Castration-resistant prostate cancer

Castration-Resistant Prostate Cancer: Current Approach

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Center for Cancer Research, NCI, NIH
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Prostate Cancer Clinical States

Prostate Cancer Clinical States

- Asymptomatic
- Non-Metastatic
- Metastatic
- Castration Sensitive
- Castration Resistant

Time

Tumor volume

Local Therapy

Castration

2nd-line Hormonal therapy

Abiraterone 2013
Enzalutamide 2014

Docetaxel 2004

Sipuleucel-T 2010

Cabazitaxel 2010
Abiraterone 2011
Enzalutamide 2012
Radium-223

Death
FDA approved therapies

Prostate Cancer FDA-Approved Therapies for Newly Metastatic (Normal Testosterone)

- Docetaxel 2015
- Abiraterone 2017
- Enzalutamide (2019)
- Apalutamide (2019)

Castration

Tumor volume

Asymptomatic

Symptoms

Patients Diagnosed with Metastatic Disease

Castration Sensitive

Castration Resistant
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

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
mCRPC treatment considerations

Considerations for the Treatment of mCRPC

Key disease questions:
- Previous therapies
- Pace of disease (e.g. time of progression on ADT, pace of mets)
- Symptoms (none, moderate or significant)

Key patient characteristics:
- Age
- Comorbidities
- Quality of life preferences
- Treatment logistics
One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

- **Minimal Symptoms**
  - Sipuleucel-T

- **Minimal to Moderate Symptoms**
  - Abiraterone or Enzalutamide

- **Significant Symptoms**
  - Docetaxel or Radium 223

- **Post chemotherapy for mCRPC**
  - Cabazitaxel, Radium 223, Enzalutamide, Abiraterone

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Rapid Pace of Disease*

- Minimal Symptoms: Sipuleucel-T
- Minimal to Moderate Symptoms: Abiraterone or Enzalutamide
- Significant Symptoms: Docetaxel or Radium 223
- Post chemotherapy for mCRPC: Cabazitaxel, Radium 223, Enzalutamide, Abiraterone

*Initial response to ADT short (e.g., less than 1 year) or
*Metastasis on scans shows rapid progression
Decision algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

- Minimal Symptoms
- Sipuleucel-T

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
Therapeutic Cancer Vaccine: Sipuleucel-T
**IMPACT**: Randomized Phase 3 Trial

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**IMPACT**: Randomized Phase 3 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: Time to Objective Disease Progression

Kantoff 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)
Median Survival: 21.7 Mos.
Sipuleucel-T: IMPACT Overall Survival

- No Change in PFS, Rare PSA Declines

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

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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS (mos)</strong></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-Y recommendations

Society of Immunotherapy of Cancer (SITC) Recommendations for Sipuleucel-T

Sipuleucel-T

- Don’t expect PSA decrease
- Use early, in less aggressive disease

My recommendation: Treat and move on to the next therapy
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.
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

Minimal Symptoms  Sipuleucel-T

Minimal to Moderate Symptoms  Abiraterone or Enzalutamide

Diagnosis of mCRPC

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
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%)
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

- Minimal Symptoms
  - Sipuleucel-T

- Minimal to Moderate Symptoms
  - Abiraterone or Enzalutamide & Prednisone

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
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 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>
</tr>
<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>
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%)
Normal pace of disease

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

- Minimal Symptoms: Sipuleucel-T
- Minimal to Moderate Symptoms: Abiraterone or Enzalutamide
  Patients may not benefit from sequential use (cross-resistance)

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
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

PROPHECY

PROPHECY: Regardless of Platform, Patients with Splice Variant AR-V7 had Worse Outcomes

Armstrong AJ et al. JCO, 2019
PROPHECY

PROPHECY: Regardless of Platform, Patients with Splice Variant AR-V7 had Worse Outcomes

Armstrong A J et al. JCO, 2019
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Rapid Pace of Disease*

- **Minimal Symptoms**
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- **Minimal to Moderate Symptoms**
  - Abiraterone or Enzalutamide

- **Significant Symptoms**
  - Docetaxel or Radium 223

- **Post chemotherapy for mCRPC**
  - Radium 223, Enzalutamide, Abiraterone

*mCRPC with rapid pace or substantial symptoms

*Initial response to ADT short (e.g., less than 1 year) or
*Metastasis on scans shows rapid progression
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

- **Docetaxel 3 wkly**: Median survival 18.9 months, Hazard ratio 0.76, P-value 0.009
- **Docetaxel wkly**: Median survival 17.3 months, Hazard ratio 0.91, P-value 0.3
- **Mitoxantrone**: Median survival 16.4 months

Probability of Surviving vs. Months
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%)
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

- Minimal Symptoms: Sipuleucel-T
- Minimal to Moderate Symptoms: Abiraterone or Enzalutamide
- Significant Symptoms: Docetaxel or Radium 223
- Post chemotherapy for mCRPC: Radium 223, Enzalutamide, Abiraterone

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
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)

Ra-223 50kBq/kg q4wks x 6

Placebo
ALSYMPCA trial

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

Survival curve

ALSYMPCA: Subgroup Analysis based on Previous Docetaxel

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%)
Algorithm

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*

1. Minimal Symptoms → Sipuleucel-T
2. Minimal to Moderate Symptoms → Abiraterone or Enzalutamide
3. Significant Symptoms → Docetaxel or Radium 223
4. Post chemotherapy for mCRPC → Cabazitaxel, Radium 223, Enzalutamide, Abiraterone

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression
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
Phase III study

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

Castration Resistant Prostate Cancer (N=755)

1:1

Cabazitaxel 25mg/m2 Q3wks + Prednisone 10mg daily

Mitoxantrone 12mg/m2 Q3wks + Prednisone 10mg daily

de Bono JS, et al. Lancet 2010
TROPIC

TROPIC: Overall Survival

- Median OS (months) for MP: 12.7, for CBZP: 15.1
- Hazard Ratio: 0.70
- 95% CI: 0.59–0.83
- P-value: <.0001

(number of patients at risk)

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de Bono JS et al. Lancet 2010
Cabazitaxel 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

Sartor OA et al. ASCO 2016
Cabazitaxel toxicity

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: 32%; 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%)

Should strongly consider the use of growth factor
Metastatic disease

Biopsy Metastatic Disease? Why? When?
PARP inhibitor

PARP Inhibitor – Breakthrough Status

- 50 patients treated with olaparib
- 16 patients had "responses"
- 14 of the 16 had DNA damage repair defects

MSI high prostate cancer

MSI High Prostate Cancer

Approval of pembrolizumab

Incidence

- Localized PC ~2%

- Autopsy series of mCRPC ~12%
  - Pritchard et al., *Nature Com* 2011
  - Ongoing testing suggests 5-6% of mCRPC

Lemery et al., *NEJM* 2017
New therapies

MSI High Prostate Cancer

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MSI

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Lemery et al., NEJM 2017
Olaparib for mCRPC (chemo-naïve)
Olaparib for mCRPC

Olaparib for mCRPC (chemo-naïve)

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de Bono E et al. J. Eng. Med. 2020
Chemo-naive

Olaparib for mCRPC (chemo-naïve)
Rucaparib

Rucaparib mCRPC (chemo-refractory)

Figure 4. Best Change from Baseline in PSA in Rucaparib-Treated Patients with a BRCA1/2 Alteration (n=96)
Current approach

Castration-Resistant Prostate Cancer: Current Approach

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Prostate cancer

Non-Metastatic Castration Resistant Prostate Cancer
Approved therapies

Prostate Cancer FDA-Approved Therapies for CRPC

- Castration
- Local Therapy
- 2nd-line Hormonal therapy
- Apalutamide 2018
- Enzalutamide 2018
- Darolutamide 2019
- Docetaxel 2004
- Abiraterone 2013
- Enzalutamide 2014
- Cabazitaxel 2010
- Abiraterone 2011
- Enzalutamide 2012
- Ipilimumab 2010
- Radium-223 2013

Tumor volume

Asymptomatic
- Non-Metastatic
  - Castration Sensitive
- Metastatic
  - Castration Resistant

Symptoms

Death
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
Apalutamide

Apalutamide in nmCRPC

Patient Baseline Characteristics

Apalutamide in M0 prostate cancer

Table 1. Demographic and Disease Characteristics at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apalutamide (N=800)</th>
<th>Placebo (N=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>Median: 74</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Range: 48–84</td>
<td>52–97</td>
</tr>
<tr>
<td>Median time from initial diagnosis to randomization — yr</td>
<td>7.95</td>
<td>7.85</td>
</tr>
<tr>
<td>Prostate-specific antigen doubling time</td>
<td>Median: 4.40</td>
<td>4.50</td>
</tr>
<tr>
<td></td>
<td>Range: 3.0–13.4</td>
<td>3.6–16.4</td>
</tr>
<tr>
<td>ab No. (%)</td>
<td>576 (71.8)</td>
<td>284 (70.8)</td>
</tr>
<tr>
<td>≥6 Mo — no. (%)</td>
<td>230 (28.5)</td>
<td>117 (29.2)</td>
</tr>
<tr>
<td>Use of bone-sparing agent — no. (%)</td>
<td>Yes: 82 (10.2)</td>
<td>39 (9.7)</td>
</tr>
<tr>
<td></td>
<td>No: 724 (90.8)</td>
<td>362 (90.3)</td>
</tr>
<tr>
<td>Classification of local or regional nodal disease — no. (%)</td>
<td>N0: 673 (83.5)</td>
<td>336 (83.8)</td>
</tr>
<tr>
<td></td>
<td>N1: 133 (16.5)</td>
<td>65 (16.2)</td>
</tr>
<tr>
<td>Previous prostate cancer treatment — no. (%)</td>
<td>Prostatectomy or radiation therapy: 617 (76.6)</td>
<td>307 (76.6)</td>
</tr>
<tr>
<td></td>
<td>Goradotestin releasing hormone analogue agonist: 780 (96.8)</td>
<td>387 (96.5)</td>
</tr>
<tr>
<td></td>
<td>First generation antiandrogens agent: 592 (73.4)</td>
<td>290 (72.3)</td>
</tr>
</tbody>
</table>

* There were no significant differences between groups in the demographic and disease characteristics at baseline.

Scully, MR et al., NEJM, 2018
Metastasis-free survival

Apalutamide Improves Metastasis-Free Survival

[Graph showing survival rates and hazard ratio with risk numbers]
Secondary progression

Secondary Progression for Patients Who were Subsequently Treated with Abiraterone

![Graph showing survival rates and hazard ratio for second progression or death. The graph compares patients treated with Apalutamide and Placebo, with a hazard ratio of 0.49 (95% CI, 0.36–0.66). The number of patients at risk is shown for each group over the months.]
Apalutamide

Apalutamide in nmCRPC

Table 3: Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Any Grade (N=880)</th>
<th>Grade 3 or 4 (N=880)</th>
<th>Any Grade (N=398)</th>
<th>Grade 3 or 4 (N=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>775 (96.5%)</td>
<td>362 (45.1%)</td>
<td>371 (93.2%)</td>
<td>136 (34.2%)</td>
</tr>
<tr>
<td>Any severe adverse event</td>
<td>199 (24.8%)</td>
<td>—</td>
<td>92 (23.1%)</td>
<td>—</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of trial regimen</td>
<td>85 (10.6%)</td>
<td>—</td>
<td>28 (7.0%)</td>
<td>—</td>
</tr>
<tr>
<td>Adverse event associated with death</td>
<td>10 (1.2%)</td>
<td>—</td>
<td>1 (0.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Adverse events that occurred in ≥15% of patients in either group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue$</td>
<td>244 (30.4%)</td>
<td>7 (0.9%)</td>
<td>84 (21.1%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>199 (24.8%)</td>
<td>115 (14.3%)</td>
<td>79 (19.8%)</td>
<td>47 (12.8%)</td>
</tr>
<tr>
<td>Rash$</td>
<td>191 (23.8%)</td>
<td>42 (5.2%)</td>
<td>22 (5.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>163 (20.3%)</td>
<td>8 (1.0%)</td>
<td>60 (15.1%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>145 (18.1%)</td>
<td>0</td>
<td>63 (15.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>129 (16.1%)</td>
<td>9 (1.2%)</td>
<td>25 (6.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>128 (15.9%)</td>
<td>0</td>
<td>30 (7.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Fall$</td>
<td>125 (15.6%)</td>
<td>14 (1.7%)</td>
<td>36 (9.0%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Other adverse events of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture$</td>
<td>94 (11.7%)</td>
<td>22 (2.7%)</td>
<td>26 (6.5%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>75 (9.3%)</td>
<td>5 (0.6%)</td>
<td>25 (6.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism$</td>
<td>65 (8.1%)</td>
<td>0</td>
<td>8 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Mental-impairment disorder</td>
<td>41 (5.1%)</td>
<td>0</td>
<td>12 (3.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Seizure$</td>
<td>2 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Smith, MR et al., NEJM, 2019
PROSPER Study Design

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

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

Primary endpoint
- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)

Statistical Design:
- Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
- Target of 440 events provides 90% power to detect a target HR of 0.72

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

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.
Enzalutamide

Enzalutamide in M0/nmCRPC: The Patients

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enzalutamide Group (N=932)</th>
<th>Placebo Group (N=460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Range</td>
<td>50–95</td>
<td>53–92</td>
</tr>
<tr>
<td>ECOG performance-status score — mo. (%)†</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>Missing data</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Serum PSA value — ng/ml</td>
<td>11.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Range</td>
<td>0.6–3071.1</td>
<td>0.3–467.5</td>
</tr>
<tr>
<td>PSA doubling time — mo</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Range — mo</td>
<td>0.4–37.4</td>
<td>0.5–71.8</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td>715 (77)</td>
<td>361 (77)</td>
</tr>
<tr>
<td>&gt;6 mo</td>
<td>217 (33)</td>
<td>107 (23)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Use of bone-targeting agent — no. (%)</td>
<td>828 (89)</td>
<td>420 (90)</td>
</tr>
<tr>
<td>No</td>
<td>105 (11)</td>
<td>48 (10)</td>
</tr>
</tbody>
</table>

* There were no significant between-group differences in these characteristics at baseline. Percentages may not total 100 because of rounding. PSA denotes prostate-specific antigen.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a scale from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death.
Mets free survival

Enzalutamide in M0/nmCRPC: Mets Free Survival

Median Metastasis-free Survival (95% CI)
- Enzalutamide: 36.6 (33.1–NR)
- Placebo: 14.7 (14.2–15.0)

Hazard ratio for metastasis or death:
- 0.29 (95% CI: 0.24–0.35)
- P<0.001
### Table 3: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th><strong>Entasotamide Group</strong> (N=990)</th>
<th><strong>Placebo Group</strong> (N=485)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>808 (81)</td>
<td>292 (31)</td>
</tr>
<tr>
<td>Any serious adverse event†</td>
<td>126 (13)</td>
<td></td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of trial regimen</td>
<td>87 (9)</td>
<td></td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>32 (3)</td>
<td></td>
</tr>
<tr>
<td>Most common adverse events, occurring in ≥5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>300 (31)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>121 (13)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (11)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>91 (10)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (12)</td>
<td>43 (5)</td>
</tr>
<tr>
<td>Fall</td>
<td>106 (11)</td>
<td>32 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>85 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>91 (10)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>78 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>82 (9)</td>
<td>33 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>89 (10)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>73 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>85 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hiccups</td>
<td>62 (7)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>38 (4)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>55 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>20 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>114 (12)</td>
<td>43 (5)</td>
</tr>
<tr>
<td>Major adverse cardiovascular event‡</td>
<td>45 (5)</td>
<td>34 (4)</td>
</tr>
<tr>
<td>Mental impairment disorders‡</td>
<td>37 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>11 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Granulosis</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Progression

## Progression Event by Type

<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>

*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).

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

Most Updated Data in nmCRPC

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>Investigation drug (N) vs placebo (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1509</td>
<td>1509</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median MFS in months (HR for metastasis or death; 95% CI, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER [4, 5]</td>
</tr>
<tr>
<td>ARAMIS [3, 8]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median time to PSA progression in months (HR of PSA progression or death; 95% CI, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER [4, 5]</td>
</tr>
<tr>
<td>ARAMIS [3, 8]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median overall survival in months (HR, 95% CI; p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER [4, 5]</td>
</tr>
<tr>
<td>ARAMIS [3, 8]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of treatment in months; Subsequent Therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER [4, 5]</td>
</tr>
<tr>
<td>ARAMIS [3, 8]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to first pain progression in months (HR, 95% CI; p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPER [4, 5]</td>
</tr>
</tbody>
</table>

N: numbers; MFS: Metastasis-free survival; NR: Not reported; HR: Hazards ratio; CI: Confidence Interval.
**nmCRPC data**

### Most Updated Data in nmCRPC

Comparison of phase III trials investigating enzalutamide, apalutamide and darolutamide in patients with non-metastatic castration resistant prostate cancer.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>1401</td>
<td>1207</td>
<td>1509</td>
</tr>
<tr>
<td>Investigational drug (N) vs placebo (N)</td>
<td>Enzalutamide (933) vs placebo (468)</td>
<td>Apalutamide (806) vs placebo (401)</td>
<td>Darolutamide (955) vs placebo (554)</td>
</tr>
<tr>
<td>Median MFS in months (HR for metastasis or death; 95% CI, p-value)</td>
<td>36.6 vs. 14.7 (0.29; 0.24 - 0.35; p &lt; 0.001)</td>
<td>40.5 vs. 16.2 (0.28; 0.23 to 0.35; p &lt; 0.001)</td>
<td>40.4 vs. 18.4 (0.41; 0.34 - 0.50; p &lt; 0.001)</td>
</tr>
<tr>
<td>Median time to PSA progression in months (HR of PSA progression or death; 95% CI, p-value)</td>
<td>37.2 vs. 3.9 (0.07; 0.05–0.08, p &lt; 0.001)</td>
<td>NR vs. 3.7 (0.06; 0.05–0.08; p-value NR)</td>
<td>33.2 vs. 7.3 (0.13; 0.11 to 0.16; p &lt; 0.001)</td>
</tr>
<tr>
<td><strong>Median overall survival in months (HR, 95% CI; p-value)</strong></td>
<td>67 vs. 56.3</td>
<td>73.9 vs 59.9</td>
<td>15.5 vs 10.6</td>
</tr>
<tr>
<td>(0.73, 0.61 – 0.89; p = 0.0011) with median 48 months follow-up</td>
<td>(0.784, N/A; p = 0.0161) with median 52 months follow-up</td>
<td>(0.69, 0.53 – 0.88; p = 0.003)</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment in months;</td>
<td>33.9 vs 14.2</td>
<td>32.9 vs 11.5</td>
<td>NR</td>
</tr>
<tr>
<td>Subsequent Therapy (%)</td>
<td>33% vs 65%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Time to first pain progression in months (HR, 95% CI, p-value)</td>
<td>NR</td>
<td>NR</td>
<td>40.3 vs 25.4</td>
</tr>
<tr>
<td>Time to subsequent antineoplastic therapy months (HR, 95% CI, p-value)</td>
<td>39.6 vs. 17.7 (0.21; 0.17–0.26; p &lt; 0.001)</td>
<td>NR</td>
<td>40.3 vs 25.4 (0.65, 0.53 – 0.79; p &lt; 0.001)</td>
</tr>
<tr>
<td>Time to first cytotoxic chemotherapy in months (HR, 95% CI, p-value)</td>
<td>NR vs NR (0.629, N/A; p = 0.0002)</td>
<td>NR vs NR</td>
<td>NR vs NR</td>
</tr>
</tbody>
</table>

N: numbers; MFS: Metastasis-free survival; NR: Not reported; HR: Hazards ratio; CI: Confidence Interval.

*Ann. Int. Med. Cancer Treatment and Research Communications, 2020*
My thoughts

My Thoughts on Treating M0 Prostate Cancer/nmCRPC

- Consider the eligibility of the trials
  - PSA Doubling Time less than 10 months
  - Minimum PSA Value (i.e. 2)

- Risk vs. Benefit in an elderly population

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

- Unknown how PET imaging will impact these populations