Prostate Cancer: The Evolving Landscape of Treatment

Philip Kantoff, MD
Chairman of Medicine
Memorial Sloan Kettering Cancer Center
### Philip Kantoff Pharma Consulting Payments Disclosures (Past Two Years)

<table>
<thead>
<tr>
<th>Company</th>
<th>Type of Relationship</th>
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<tbody>
<tr>
<td>BIND Biosciences, Inc. (2016)</td>
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<td>BN Immunotherapeutics (2016)</td>
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<td>Context Therapeutics LLC (2017)</td>
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<td>Janssen (2016)</td>
<td>SAB</td>
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<td>Metamark (2017)-no longer in business</td>
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<td>Merck (2017)</td>
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<td>Tarveda Therapeutics (previously Blend) (2016)</td>
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**SAB = scientific advisory board/consulting**  
**INV = investment interest**  
**DSMB = data safety monitoring board**

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**Off Label/Investigational Discussion**

In accordance with Annenberg Center policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
A 65 year old man presents to his MD with back pain. The work up includes a PSA which returns at 120 ng/ml. This prompts a bone scan which is extensively positive in the axial and appendicular skeleton. A biopsy of his prostate reveals Gleason 4+5 cancer in 12/12 cores. The patient is referred to you. The best option for this man is:

1. ADT with leuprolide and bicalutamide
2. XRT to spine and leuprolide and bicalutamide
3. XRT to spine and observation until PSA progression
4. ADT with leuprolide and either docetaxel or abiraterone
5. ADT with leuprolide and bicalutamide and either docetaxel or enzalutamide
Q2-Which is true?

1. AR splice variants have been shown to be associated with resistance to primary ADT
2. Enzalutamide when added to standard ADT for MoCRPC prolongs MFS but not OS
3. ERG overexpression is associated with a poor prognosis
4. BRCA1 mutations occur in 10-15% of men with mCRPC
5. AR splice variants are associated with docetaxel resistance
The Old Treatment Paradigm

- **The Old Treatment Paradigm**

- **Post Chemo**
- **CRPC**

- **Hormone Sensitive**
- **Castration Resistant**

- **Therapies after LHRH agonists**
- **anti-androgens etc.**

- **Death**

**Diagram Details:**
- **Tumor volume & activity**
- **Local Therapy**
- **Androgen Deprivation**
- **Chemotherapy**
- **Post Chemo**

**Time Phases:**
- **Asymptomatic**
- **Symptomatic**
- **Non-Metastatic**
- **Metastatic**
- **Hormone Sensitive**
- **Castration Resistant**

**CRPC**
The Treatment Landscape in 2018

- **Local Therapy**
- **Androgen Deprivation**
- **Therapies After LHRH Agonists and Antiandrogens**
- **Sipuleucel-T**
- **Docetaxel**
- **Enzalutamide**
- **Abiraterone**
- **Apalutamide**
- **Standard Androgen Deprivation Therapy**
  - **DenoSUMab, Zoledronic Acid**
  - **Radium-223**
- **Postchemotherapy**
- **Death**
- **Cabazitaxel**
- **Olaparib**
- **Pembrolizumab (MSI-high)**
“Advanced” Prostate Cancer-Recurrent or Metastatic Disease

• In 2018, ~164,690 new cases of prostate cancer will be diagnosed in US most diagnosed as a result of an elevated or increase in PSA
• 5-10% will present with metastatic disease
• In 2018, ~29,430 men will die of prostate cancer
• About ½ of men who die of prostate cancer present with localized disease
• Not everyone with advanced prostate cancer will die of their disease
What is the Natural History Of Patients Who Relapse After Local Therapy?

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

First Rise in PSA → 8 yrs → Bone scan (+) → 5 yrs → Death

Pound JAMA 1999
Patients with a Rising PSA - Importance of PSADT

Freedland et al (JAMA 2005)
Patients with a Rising PSA-Importance of PSADT

Freedland et al (JAMA 2005)
Patients with a Rising PSA-Importance of PSADT

Freedland et al (JAMA 2005)
Androgen Deprivation Therapy (ADT)

- Decreases serum testosterone to “castrate” levels
- Primary treatment for men with metastatic disease
  - Most men are treated with ADT before they develop metastases
- “PSA response rate” very high (> 99%)
- “PSA response” is a result of
  - Decreased expression of PSA gene
  - Renders cells quiescent
  - Cell kill-apoptosis
What is the Optimal Form of ADT?
ADT

• Orchiectomy
• LHRH agonists
• LHRH antagonists
• Estrogens
• Combined androgen blockade
• Antiandrogen monotherapy
ADT

• Orchiectomy
• LHRH agonists
• LHRH antagonists
• Estrogens
• Combined androgen blockade
• Antiandrogen monotherapy
• Existing therapies do not adequately suppress adrenal or intratumoral production of androgen-better drugs soon to be available
Intermittent versus Continuous ADT
NCIC/PR7-Intermittent vs Continuous: Non-Metastatic Disease

Overall Survival (%)

Years since Randomization

Hazard ratio, 1.03 (95% CI, 0.87–1.22)
P = 0.009

No. at Risk

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Crook et al (NEJM 2010)
**SWOG 9346-Intermittent vs Continuous: Metastatic Disease**

SWOG led Intergroup trial
Metastatic Prostate Ca
Starting ADT (3040 men)

- PSA < 4 (1535 men = selected group)

- Randomized to continuous vs. int ADT

Hazard Ratio for death with int Rx 1.10; 90% CI - 0.99 to 1.23

Exceeded the upper boundary for noninferiority (cannot rule out a 20% greater risk of death with int Rx vs Cont)

Hussain et al (NEJM 2013)
Intermittent versus Continuous ADT

• NCIC/PR7-non metastatic (Crook et al NEJM 2010)-NS difference
• SWOG 9346-metastatic (Hussain et al NEJM 2013)-HR 1.09 (intermittent slightly inferior)
• Intermittent reasonable option and preferable for patients with non-metastatic
• For patients with metastases, needs to be individualized
What are the Side Effects of ADT?
Side Effects

• Accelerated osteoporosis
• Hot flashes
• Sexual dysfunction
• Weight gain
• Decreased muscle mass
• Increased glucose intolerance
• Altered lipid profile

• Gynecomastia
• Anemia
• Decreased penile size
• Increased CV risk
• Fatigue
• Cognitive changes*
What is a Good Response to ADT?

SWOG 9346 Intermittent ADT Trial

1345 eligible patients

Level of PSA after 7 months of ADT

Hussain et al (JCO 2006)
Overall Survival in M+ Patients as Determined by Nadir PSA 7 months after ADT

Hussain et al (JCO 2006)
Castration Resistant Prostate Cancer (CRPC)
Importance of Persistent AR Pathway Signaling in CRPC

Genetic evidence-AR-Mutated or amplified AR

Persistent AR expression and expression of androgen regulated genes “androgen signature”

“Persistent intratumoral ligand”-T or DHT or precursors
Androgen Signaling Pathway Inhibitors

• CYP 17, 20 lyase inhibitors—
  androgen biosynthesis inhibitors
  - Abiraterone acetate

• Antiandrogens—block AR action
  - Enzalutamide or apalutamide
Abiraterone Acetate in mCRPC Pre and Post-Chemotherapy*

- COU-AA-302
  - Co-Primary Endpoints: OS, rPFS
    - Ryan et al NEJM 2013

- COU-AA-301
  - Primary Endpoint: OS
    - DeBono et al NEJM 2011

*FDA approved indications
Enzalutamide in mCRPC Pre and Post-Chemotherapy*

PREVAIL
Co-Primary Endpoints:
OS and rPFS
Beer et al NEJM 2014

AFFIRM
Primary Endpoint:
OS
Scher et al NEJM 2012

*FDA approved indications
Conclusions

• Understanding the persistence of the androgen signaling pathway in CRPC has been transformative

• Multiple agents with varied mechanisms extend survival and delay progression

• Cross resistance occurs between agents
What about use of androgen signaling inhibitors in non-metastatic CRPC (MoCRPC)?- enzalutamide and apalutamide
PROSPER Study Design

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

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

**Primary endpoint**
- MFS

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

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

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

Hussain et al ASCO GU 2018
### PROSPER-Baseline Patient Characteristics (N=1401)

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

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

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

Hussain et al ASCO GU 2018
PROSPER - Primary Endpoint: MFS

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

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

Hussain et al ASCO GU 2018
There was a 20% reduction in the relative risk of death with enzalutamide vs placebo.

**Hussain et al ASCO GU 2018**
<table>
<thead>
<tr>
<th>Event, No. (%)</th>
<th>Enzalutamide + ADT (n = 933)</th>
<th>Placebo + ADT (n = 468)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All progression events*</td>
<td>219 (23%)</td>
<td>228 (49%)</td>
</tr>
<tr>
<td>Radiographic progression†</td>
<td>187 (85%)</td>
<td>224 (98%)</td>
</tr>
<tr>
<td>New bone metastases</td>
<td>71 (32%)</td>
<td>79 (35%)</td>
</tr>
<tr>
<td>New soft-tissue metastases</td>
<td>109 (50%)</td>
<td>132 (58%)</td>
</tr>
<tr>
<td>Concurrent new bone and soft-tissue metastases</td>
<td>7 (3%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Death without documented radiographic progression within 112 days of study treatment discontinuation†</td>
<td>32 (15%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

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

*Event percentages are based on total number of patients randomized in each arm (enzalutamide + ADT, n = 933; placebo + ADT, n = 468)
†Partition of event percentages are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228).
SPARTAN-Overall Study Design

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

On-Study Requirement
- Continuous ADT

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

2:1 (N = 1207)

Apatutamide (APA)
- 240 mg QD
- + ADT
- (n = 406)

Open-label Abiraterone acetate
+ Prednisone

Placebo (PBO)
- + ADT
- (n = 806)

Randomization

Metastasis-free survival (MFS) (primary end point)

2nd progression-free survival (PFS2)

Small et al NEJM 2018
SPARTAN-Metastasis-free Survival-primary endpoint

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

HR, 0.28 (95% CI, 0.23-0.35)

P < 0.0001
SPARTAN-Time to Symptomatic Progression
55% risk reduction of SRE, pain progression/worsening sx, clinically significant sx (PSA blinded)

Patients Without Symptomatic Progression (%)

No. at risk

Months

APA

PBO

Small et al NEJM 2018

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

Overall Survival

No. at risk

APA

PBO

Months

0 4 8 12 16 20 24 28 32 36 40 44

Overall Survival

0 20 40 60 80 100

APA, not reached

PBO, 39.0 mo

HR, 0.70 (95% CI, 0.47-1.04)

P = 0.07

Small et al NEJM 2018
<table>
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<tr>
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<th>APA (n = 803)</th>
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<td></td>
<td>All</td>
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<td>Gr 3/4</td>
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<tr>
<td>Fatigue</td>
<td>30.4%</td>
<td>0.9%</td>
<td>21.1%</td>
<td>0.3%</td>
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<tr>
<td>Rash</td>
<td>23.8%</td>
<td>5.2%</td>
<td>5.5%</td>
<td>0.3%</td>
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<tr>
<td>Weight loss</td>
<td>16.1%</td>
<td>1.1%</td>
<td>6.3%</td>
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<tr>
<td>Arthralgia</td>
<td>15.9%</td>
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<tr>
<td>Fall</td>
<td>15.6%</td>
<td>1.7%</td>
<td>9.0%</td>
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<tr>
<td>Fracture</td>
<td>11.7%</td>
<td>2.7%</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Seizure</td>
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Small et al NEJM 2018
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Small et al NEJM 2018
## SPARTAN- Adverse Events

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Small et al NEJM 2018
Conclusions-MoCRPC

• APA (now FDA approved) and ENZA delay MFS in men with Mo CRPC an impressive 2 years
• This potentially gives us 2 new options for men with Mo CRPC
• Delaying the onset of disease-related symptoms, as seen in SPARTAN, represents clinical benefit
Conclusions-MoCRPC

• BUT-Treating asymptomatic patients carries a certain burden of proof of clinical benefit
• Some untoward effects need to be better defined
  • More deaths from other causes-needs to be understood to minimize risk
  • More side effects-falls and fractures-need to better understand who is at high risk to minimize risk
• We need to be cognizant of the toxicities and understand how care patterns in these studies compare with actual practice
Numerous Mechanisms of Resistance to ADT/Abiraterone/Enzalutamide

• Androgen receptor mediated mechanisms
  • AR amplification
  • Activating mutations in AR
  • Epigenetic reprogramming of AR
  • AR splice variants

• Up-regulation of other steroidogenic enzymes

• Glucocorticoid receptor mediated transcriptional activation (enzalutamide)
Biomarkers of Resistance to Androgen Signaling Inhibitors
AR Variants associated With Resistance to AR-Targeted Therapy
AR-V7=Non-Responders to ABI/ENZA

Antonarakis E, et al. 
NEJM. 
Antonarakis et al NEJM 2016
A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC
**Study Schema**

**Plasma and Whole Blood**

- **Randomize 1:1**
- **Abiraterone 1000 mg**
- **Prednisone 10 mg**
- **Enzalutamide 160 mg**

**Progression 1**

- **Enzalutamide 160 mg**
- **Abiraterone 1000 mg**
- **Prednisone 10 mg**

**Progression 2**

- **Enzalutamide 160 mg**
- **Abiraterone 1000 mg**
- **Prednisone 10 mg**

**Primary Objective**
- Response and Time to PSA progression (TTPP) after 2nd line therapy

**Secondary Objectives**
- TTP/TTPP with 1st line therapy
- PSA decline from baseline
- Correlation with deep targeted sequencing of cfDNA

---

**ClinicalTrials.gov: NCT02125357**

---

**Presented At:** ASCO ANNUAL MEETING '17 | #ASCO17

**Chi et al Canc Disc 2018**
Best PSA decline: 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone + P</th>
<th>Enzalutamide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Decline ≥ 30%</td>
<td>64 (65%)</td>
<td>83 (85%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>PSA Decline ≥ 50%</td>
<td>54 (55%)</td>
<td>75 (77%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>No PSA Decline</td>
<td>20 (20%)</td>
<td>10 (10%)</td>
<td>0.0501</td>
</tr>
</tbody>
</table>

Chi et al Canc Disc 2018
Time to Progression

ENZ Median TTP: 7.4 m (95% CI: 4.8, 10.0)
ABI + P Median TTP: 7.4 m (95% CI: 5.1, 9.7)
HR = 0.82, 95%CI: 0.58-1.16

*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease

Chi et al Canc Disc 2018
# Genomic Correlates with TTP

<table>
<thead>
<tr>
<th>Genomic Alteration</th>
<th>Median TTP Positive vs Negative* (months)</th>
<th>Univariate</th>
<th></th>
<th>Multivariate***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>P-value</td>
<td>HR</td>
</tr>
<tr>
<td>BRCA2/ATM truncating mutation</td>
<td>1.8 vs 8.0</td>
<td>6.14 (3.35-11.26)</td>
<td>&lt;0.001</td>
<td>5.34 (2.84-10.03)</td>
</tr>
<tr>
<td>TP53 inactivation**</td>
<td>3.3 vs 10.2</td>
<td>2.78 (1.92-4.03)</td>
<td>&lt;0.001</td>
<td>2.21 (1.38-3.55)</td>
</tr>
<tr>
<td>PI3K pathway</td>
<td>3.3 vs 10.4</td>
<td>2.73 (1.91-3.90)</td>
<td>&lt;0.001</td>
<td>1.95 (1.31-2.90)</td>
</tr>
<tr>
<td>AR amplification</td>
<td>5.0 vs 9.3</td>
<td>2.05 (1.43-2.93)</td>
<td>&lt;0.001</td>
<td>1.29 (0.85-2.09)</td>
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<td>RB1 inactivation**</td>
<td>3.6 vs 8.2</td>
<td>2.03 (1.36-3.04)</td>
<td>&lt;0.001</td>
<td>1.45 (0.95-2.21)</td>
</tr>
<tr>
<td>SPOP mutation</td>
<td>7.3 vs 7.4</td>
<td>1.00 (0.51-1.97)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AR mutation</td>
<td>6.2 vs 7.4</td>
<td>1.02 (0.53-1.95)</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Includes patients without detectable ctDNA; ** Mutation, deletion, or rearrangement
*** MVA includes trial arm, presence of quantifiable ctDNA, and clinical prognostic factors (LDH, ALP, Visceral Mets, ECOG PS)

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Chi et al Canc Disc 2018
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Chi et al Canc Disc 2018
## PSA Responses Diminish With Second-Line AR Therapy

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<tr>
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<th>ENZA $\rightarrow$ ABI</th>
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<tr>
<td><strong>First Line</strong></td>
<td></td>
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</tr>
<tr>
<td>≥50% PSA Decline</td>
<td>55-60%</td>
<td>13-29%</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td>4-8%</td>
<td>38-46%</td>
</tr>
</tbody>
</table>
Questions

• What is the optimal sequencing and/or combination of agents?

• Can we develop predictive biomarkers of efficacy?

• Can we cure patients by using these drugs earlier in the treatment paradigm (adjuvantly)?

• How much further can we get by extinguishing the AR pathway completely?
• Sipuleucel-T
Sipuleucel-T: Mechanism of Action

Antigen (PAP-GMCSF) is exposed to an Antigen Presenting Cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T and is collected

T-cells proliferate and attack cancer cells

sipuleucel-T activates T-cells in the body

INFUSE PATIENT
Randomized Phase 3 IMPACT Trial (Immunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (N = 512)

Sipuleucel-T Q 2 weeks x 3

Placebo Q 2 weeks x 3

2:1

PROGRESSION

Treated at physician discretion

Treated at physician discretion and/or salvage protocol

SURVIVAL

Primary endpoint: Overall survival
Secondary endpoint: Objective disease progression

Kantoff et al NEJM 2010
IMPACT Overall Survival: Final Analysis (349 events)

36.5 mo median f/u
HR = 0.759 (95% CI, 0.606, 0.951)
P = 0.017 (Cox model)
Median survival benefit = 4.1 months

Placebo (n = 171)
Median survival: 21.7 mo.
36 mo. survival: 23.0%

Sipuleucel-T (n = 341)
Median survival: 25.8 mo.
36 mo. survival: 32.1%
Sipuleucel T-Questions

• While this was a breakthrough in terms of validating a new MOA and validating the principles of immunotherapy, use has been low:
  • Controversial MOA—does it really work the way we thought
  • Few PSA declines
  • No measurable prolongation in TTP (NB-time to first progression)
  • Other agents with more “straightforward” MOAs have been developed
  • Cost
Prevention of skeletal-related events (SREs) in men with metastatic CRPC

- Zoledronic acid reduces SREs by 20% (Saad 2004)
- Zoledronic acid (Z) versus denosumab (D)
  - 1,901 patients with mCRPC
  - Patients randomized to either D (120 mg SC q 4 weeks) or Z (4 mg IV q 4 weeks).
  - D significantly delayed the time to the first on-study SRE (a fracture, need for bone radiation, need for bone surgery, or spinal cord compression) compared with Z (hazard ratio = 0.82).
  - D also significantly reduced the rate of multiple SREs compared to Z (HR = 0.82).
  - OS and TTP were same.

Fizazi et al. Lancet. 2011
Adverse Events

- More hypocalcemia with denosumab (13% vs 6%)
  - Calcium and vitamin D supplements will decrease likelihood

- Osteonecrosis of jaw (ONJ) incidence low
  - 2% denosumab vs 1% zoledronic acid, $P=0.09$

- Acute phase reactions
  - 8% denosumab vs 18% zoledronic acid

Fizazi et al. Lancet. 2011
Conclusions—Prevention of SREs

- Place on bone protective agent—zoledronic acid or denosumab are reasonable alternatives (NCCN guidelines)

- Considerations for individualizing
  - Poor dentition (may not use at all—ONJ);
  - Impaired renal function problematic with both drugs;
  - Underappreciated frequency and severity of hypocalcemia with denosumab—check renal function, Vitamin D, Ca, P, Mg levels at baseline; and
  - Are these agents necessary when other active agents are being used?
Radium-223 Targets Bone Metastases

Radium-223 acts as a calcium mimic

Naturally targets new bone growth in and around bone metastases

Short penetrating alpha-particles induce double-strand DNA breaks in adjacent tumour cells
ALSYPACA Phase III Study Design

**PATIENTS**
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases or >3 cm nodes
- Post-docetaxel or unfit for docetaxel or refusing docetaxel

**STRATIFICATION**
- Total ALP: < 220 U/L vs ≥ 220
- Bisphosphonates: Yes vs No
- Prior docetaxel: Yes vs No

**TREATMENT**
6 injections at 4-week intervals
- Radium-223 (50 kBq/kg) + Best standard of care
- Placebo (saline) + Best standard of care

**RANDOMISED**
2:1
N = 922
ALSYMPCA Updated Analysis: Overall Survival

HR = 0.695
95% CI, 0.581, 0.832
P = 0.00007

Radium-223, n = 614
Median OS: 14.9 months

Placebo, n = 307
Median OS: 11.3 months

Sartor et al Lancet Onc 2014
<table>
<thead>
<tr>
<th>Adverse Events of Interest</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 (n = 509)</td>
<td>Placebo (n = 253)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>136 (27)</td>
<td>69 (27)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (8)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>217 (43)</td>
<td>147 (58)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>112 (22)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>174 (34)</td>
<td>80 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>88 (17)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>89 (18)</td>
<td>46 (18)</td>
</tr>
</tbody>
</table>
ALSYMPCA Updated Analysis OS by Stratification Variables: Prior Docetaxel Use

Prior docetaxel use

HR = 0.710
95% CI, 0.565, 0.891
P = 0.00307

Radium-223, n = 352
Median: 14.4 months

Placebo, n = 174
Median: 11.3 months

NO prior docetaxel use

HR = 0.745
95% CI, 0.562, 0.987
P = 0.03932

Radium-223, n = 262
Median: 16.1 months

Placebo, n = 133
Median: 11.5 months

Sartor et al Lancet Onc 2014
Radium-223 Conclusions

- Radium-223:
  - Significantly prolonged median OS
  - Significantly prolonged median time to first SRE by 5.5 months
  - Benefit to pre and post chemotherapy patients
Radium-223-Questions

Radium-223:

- Rare declines in PSA
- Given over 6 months
- Optimal timing
- Can it be used earlier successfully and safely
- Can it be successfully combined with other agents
ERA 223-UNPUBLISHED

- 806 patients with mCRPC randomized to Rad 223 +/- abiraterone acetate
- Unblinded early due to more fractures and excess deaths in the combination arm.
Primary Chemotherapy

• Every 3 week docetaxel +/- prednisone is the standard first line therapy for metastatic CRPC

• Every 2 week docetaxel (50mg/m²) +/- prednisone is reasonable alternative

  - 177 patient randomized Phase II showing better tolerated and longer time to treatment failure

  Kellokumpo-Lehtinen et al Lancet Onc 2013
# Phase 3 Trials of Docetaxel Combinations

<table>
<thead>
<tr>
<th>Docetaxel/Pred vs Docetaxel+/−Pred Combined With:</th>
<th>Status</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN-101</td>
<td>Terminated early</td>
<td>Negative</td>
</tr>
<tr>
<td>GVAX</td>
<td>Terminated early</td>
<td>Negative</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Atrasentan</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>ZD4054</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Terminated early</td>
<td>Negative</td>
</tr>
<tr>
<td>VEGF-Trap</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Custiersin (OGX-011)</td>
<td>Completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Oncovax</td>
<td>Ongoing</td>
<td>Pending</td>
</tr>
</tbody>
</table>
Cabazitaxel

• Semi-synthetic taxane

• Preclinical data
  - As potent as docetaxel against sensitive cell lines and tumor models
  - Activity against tumor cells and tumor models that are resistant to, or not sensitive to currently available taxanes

• Clinical data
  - In Phase I trials, DLT was neutropenia
  - Antitumor activity in mCRPC in Phase I trials including docetaxel-resistant disease
TROPIC: Phase III Study: 146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N = 755)

Stratification factors
ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

Cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n = 378)
Mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n = 377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression
Primary Endpoint: Overall Survival (ITT Analysis)

Proportion of OS (%)

Median OS (months)  
MP 12.7  
CBZP 15.1  

Hazard Ratio 0.70  
95% CI 0.59–0.83  
P-value < 0.0001

Number at risk

MP CBZ
0 months 377 378
6 months 300 321
12 months 188 231
18 months 67 90
24 months 11 28
30 months 11 4

DeBono et al Lancet 2010
Cabazitaxel Conclusions

- Cabazitaxel
  - 30% risk reduction of death ($HR = 0.70, P < 0.0001$)
  - Median OS improvement: 15.1 months vs 12.7 months
- Granulocytopenia fever 7%
Questions?

What is the optimal dose of cabazitaxel?

Is cabazitaxel better than docetaxel?
**FIRSTANA: Study Design**

**Endpoints**
- **Primary:** Overall survival
- **Secondary:** Safety, PFS (based on tumor, PSA, pain progression or death), tumor response, PSA response, pain response, time to skeletal-related events, HROoL, pharmacokinetics, pharmacogenomics
- **Exploratory:** cfDNA

**Randomization**
- **CBZ 20 + PRED**
  - Cabazitaxel 20 mg/m² Q3W
  - + prednisone 10 mg/d
  - n = 389

- **CBZ 25 + PRED**
  - Cabazitaxel 25 mg/m² Q3W
  - + prednisone 10 mg/d
  - n = 388

- **DOC + PRED**
  - Docetaxel 75 mg/m² Q3W
  - + prednisone 10 mg/d
  - n = 391

**Inclusion Criteria**
- mCRPC and no prior chemotherapy
- ECOG PS 0-2
- N = 1,168 pts

**Location**
- 159 centers worldwide

*Oudard et al., J Clin Oncol 2017*
FIRSTANA: Overall Survival

Median OS, months (95% CI)
- DOC + PRED 24.3 (22.18–27.60)
- CBZ 20 + PRED 24.5 (21.75–27.20)
- CBZ 25 + PRED 25.2 (22.90–26.97)

CBZ 20 vs DOC
HR 1.009 (0.85–1.197)
P = 0.9967

CBZ 25 vs DOC
HR 0.97 (0.819–1.16)
P = 0.7574
### FIRSTANA: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>DOC + PRED N = 387</th>
<th>CBZ 20 + PRED N = 369</th>
<th>CBZ 25 + PRED N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade TEAE</td>
<td>376 (97.2)</td>
<td>354 (95.9)</td>
<td>376 (96.2)</td>
</tr>
<tr>
<td>Grade 3–4 TEAE</td>
<td>178 (46.0)</td>
<td>152 (41.2)</td>
<td>235 (60.1)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>126 (32.6)</td>
<td>127 (34.4)</td>
<td>186 (47.6)</td>
</tr>
<tr>
<td>TEAE leading to permanent treatment discontinuation</td>
<td>131 (33.9)</td>
<td>93 (25.2)</td>
<td>124 (31.7)</td>
</tr>
</tbody>
</table>
• This study did not demonstrate superiority of CBZ over DOC

• PFS and OS did not differ significantly across treatment arms

• No new safety concerns were identified, but differences in toxicity profiles between the two taxanes are noted

• Docetaxel remains first line treatment

• Cabazitaxel 20 preferred in second line treatment

Oudard et al., J Clin Oncol, 2017
## OS Benefit in Recent mCRPC Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Disease State</th>
<th>Comparator</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>IMPACT</td>
<td>Chemo-naive CRPC</td>
<td>Placebo</td>
<td>25.8</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>TAX327</td>
<td>Chemo-naive CRPC</td>
<td>Mitoxantrone + Prednisone</td>
<td>18.9</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>TROPIC</td>
<td>Post-docetaxel CRPC</td>
<td>Mitoxantrone + Prednisone</td>
<td>15.1</td>
</tr>
<tr>
<td>Abiraterone acetate + Prednisone</td>
<td>COU-AA-301</td>
<td>Post-docetaxel CRPC</td>
<td>Placebo + Prednisone</td>
<td>14.8</td>
</tr>
<tr>
<td>Abiraterone acetate + Prednisone</td>
<td>COU-AA-302</td>
<td>Progressive chemo-naive CRPC</td>
<td>Placebo + Prednisone</td>
<td>Not Reached</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>AFFIRM</td>
<td>Post-docetaxel CRPC</td>
<td>Placebo</td>
<td>18.4</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>PREVAIL</td>
<td>Progressive chemo-naive CRPC</td>
<td>Placebo</td>
<td>32.4</td>
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<tr>
<td>Radium-223</td>
<td>ALSYMPCA</td>
<td>Post-docetaxel CRPC</td>
<td>Placebo</td>
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## Change in outcomes for mCRPC since 2010

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<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Median OS (95% CI)</th>
<th>5-yr OS % (SE)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<td><strong>Cohort A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2004-2007</td>
<td>317 (54%)</td>
<td>2.2 (2 – 2.4)</td>
<td>10 (1.7)</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Cohort B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-2013</td>
<td>266 (46%)</td>
<td>2.8 (2.5 – 3.2)</td>
<td>26 (3.1)</td>
<td>0.69 (0.57 – 0.83)</td>
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Francini et al GU ASCO 2018
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Francini et al GU ASCO 2018
## Change in outcomes for mCRPC since 2010

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Median OS (95% CI)</th>
<th>5-yr OS % (SE)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td></td>
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<tr>
<td>2004-2007</td>
<td>317 (54%)</td>
<td>2.2 (2 – 2.4)</td>
<td>10 (1.7)</td>
<td>1</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Cohort B</strong></td>
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<tr>
<td>2010-2013</td>
<td>266 (46%)</td>
<td>2.8 (2.5 – 3.2)</td>
<td>26 (3.1)</td>
<td>0.69 (0.57 – 0.83)</td>
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</tbody>
</table>

Francini et al GU ASCO 2018
SU2C/PCF International Prostate Cancer Team

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DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

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Olaparib in mCRPC

• 50 patients with mCRPC treated with Olaparib;

• Of the 16 patients who responded to Olaparib, 14 were found to have mutations in known DNA damage-repair genes, while only 2 of the 33 non-responders had mutations in any of these genes;

• Altered DNA damage-repair genes identified in the tumors of responders included BRCA2, BRCA1, ATM, FANCA, CHEK2, PALB2, HDAC2, MRE11, and NBN; and

• Germline or somatic alteration of DNA repair was 94% predictive of response.
Olaparib received an FDA breakthrough therapy designation as a treatment for patients with BRCA1/2 or ATM-mutated mCRPC in those who have received a prior taxane-based chemotherapy and at least either hormonal agent enzalutamide or abiraterone acetate.
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le1,2,3, Jennifer N. Durham1,2,3,*, Kellie N. Smith1,3,*, Hao Wang3,*, Bjarne R. Bartlett2,4,*, Laveet...

+ See all authors and affiliations

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DOI: 10.1126/science.aan6733
Mismatch Repair Deficiency

Le et al. Science 2017
Management of mHSPC-Docetaxel
Metastatic HSPC: CHAARTED

**Stratify**

- **Age**
  - > 70 vs < 70
- **ECOG PS**
  - 0-1 vs 2
- **CAB > 30 DAYS**
  - Yes
  - No
- **Prior Adjuvant Hormonal Therapy**
  - > 12 months
  - < 12 months
- **Bisphosphonate**
  - Yes
  - No

**Randomize**

**ARM A:**
- Androgen Deprivation
  - plus Docetaxel 75 mg/m² every 21 days for maximum of 6 cycles

**Evaluate every 3 weeks while receiving Docetaxel and at week 24 then every 12 weeks**

- Follow for time to progression and overall survival.
- Chemotherapy at Investigator's discretion at progression

**ARM B:**
- Androgen Deprivation Alone

**Evaluate every 12 weeks**

- Follow for time to progression and overall survival.
- Chemotherapy at Investigator's discretion at progression

---

ECOG: CHAARTED Study; PI: Sweeney
Primary Endpoint: Overall Survival

HR = 0.61 (0.47-0.80)  P = .0006
Median OS:
ADT + D: 57.6 months
ADT: 44.0 months
OS by Extent of Metastatic Disease at Start of ADT

High-volume disease: 17 month improvement in median OS
49.2 versus 32.2 months
Long term follow-up of CHAARTED: Overall Population

Median Follow-up
28.9 months

Median Follow-up: 53.7 months

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016

13 months / HR 0.61

10 months / HR 0.73

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016
Long term follow-up of CHAARTED: High volume

Median Follow-up
28.9 months

Median Follow-up: 53.7 months

17 months / HR 0.6
Sweeney et al NEJM 2015, Sweeney et al ESMO 2016
Long term follow-up of CHAARTED: Low volume patients do not benefit

(few low volume pts have aggressive disease and benefit from early docetaxel?)

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016
Open: Oct-2005
Closed: Mar-2013
Accrual: 2962

Number of patients
1184 A Standard-of-care (SOC)
593  B SOC + zoledronic acid
592  C SOC + docetaxel
593  E SOC + zoledronic acid + docetaxel
Docetaxel: Survival – M1 Patients

- **SOC**
  - Median OS (95% CI): 43m (24, 88m)
  - SOC+Doc: 65m (27, NR)

- **SOC+Doc**

**HR (95% CI)**: 0.73
(0.59, 0.89)

**P-value**: 0.002

**At risk (events)**
- SOC: 725 (66)
- SOC+Doc: 362 (27)
Management of mHSPC-Aбиратерон
LATITUDE

Patients
- Newly diagnosed adult men with high-risk mHNPC

Stratification factors
- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

Randomized 1:1

ADT + Abiraterone acetate 1000 mg QD
+ Prednisone 5 mg QD (n = 597)

ADT + placebos (n = 602)

Efficacy end points
Co-primary:
- OS
- rPFS

Secondary: time to
- pain progression
- PSA progression
- next symptomatic skeletal event
- chemotherapy
- subsequent PC therapy

Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Fizazi et al NEJM 2017
Statistically significant 38% risk reduction of death
Statistically significant 53% risk reduction of radiographic progression or death

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

Fizazi et al NEJM 2017
Comparison

Open: Nov-2011
Closed: Jan-2014
Accrual: 1917

Number of patients

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<tr>
<td>957</td>
<td>A</td>
<td>Standard-of-care* (SOC)</td>
</tr>
<tr>
<td>960</td>
<td>G</td>
<td>SOC + abiraterone acetate + prednisolone (SOC+AAP)</td>
</tr>
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</table>

*SOC = ADT ± RT

James et al NEJM 2017
Overall Survival – STAMPEDE “abiraterone comparison”

Events
262 Control | 184 Abiraterone

SOC+AAP

SOC

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

James et al
NEJM 2017
### mHSPC Treatment in Addition to ADT: Opinion

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Option</th>
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<tr>
<td><em>De novo</em> or high volume</td>
<td>Either AA or docetaxel but favor docetaxel</td>
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<tr>
<td>Non-<em>de novo</em> mets</td>
<td>ADT, probably with either AA or docetaxel</td>
</tr>
<tr>
<td>Non-high volume mets</td>
<td>ADT, probably with either AA or docetaxel</td>
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