Treatment Challenges in Castrate Resistant Prostate Cancer
Prostate Cancer Clinical States

[Diagram showing the progression of prostate cancer clinical states, including stages like Asymptomatic, Local Therapy, Castration, 2nd-line Hormonal therapy, and different treatments like Docetaxel 2004, Abiraterone 2013, Enzalutamide 2014, Cabazitaxel 2010, Abiraterone 2011, Enzalutamide 2012, Radium-223.]
Castrate resistant prostate cancer

What is Castration Resistance Prostate Cancer?

- Progressive disease despite castration levels of testosterone (50 ng/dL)
- Progression could be PSA or Imaging
- The androgen receptor drives prostate cancer growth
  - Depriving the tumor of testosterone is the primary therapy for metastatic disease
Anti-androgen therapy

So why do we use Anti-Androgen therapy in CRPC?

Resistance Mechanisms:
- AR Amplification
- Secondary androgen production
- Ligand independent growth
- Intranuclear changes

Integrative clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer

Prostate cancer rules

Rules of the Game: Prostate Cancer Working Group

• PSA is **NOT** the primary measure of progression in mCRPC

• Radiographic imaging is the primary objective measure

• Patient symptoms and treatment tolerability also paramount

Scher, HI et al J. Clin Oncol, 2008
Optimal treatment sequence

Optimal Treatment Sequence?

- No clear data for sequencing treatment in metastatic castration resistant prostate cancer (mCRPC)

- Ongoing trials will evaluate this question further

- In the absence of data I will provide my opinion on treatment selection

- Treatment decisions should be made with understanding of the following factors
  - Treatment side effects
  - Patient co-morbidities
  - Patient symptoms
  - Pace of disease
Prostate cancer menu

**MENU**

**Appetizer**
Sipuleucel-T

**First Course**
Enzalutamide
Abiraterone

**Second Course**
Docetaxel
Radium-223

**Third Course**
Cabazitaxel
Options from *1st* or *2nd* Course
Prostate cancer appetizer

MENU

Appetizer
Sipuleucel-T
early mCRPC
minimal symptoms, low volume, slow pace

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Options: 1st or 2nd Course
Therapeutic Cancer Vaccine: Sipuleucel-T
IMPACT: Randomized Phase 3 Trial

IMPACT: Randomized Phase 3 Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=512)

2:1

Sipuleucel-T Q 2 weeks x 3

Placbo Q 2 weeks x 3

PROGRESSION

Treated at Physician discretion

Treated at Physician discretion and/or Salvage Protocol

SURVIVAL

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression

Kassoff PW et al. NEJM. 2010;363:411-22
Sipuleucel-T: IMPACT Overall Survival

- **P = 0.032** (Cox model)
- **HR = 0.775 [95% CI: 0.614, 0.979]**

**Median Survival Benefit = 4.1 Mos.**

- **Sipuleucel-T (n = 341)**
  - Median Survival: 25.8 Mos.

- **Placebo (n = 171)**
Sipuleucel-T

Sipuleucel-T: IMPACT Overall Survival

No Change in PFS, Rare PSA Declines

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]

Median Survival Benefit = 4.1 Mos.
Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.

Kantoff PW et al. NEJM. 2010
PSA and Sipuleucel-T

Patients with Lower PSA Had Greater OS Benefit After Sipuleucel-T

<table>
<thead>
<tr>
<th>Baseline PSA (ng/ml)</th>
<th>&lt;22 (n=188)</th>
<th>22-50 (n=128)</th>
<th>50-134 (n=128)</th>
<th>&gt;134</th>
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<tbody>
<tr>
<td>Median OS (mos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference</td>
<td>13.0</td>
<td>7.0</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.51</td>
<td>0.74</td>
<td>0.81</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Schellhammer PF et al. Urol. 2013
Sipuleucel-T Toxicity

- Chills, fatigue, fever, nausea, and headache

- Cerebrovascular events were reported in 3.5 percent of patients treated with sipuleucel-T patients and 2.4 percent of patients who received placebo.
Prostate cancer first course

**First Course**

- minimal to moderate symptoms
- **Enzalutamide**
  - minimal side effects, optimal in low volume, slow pace of disease
- **Abiraterone**

**Second Course**
- Docetaxel
- Radium-223

**Third Course**
- Cabozantinib
Enzalutamide

**MENU**

- Apoptosis
- Sipuleucel-T

**First Course**
minimal to moderate symptoms
- Enzalutamide
- Abiraterone
  requires concomitant prednisone

**Second Course**
- Docetaxel
- Radium-223

**Third Course**
- Cabazitaxel
Enzalutamide

A small molecule AR antagonist

Affinity 30 folds of bicalutamide

Prevent nuclear translocation

Prevents co-activator recruitment
AFFIRM

AFFIRM: Randomized Phase III Study of MDV3100 vs. Placebo in mCRPC after Progression on Docetaxel

Castration Resistant Prostate Cancer (N=1199)

2:1

Enzalutamide 160mg/day Corticosteroids allowed but not required

Placebo
**AFFIRM**: Phase III trial with 1199 patients with mCRPC Previously treated with docetaxel  OS: 18/4 to 13.6 mos (HR: 0.63; P<0.001) TTP: 8.3 vs 2.9 mos (HR: 0.40; P <0.001) FDA approved on 8/31/2012
PREVAIL: Randomized Phase III Study of Enzalutamide vs Placebo in mCRPC before chemotherapy
Enzalutamide Toxicity

Cardiovascular: Peripheral edema (15%)
Central nervous system: Fatigue (51%), headache (12%)
Endocrine & metabolic: Hot flashes (20%)
Gastrointestinal: Diarrhea (22%)
Hematologic: Neutropenia (15%; grades 3/4: 1%)
Neuromuscular & skeletal: Back pain (26%), arthralgia (21%), musculoskeletal pain (15%)
Respiratory: Upper respiratory tract infection (11%)
Abiraterone

First Course
Enzalutamide
Abiraterone
requires concomitant prednisone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Options: 10-15 h E-dose
Abiraterone rationale

Rationale for Abiraterone in CRPC

- There is up-regulation of androgen biosynthesis enzymes in CRPC

- Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue

Abiraterone study

Abiraterone: COU-AA-301 Study Design

- N = 1195
- Progressive, mCRPC
- Previous docetaxel
- ECOG 0 – 2
- Medical or surgical castration with serum testosterone < 50 ng/dL

Randomized 2:1

Abiraterone acetate
1000 mg orally daily
Prednisone
5 mg orally twice daily
n = 797

Placebo orally daily
Prednisone 5 mg orally
twice daily
n = 398

Primary end point:
- Overall Survival (OS)

- This study was conducted in 147 sites in 13 countries
- Patients were enrolled from May 2008 through July 2009

De Bono J, et al. NEJM 2011
Abiraterone: COU-AA-301 Trial
## Abiraterone: COU-AA-301 Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abiraterone Acetate (N = 797)</th>
<th>Placebo (N = 398)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to PSA progression (mo)</td>
<td>10.2</td>
<td>6.6</td>
<td>0.58 (0.46–0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression-free survival according to radiographic evidence (mo)</td>
<td>5.6</td>
<td>3.6</td>
<td>0.67 (0.59–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA response rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>38.0</td>
<td>10.1</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Confirmed response on the basis of the PSA concentration</td>
<td>29.1</td>
<td>5.5</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Objective response on the basis of imaging studies</td>
<td>14.0</td>
<td>2.8</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

de Bono JS et al. NEJM 2011
COU-AA-302

COU-AA-302 (chemo-naïve)

Ryan CJ, Lancet Oncol, 2015
Abiraterone Toxicity

Cardiovascular: Edema (25% to 27%), hypertension (9% to 22%; grades 3/4: 1% to 4%)

Central nervous system: Fatigue (39%), insomnia (14%)

Dermatologic: Bruise (13%)

Endocrine & metabolic: Increased serum triglycerides (63%), hyperglycemia (57%), hypernatremia (33%), hypokalemia (17% to 28%; grades 3/4: 3% to 5%), hypophosphatemia (24%; grades 3/4: 7%), hot flash (19% to 22%)

Gastrointestinal: Constipation (23%), diarrhea (18% to 22%), dyspepsia (6% to 11%)

Genitourinary: Urinary tract infection (12%)

Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

Hepatic: Increased serum ALT (11% to 42%; grades 3/4: 1% to 6%), increased serum AST (31% to 37%; grades 3/4: 2% to 3%)

Neuromuscular & skeletal: Joint swelling (30%, including joint discomfort), myalgia (26%)

Respiratory: Cough (11% to 17%), upper respiratory infection (5% to 13%), dyspnea (12%), nasopharyngitis (11%)
Cross resistance

Evidence for cross-resistance

First Course
- Enzalutamide
- Abiraterone

Many patients may not benefit from sequential use

Second Course
- Docetaxel
- Radium-223

Third Course
- Cabazitaxel
- Options from 1st or 2nd Course
Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constitutently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.
- Thus sequential abiraterone and enzalutamide use may not have additive benefits

**Docetaxel**

*Menu*

First Course
- Sipuleucel-T
- Enzalutamide
- Abiraterone

Second Course
- Moderate to substantial symptoms
  - **Docetaxel**
  - Radium-223

Third Course
- Cabazitaxel
- Options from 1st or 2nd Course
For fast paced disease

**First Course**
- Enzalutamide
- Abiraterone

**Second Course**
*Moderate to substantial symptoms*  
**Docetaxel**
perhaps the best option for patients with substantial symptoms, fast paced disease
- Radium-223

**Third Course**
- Cabazitaxel
  - Following from 1st or 2nd course
Docetaxel

• In 1960s, crude extract of the bark of the Pacific yew tree, Taxus brevifolia, was shown to have suppressive activity in preclinical tumor models.

• By 1971, paclitaxel was identified as the active constituent of the bark extract.

• Taxanes exhibit antimicrotubule and antitumor activity

• Emerging data suggests that taxanes inhibit AR translocation via microtubules
Phase III study

TAX327: A Multicenter, Randomized Phase III Study of 3 weekly Docetaxel + Prednisone vs. Weekly Docetaxel + Prednisone vs. Mitoxantrone + Prednisone

Castration Resistant Prostate Cancer (N=1006)

- Docetaxel 75mg/m2 Q3wks + Prednisone 10mg daily
- Docetaxel 30mg/m2 Q1wk + Prednisone 10mg daily
- Mitoxantrone 12mg/m2 Q3wks + Prednisone 10mg daily

TAX327: Overall Survival

- **TAX327: Overall Survival**

- **Graph showing survival rates**
  - **Docetaxel 3 wkly**
  - **Docetaxel wkly**
  - **Mitoxantrone**

- **Median survival (mos)**
  - D 3wkly: 18.9
  - D wkly: 17.3
  - Mitoxantrone: 16.4

- **Hazard ratio**
  - 0.76
  - 0.91
  - 1.3

- **P-value**
  - 0.009
  - 0.3
Docetaxel Toxicity

Central nervous system: Central nervous system toxicity (20% to 58%; severe: 6%; including neuropathy)
Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)
Endocrine & metabolic: Fluid retention (13% to 60%; severe: 7% to 9%; dose dependent)
Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
Hematologic & oncologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 97%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (5% to 14%; dose dependent)
Hepatic: Increased serum transaminases (4% to 19%)
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)
Infection: Infection (1% to 34%; dose dependent)
Neuromuscular & skeletal: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%), neuromuscular reaction (16%)
Respiratory: Pulmonary reaction (41%)
Radium

MENU

First Course
Enzalutamide
Abiraterone

Second Course
Moderate to substantial symptoms
Docetaxel
Radium-223

symptomatic bone disease, no visceral disease; ideal patient population unknown

Third Course
Cabazitaxel

Ganitumab PRRT as 2nd Course
Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical
High energy alpha-particles with short range (<100μm) hence less bone marrow toxicity
Radium trial

ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases

CRPC
Symptomatic
≥2 bone mets
(N=922)

RANDOMIZED
2:1

Ra-223 50kBq/kg q4wks x 6

Placebo
Phase III study of Radium-223

ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases

A Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001

Radium-223
(median overall survival, 14.9 mo)

Placebo
(median overall survival, 11.3 mo)

No. at Risk
Radium-223: 614, 578, 504, 369, 274, 178, 105, 60, 41, 18, 7, 1, 0, 0
Placebo: 307, 288, 228, 157, 103, 67, 39, 24, 14, 7, 4, 2, 1, 0

Survival curves
Radium toxicity

Radium 223 AEs

- Cardiovascular: Peripheral edema (13%)
- Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)
- Hematologic: Anemia (93%; grades 3/4: 6%), lymphocytopenia (72%; grades 3/4: 20%), leukopenia (35%; grades 3/4: 3%), thrombocytopenia (31%; grades 3/4: 1% to 6%), neutropenia (18%; grades 3/4: 1% to 3%)

Third course

MENU

Appetizers
sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Docetaxel refractory
Cabazitaxel
Options from 1st or 2nd Course
Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump
Methoxyl side chain instead of hydroxyl groups found in docetaxel
TROPIC protocol

TROPIC: Randomized Phase III Study of Cabazitaxel vs. Mitoxantrone in mCRPC after Progression on Docetaxel

- Cabazitaxel 25mg/m² Q3wks + Prednisone 10mg daily
- Mitoxantrone 12mg/m² Q3wks + Prednisone 10mg daily

Castration Resistant Prostate Cancer (N=755)
TROPIC: Progression-Free Survival
TROPIC: Overall Survival
Cabazitaxel and ASCO

Cabazitaxel at ASCO 2016

- Cabazitaxel was not superior to docetaxel in front-line chemotherapy setting
- Cabazitaxel at 20 mg has same long term outcomes as Cabazitaxel at 25 mg

Sartor OA et al. ASCO 2016
Cabazitaxel Toxicity

Central nervous system: Fatigue (37%), fever (12%)
Gastrointestinal: Diarrhea (47%; grades 3/4: 6%), nausea (34%), vomiting (22%), constipation (20%), abdominal pain (17%), anorexia (16%), taste alteration (11%)
Hematologic: Anemia (98%; grades 3/4: 11%), leukopenia (96%; grades 3/4: 69%), neutropenia (94%; grades 3/4: 82%; nadir: 12 days [range: 4-17 days]), thrombocytopenia (48%; grades 3/4: 4%)
Neuromuscular & skeletal: Weakness (20%), back pain (16%), peripheral neuropathy (13%; grades 3/4: <1%), arthralgia (11%)
Renal: Hematuria (17%)
Respiratory: Dyspnea (12%), cough (11%)
Third course

- Docetaxel refractory
- Cabazitaxel
- Enzalutamide
- Abiraterone
- Radium-223

OS data post docetaxel
Complete menu

Menu

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223

Ultimate Goal: Use as many items on the menu while also maximizing quality of life
Specials

Specials

Break Through Status

PARP Inhibition
PARP Inhibitor

PARP Inhibitor – Breakthrough Status

• 50 patients treated with olaparib
• 16 patients had “responses”
• 14 of the 16 had DNA damage repair defects
• Total of 16 patients overall had DNA damage repair defects

The NEW ENGLAND JOURNAL of MEDICINE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer

E3805 CHAARTED Treatment

**STRATIFICATION**
- Extent of Mets
  - High vs Low
- Age
  - ≥70 vs < 70yo
- ECOG PS
  - 0 vs 1 vs 2
- CAB > 30 days
  - Yes vs No
- SRE Prevention
  - Yes vs No
- Prior Adjuvant ADT
  - ≤12 vs > 12 months

**RANDOMIZE**
- **ARMA:**
  - ADT + Docetaxel
  - 75mg/m² every 21 days for a maximum of 6 cycles
- **ARM B:**
  - ADT (androgen deprivation therapy alone)

**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

- ADT allowed up to 120 days prior to randomization
- Intermittent ADT was not allowed
- Standard dexamethasone premedication but no daily prednisone

Presented by Christopher J. Sweeney, MBBS

Presented by Christopher Sweeney at 2014 ASCO Annual Meeting
Survival curve

Hazard ratio for death with ADT+docetaxel, 0.61 (95% CI, 0.47–0.80) P<0.001

ADT+docetaxel (median overall survival, 57.6 mo)

ADT alone (median overall survival, 44.0 mo)

Sweeney, CJ et al. NEJM. 2015
Prostate Cancer Clinical States
Docetaxel

CHAARTED/E3805 supports docetaxel in metastatic castration-sensitive prostate cancer

Castration

2nd-line Hormonal therapy

Abiraterone 2013
Enzalutamide 2014

Docetaxel 2004

Cabanitaxel 2010
Abiraterone 2011
Enzalutamide 2012

Sipuleucel-T 2010
Radium-223 2013

Asymptomatic

Symptoms

Metastatic

Castration Sensitive

Castration Resistant

Time →
LATITUDE study
Survival curve
Summary

Menu

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223

Ultimate Goal: Use as many items on the menu while also maximizing quality of life
Third course

Appetizer
Sipuleucel-T

First Course
Enzalutamide
Abiraterone

Second Course
Docetaxel
Radium-223

Third Course
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223

Ultimate Goal: Use as many items on the menu while also maximizing quality of life
Carbazitaxel vs. Docetaxel

- Cabazitaxel was not superior to docetaxel in front-line chemotherapy setting
- Cabazitaxel at 20 mg has same long term outcomes as Cabazitaxel at 25 mg

Sarter OA et al. ASCO 2016
Dilemmas in treatment
Dilemmas in Treatment

Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- What is Metastatic Castration Sensitive Prostate Cancer?
  - Newly diagnosed patients who have metastatic disease
  - Patients who had been previously treated with definitive surgery or radiation but then develop metastasis
  - All patients have NORMAL Testosterone
CHAARTED Treatment

E3805 – CHAARTED Treatment

**STRATIFICATION**
- Extent of Metts
  - High vs. Low
- Age
  - 65 vs. < 70 yrs
- ECOG PS
  - 0-1 vs. 2
- CABG 30 days
- HER2 vs. No
- SRE Prevention
- Yes vs. No
- Prior Adjuvant ADT
  - ≤12 vs. > 12 months

**RANDOMIZE**

**ARM A:**
- ADT + Docetaxel
  - 1mg/m² every 28 days for maximum 8 cycles

**ARM B:**
- ADT (androgen deprivation therapy alone)

**Evaluate every 3 weeks while receiving docetaxel and then every 12 weeks**

**Evaluative every 12 weeks**

**Advance to progression and overall survival**

**Chemotherapy at investigator’s discretion at progression**

---

*ADT allowed up to 120 days prior to randomization.
Intermittent ADT dosing was not allowed.
Standard dexamethasone premedication but no daily prednisone.

**ASCO**

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*Presented by Christopher J. Swanson, MD, PhD*
Survival curve
Docetaxel overall survival

Docetaxel OS based on Volume of Disease

- Pre-defined categories
- High Volume – more than 4 bone lesions (1 of which must be beyond the spine/pelvis)
  - or any visceral disease
- Low Volume – disease confined to the axial skeleton (spine and pelvis)
  - or less than 3 lesions
  - no visceral disease
- Lymph node disease is not factored in
Docetaxel overall survival

Docetaxel OS based on Volume of Disease
Docetaxel Tolerability
Study design

Overall study design of LATITUDE

- **Patients**
  - Newly diagnosed adult men with metastatic castration-resistant PC
  - Risk factors
    - Presence of visceral disease (PSA > 100)
    - ECOG PS 0-1 (T1-T2)
  - Exclusion criteria
    - Prior antineoplastic therapy
    - PSA < 50 ng/mL
  - Randomization
    - 1:1

- **ADT**
  - Nilutamide
  - Flutamide
  - Megestrol acetate 1000 mg/1200 mg
  - Prednisone 5 mg/16 mg/8 mg (n = 987)

- **ADTF**
  - Placebo
  - (n = 662)

- **Efficacy end points**
  - PSA
  - ADTF
  - Secondary time to:
    - PSA progression
    - PSA progression:
      - Initial symptomatic skeletal event
      - Chemotherapy
      - Subsequent ADT 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/SAPPEDE results
Patient Eligibility

Patient Eligibility: “Defining High Risk” In LATITUDE

- Different than docetaxel study

- At least 2 of the following 3 were required:
  - Gleason 8 or higher
  - More than 3 bone lesions (sites unspecified)
  - Visceral disease.
Abiraterone outcomes
Abiraterone toxicity
Abiraterone

This was NOT a Study of Early Abiraterone vs. Late Abiraterone (at mCRPC)

![Table showing the comparison of subsequent life-prolonging therapy for prostate cancer between Abiraterone Group (n=404) and Placebo Group (n=404).]

*Fizazi K et al. NIMA, 2017*
Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- Abiraterone (indeinitely) vs 6 infusions of docetaxel
- ADT is continued indefinitely with both options
- Risk benefit discussion with the patient
- Can you retreat with docetaxel if you give 6 cycles of docetaxel?
- High volume vs. Low volume – should they be treated differently?
Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- Abiraterone (indefinitely) vs 6 infusions of docetaxel
- ADT is continued indefinitely with both options
- Risk benefit discussion with the patient
- Can you retreat with docetaxel if you give 6 cycles of docetaxel?
- High volume vs. Low volume – should they be treated differently?
New Treatments for M0 Prostate Cancer

• What is M0 prostate cancer
  - Rising PSA despite castrate levels of testosterone
  - No evidence of metastasis on conventional imaging (CT and bone scan)
  - Metastatic castration sensitive prostate cancer

• What were the previous “standard approaches”
  - All patients are on androgen deprivation therapy (ADT) or post-orchiectomy
  - In addition, sequential anti-androgens could be used (bicalutamide, flutamide, nilutamide, ketoconazole)
Apalutamide

- Nonsteroidal antiandrogen
- Binds to the ligand-binding domain of the androgen receptor (AR)
- Limits androgen-receptor translocation to the nucleus
- Limits DNA binding of the AR in the nucleus
- Limits androgen-receptor-mediated transcription
SPARTAN
Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apalutamide (n=192)</th>
<th>Placebo (n=200)</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
</tr>
<tr>
<td>Range</td>
<td>50-70</td>
<td>60-80</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior androgen deprivation</td>
<td></td>
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<tr>
<td>Prior androgen deprivation</td>
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There were no significant differences between the groups in the baseline characteristics of the patients.
Apalutamide improves metastasis-free survival.
Secondary Progression

Secondary Progression for Patients Who were Subsequently Treated with Abiraterone
Abiraterone administration
Prosper Study Design
Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enzalutamide + ADT (n = 933)</th>
<th>Placebo + ADT (n = 468)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>76 (60-95)</td>
<td>73 (60-90)</td>
</tr>
<tr>
<td>ECOG PS, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>167 (26%)</td>
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<tr>
<td>1</td>
<td>168 (21%)</td>
<td>85 (18%)</td>
</tr>
<tr>
<td>Median serum PSA (range), ng/mL</td>
<td>11.1 (0.2-1071.1)</td>
<td>10.2 (0.2-487.5)</td>
</tr>
<tr>
<td>Median PSA doubling time (range), mo</td>
<td>3.6 (0.3-37.4)</td>
<td>3.8 (0.4-71.9)</td>
</tr>
<tr>
<td>PSA doubling time category, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 mo</td>
<td>719 (77%)</td>
<td>363 (77%)</td>
</tr>
<tr>
<td>≥ 6 mo</td>
<td>217 (23%)</td>
<td>197 (23%)</td>
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<tr>
<td>Baseline use of hormone-targeting agent, no. (%)</td>
<td>629 (69%)</td>
<td>420 (90%)</td>
</tr>
<tr>
<td>No</td>
<td>169 (17%)</td>
<td>48 (10%)</td>
</tr>
</tbody>
</table>

- Median duration of therapy was 15.4 (range, 6.4-31.9) months for enzalutamide and 11.1 (range, 6.4-42.8) months for placebo.
- Patients on treatment as of 28 June 2017 (cut-off date): 434 patients (69%) on enzalutamide and 170 patients (31%) on placebo.
Adverse events
Primary endpoint
Overall survival
Progression event

### Progression Event by Type

<table>
<thead>
<tr>
<th>Event, No. (%)</th>
<th>Enzalutamide + ADT (n = 332)</th>
<th>Placebo + ADT (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All progression events</td>
<td>219 (23%)</td>
<td>220 (49%)</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New bone metastases</td>
<td>187 (56%)</td>
<td>224 (69%)</td>
</tr>
<tr>
<td>New soft-tissue metastases</td>
<td>71 (32%)</td>
<td>79 (37%)</td>
</tr>
<tr>
<td>Concurrent new bone and soft-tissue metastases</td>
<td>109 (50%)</td>
<td>132 (58%)</td>
</tr>
<tr>
<td>Death without documented radiographic progression within 112 days of study treatment discontinuation</td>
<td>7 (3%)</td>
<td>13 (6%)</td>
</tr>
</tbody>
</table>

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

Note: Percentages are based on total number of patients randomized to each arm. enzalutamide = ADT, n = 332; placebo = ADT, n = 331.

Proportion of patients randomized to enzalutamide + ADT, n = 332; placebo + ADT, n = 331.
Treating MO Prostate Cancer

My Thoughts on Treating MO Prostate Cancer

- Consider the eligibility of the trial
  - PSA Doubling Time less than 10 months
  - Minimum PSA Value

- Risk vs. Benefit in an elderly population

- We still do not know if earlier Enzalutamide or Apalutamide is better (i.e. MO vs. at mCRPC)

- OS benefit still unclear (with either treatment or head to head)

- Personally, I may still consider an older agent (i.e. bicalutamide) first, but apalutamide/enzalutamide will be a good for a subset of patients
Future Investigations

- Identify best sequence of therapy
- Biomarkers to select best therapy
- Are combinations better than sequence
- How will more sensitive imaging change the disease
- Can you cure oligometastatic disease
- How does immunotherapy fit in the treatment of prostate cancer