrolizumab + Abiraterone + Prednisone

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

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

<table>
<thead>
<tr>
<th>Pembrolizumab + Olaparib</th>
<th>(N = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardant360 ctDNA panel, (n)</td>
<td></td>
</tr>
<tr>
<td>Patients with detectable ctDNA</td>
<td>37</td>
</tr>
<tr>
<td>HRP</td>
<td>36</td>
</tr>
<tr>
<td>ATM R3008H mutation(^b)</td>
<td>1</td>
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<tr>
<td>WES analysis, (n)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue available for analysis</td>
<td>17</td>
</tr>
<tr>
<td>Qualified WES results</td>
<td>12</td>
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<tr>
<td>HRP</td>
<td>11</td>
</tr>
<tr>
<td>BRIP1 frameshift mutation(^c)</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\)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

- RECIST Measurable: 14% (4/28)
- RECIST Nonmeasurable: 8% (1/13)
- Total Population: 12% (5/41)

PSA decrease from baseline:
- RECIST measurable disease: 14/28 (50%)
- PSA decrease ≥50%: 5/28 (18%)
- RECIST nonmeasurable disease: 7/13 (54%)
- PSA decrease ≥50%: 2/13 (15%)

*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

PCW3-Modified RECIST v1.1

- 11/28 (39%) experienced reduction in tumor burden
- 8/28 (29%) experienced reduction ≥30%

Percentage Change From Baseline

<table>
<thead>
<tr>
<th>Confirmed Response</th>
<th>RECIST-Measurable Disease n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>7 (1-23)</td>
</tr>
<tr>
<td>DCR ≥6 mo, % (95% CI)</td>
<td>32 (16-52)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2 (7)</td>
</tr>
<tr>
<td>SD of any duration</td>
<td>13 (46)</td>
</tr>
<tr>
<td>PD</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on investigator assessment. Includes confirmed and unconfirmed responses. <sup>b</sup> Patients who received ≥1 dose of study drug and had a baseline scan and a postbaseline assessment (n = 24). <sup>c</sup>Includes patients who discontinued or died before first postbaseline scan. <sup>d</sup>Includes patients with insufficient data for response assessment.

Kaplan-Meier Estimates of rPFS\textsuperscript{a} and OS

rPFS, median (95% CI): 4.7 months (4.0-7.7)
6-month rPFS rate: 48%

OS, median (95% CI): 13.5 months (7.7-NR)
6-month OS rate: 73%

\textsuperscript{a}Based on investigator assessment per PCWG3-modified RECIST v1.1.
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)