Prostate Cancer: An Evolving Treatment Landscape

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Disclosures

Consultant/SAB: Amgen, Astellas, Bayer, Astra-Zeneca, Genzyme-Sanofi, Janssen, Pfizer, Sema4
### Male

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Male</th>
<th>164,690</th>
<th>19%</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>121,680</td>
<td>14%</td>
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</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,610</td>
<td>9%</td>
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<tr>
<td>Urinary bladder</td>
<td>62,380</td>
<td>7%</td>
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<tr>
<td>Melanoma of the skin</td>
<td>55,150</td>
<td>6%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>42,680</td>
<td>5%</td>
<td></td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,730</td>
<td>5%</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>37,160</td>
<td>4%</td>
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<tr>
<td>Leukemia</td>
<td>35,030</td>
<td>4%</td>
<td></td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>30,610</td>
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<tr>
<td>All sites</td>
<td>856,370</td>
<td>100%</td>
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### Male

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Male</th>
<th>83,550</th>
<th>26%</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td></td>
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<tr>
<td>Prostate</td>
<td>29,430</td>
<td>9%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>27,390</td>
<td>8%</td>
<td></td>
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<tr>
<td>Pancreas</td>
<td>23,020</td>
<td>7%</td>
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</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,540</td>
<td>6%</td>
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<tr>
<td>Leukemia</td>
<td>14,270</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,850</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,520</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,010</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>323,630</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
Cancer Death Rates Among Men, US, 1930-2016

Deaths per 100,000 males

Males, by site

- Stomach
- Colorectum
- Liver & intrahepatic bile duct
- Pancreas
- Lung & bronchus
- Prostate
- Leukemia

American Cancer Society 2019
Clinical States of Prostate Cancer

- Clinically localized
- "Rising PSA" state
- Non-metastatic, castration-sensitive
- Metastatic, castration-sensitive
- Non-metastatic CRPC
- Metastatic CRPC

Death from prostate cancer
Death from other causes
10-15 years +
Clinical States of Prostate Cancer

Clinically localized

“Rising PSA” state

Non-metastatic, castration-sensitive

Non-metastatic CRPC

Metastatic, castration-sensitive

Metastatic CRPC

Death from prostate cancer

Death from other causes

10-15 years +
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

Pound et al. JAMA; 1999 May 5;281(17):1591
Short PSA Doubling Time Strongly Predicts Worse Survival

Figure 3. Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer-Specific Survival Curves by PSADT

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

Is There an Optimal Form of ADT?
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
### Oral Relugolix for Advanced Prostate Cancer

#### HERO, A MULTINATIONAL, OPEN-LABEL, PHASE 3, RANDOMIZED TRIAL

<table>
<thead>
<tr>
<th>Relugolix</th>
<th>Leuprolide Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>930 Patients with prostate adenocarcinoma</td>
<td>96.7% (N=622)</td>
</tr>
<tr>
<td>Sustained testosterone suppression</td>
<td>Difference, 7.9 percentage points; 95% CI, 4.1 to 11.8; ( P&lt;0.001 )</td>
</tr>
<tr>
<td>Mean testosterone level on day 4</td>
<td>38 ng/dl (137 patients)</td>
</tr>
<tr>
<td>Mean testosterone level 90 days after treatment discontinuation</td>
<td>288.4 ng/dl</td>
</tr>
</tbody>
</table>

Oral relugolix was superior to leuprolide injection for rapid testosterone suppression.

N.D. Shore et al. 10.1056/NEJMoA2004325
Intermittent vs Continuous ADT

- Non metastatic “rising PSA” patients: NCIC/PR7-NS difference
- Metastatic patients: SWOG 9346 - HR 1.09 (intermittent slightly inferior)

- Intermittent reasonable option and preferable for patients with non-metastatic disease
- For patients with metastases, needs to be individualized but favor continuous

Crook et al NEJM 2010
Hussain et al NEJM 2013
Side Effects of ADT Are Significant

- 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
Clinical States of Prostate Cancer

- Clinically localized
- "Rising PSA" state
- Non-metastatic, castration-sensitive
- Non-metastatic CRPC
- Metastatic, castration-sensitive
- Metastatic CRPC

Death from prostate cancer
Death from other causes

10-15 years +
Docetaxel in mCSPC

**CHAARTED**

- 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)

**STAMPEDE (M1)**

- HR (95%CI) 0.73 (0.59, 0.89)
- P-value 0.002
- Median OS (95% CI)
  - SOC 43m (24, 88m)
  - SOC+Doc 65m (27, NR)

Sweeney et al. *NEJM* 2015; 373, 737-46

James et al. *Lancet* 2016; 387, 1163-77
Abiraterone in mCSPC

LATITUDE

STAMPEDE (M1)

Hazard ratio, 0.62 (95% CI, 0.51–0.76)
P<0.001

HR (95%CI)
P-value
0.61 (0.49, 0.75)
<0.001 (all)

Fizazi et al.  NEJM 2017; 377, 352-360

James et al.  NEJM 2017; 377, 338-51
More Choices in mCSPC

ARCHES\(^1\) enzalutamide vs placebo

ENZAMET\(^2\) SOC ± enzalutamide

TITAN\(^3\) apalutamide vs placebo

Key Eligibility Criteria
- mCSPC (confirmed by bone scan, CT, or MRI)
- ECOG PS 0 or 1
ARCHES: rPFS Improved with Enzalutamide in mCSPC


No. at Risk
Enzalutamide + ADT  574  493  257  63  5  0
Placebo + ADT  576  445  192  39  0  0

Time, mo
0  3  6  9  12  15  18  21  24  27  30  33

rPFS, %
0  20  40  60  80  100

Enzalutamide + ADT
Median (95% CI): NR (NR-NR)
12-mo event-free rate estimate: 0.84

Placebo + ADT
Median (95% CI): 19.45 mo (16.59-NR)
12-mo event-free rate estimate: 0.64

HR (95% CI) = 0.39 (0.30-0.50)
P < .0001
ENZAMET: Study Design

- Phase III, randomized, open-label, multicenter clinical trial
  - Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)

- Patients with metastatic prostate cancer, starting first-line ADT (max 12 wks prior to randomization); ECOG PS 0-2; 2 cycles prior docetaxel allowed (N = 1125)

- Enzalutamide 160 mg/day + testosterone suppression (n = 563)
  - Evaluate every 12 wks

- Standard NSAA* + testosterone suppression (n = 562)
  - Evaluate every 12 wks

- CRPC tx at PD (investigator discretion)
  - Follow for time to progression and OS

- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL
Enzalutamide in mHSPC: OS

Enzalutamide was associated with significantly longer overall survival vs standard care in men with metastatic, hormone-sensitive prostate cancer.

ENZAMET: OS Stratified by No Early Docetaxel Use and Volume of Disease

no early-docetaxel, high-volume

HR (95%CI): 0.645 (0.417-0.986)
P = 0.0433 (log-rank test)

Median (95%CI):
No early-docetaxel, high-volume, Enzalutamide: NR, NSAA: NR

Enzalutamide (n=114)
NSAA (n=118)

No. at risk
Enzalutamide 114 114 111 105 101 98 87 72 61 46 33 26 16 8 3 0
NSAA 118 117 113 108 99 96 83 69 50 39 31 23 13 5 2 0 ITT

NR: not reached

no early-docetaxel, low-volume

HR (95%CI): 0.377 (0.200-0.675)
P = 0.0010 (log-rank test)

Median (95%CI):
No early-docetaxel, low-volume, Enzalutamide: NR, NSAA: NR

Enzalutamide (n=195)
NSAA (n=195)

No. at risk
Enzalutamide 195 192 192 190 189 187 183 146 115 89 72 43 26 15 3 0
NSAA 195 194 194 188 185 178 166 132 103 79 59 29 17 9 2 0 ITT

NR: not reached
ENZAMET: OS Stratified by Early Docetaxel Use and Volume of Disease

**early docetaxel, high-volume**

- **Enzalutamide (n=177)**
- **NSAA (n=179)**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
<th>56</th>
<th>60</th>
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<tbody>
<tr>
<td>No. at risk</td>
<td>177</td>
<td>176</td>
<td>173</td>
<td>170</td>
<td>167</td>
<td>159</td>
<td>140</td>
<td>105</td>
<td>72</td>
<td>34</td>
<td>20</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>NR</td>
<td>Enzalutamide</td>
<td>177</td>
<td>176</td>
<td>173</td>
<td>170</td>
<td>167</td>
<td>159</td>
<td>140</td>
<td>105</td>
<td>72</td>
<td>34</td>
<td>20</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NSAA</td>
<td>179</td>
<td>174</td>
<td>171</td>
<td>166</td>
<td>157</td>
<td>150</td>
<td>137</td>
<td>106</td>
<td>72</td>
<td>40</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (42.15 months - NR)</td>
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**early docetaxel, low-volume**

- **Enzalutamide (n=77)**
- **NSAA (n=70)**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
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<th>56</th>
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<td>No. at risk</td>
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<td>76</td>
<td>76</td>
<td>75</td>
<td>70</td>
<td>55</td>
<td>53</td>
<td>52</td>
<td>50</td>
<td>49</td>
<td>43</td>
<td>33</td>
<td>16</td>
<td>6</td>
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<tr>
<td>NR</td>
<td>Enzalutamide</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>76</td>
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<td>75</td>
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<td>43</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>NSAA</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>68</td>
<td>66</td>
<td>49</td>
<td>33</td>
<td>16</td>
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<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (38.70 months - NR)</td>
<td>100</td>
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</table>

HR (95% CI) = 0.967 (0.638-1.464)
P = 0.8728 (log-rank test)

HR (95% CI) = 0.649 (0.236-1.691)
P = 0.3773 (log-rank test)

NR: not reached
TITAN: Apalutamide Improves OS in mCSPC

The addition of apalutamide to ADT resulted in significantly longer OS compared to placebo plus ADT in men with mCSPC

The addition of prostate EBRT to ADT in low metastatic burden (<4 bone mets) mCSPC was associated with improved FFS and OS.
Summary: mCSPC

- Upfront treatment with either abiraterone + prednisone, apalutamide, enzalutamide, or docetaxel is the new SOC for men with mCSPC
- Low volume patients may not benefit from docetaxel but may benefit from prostate EBRT
  - No evidence yet that triple therapy with a novel hormonal therapy + ADT + docetaxel improves OS
  - No recommendation on sequencing can be made until we have prospective data
Unanswered Questions: mCSPC

• How do you choose?
  • Age, performance status, patient preference
  • Toxicity profiles
  • Duration of therapy
  • Cost
  ▪ Is there an optimal sequence of treatment?
  ▪ What about combinations?
  ▪ Can biomarkers direct therapy for mCSPC?
Clinical States of Prostate Cancer

- Clinically localized
- “Rising PSA” state
- Non-metastatic, castration-sensitive
- Non-metastatic CRPC
- Metastatic, castration-sensitive
- Metastatic CRPC

10-15 years +

Death from other causes
Death from prostate cancer
nmCRPC: Where We Stand With Evidence on Hormonal Therapy?

Key Eligibility Criteria
- nmCRPC
- Baseline PSA ≥2 ng/mL
- PSADT ≤10 months

Metastases Increase as PSA Doubling Time (PSADT) Decreases

SPARTAN: Apalutamide in Non-Metastatic CRPC (M0)

Overall Study Design

Eligibility
- nmCRPC
  - Pelvic nodes < 2 cm below iliac bifurcation (N1) allowed
- PSADT ≤ 10 months (rapidly rising PSA)

On-Study Requirement
- Continuous ADT

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

Randomization

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

Second progression-free survival (PFS2)

2:1 (N = 1207)

APA 240 mg QD + ADT (n = 806)

PBO + ADT (n = 401)

Second Rx at MD's discretion including open-label ABI/PRED

APA, apalutamide; PBO, placebo; ABI, abiraterone acetate; PRED, prednisone.

SPARTAN: Metastasis-Free Survival

A Kaplan-Meier Estimates of Metastasis-free Survival

- 16.2mo median MFS (Placebo)
- 40.5mo median MFS (Apalutamide)

Hazard ratio for metastasis or death, 0.28 (95% CI, 0.23–0.35)
P < 0.001
Men had:
- PSADT ≤ 10 mos
- M0 CRPC on central review
- PSA ≥ 2 ng/mL

Stratified by:
- PSADT <6 months vs 6-10 mos
- Baseline use of bone targeted agent, yes vs no

PROSPER: Enzalutamide in nmCRPC

Men with M0 CRPC N = 1401

Enzalutamide 160mg daily N = 933

Placebo N = 468

PRIMARY ENDPOINT: Metastasis-free survival

SECONDARY ENDPOINTS: Time to pain progression, Time to first cytotoxic therapy, Time to opiate use for cancer pain, Time to first antineoplastic therapy, Time to PSA progression, FACT-P global score, QOL assessment
PROSPER: Metastasis-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

No. at Risk
- Enzalutamide: 933, 865, 759, 637, 528, 431, 418, 328, 239, 159, 87, 77, 31, 16, 11, 5, 4, 0
- Placebo: 468, 420, 296, 212, 157, 105, 98, 64, 49, 31, 16, 11, 5, 1, 0

ARAMIS: Darolutamide vs Placebo

Key eligibility criteria
- nmCRPC
- PSADT ≤10 mo

Stratification factors
- PSADT (≤6 months vs >6 months)
- Osteoclast-targeted therapy (yes vs no)

Darolutamide (1,200 mg) + ADT (2 x 300 mg tablets BID) n = 955

Placebo BID + ADT n = 554

N = 1,509

Primary analysis: MFS
Final analysis: OS

Primary endpoint: MFS
Secondary endpoints: OS, time to first symptomatic skeletal event, time to initiation of first cytotoxic chemotherapeutic, time to pain progression, safety, and tolerability

ARAMIS: Metastasis-Free Survival

Survival Probability

Darolutamide
Placebo

HR = 0.41 (95% CI, 0.34-0.50)
P < .0001

Darolutamide
Median MFS: 40.4 mo

Placebo
Median MFS: 18.4 mo

59% reduction in risk of distant metastases or death

Primary Endpoint: Metastasis-Free Survival

**SPARTAN**
- Apalutamide
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

**PROSPER**
- Enzalutamide
- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month MFS benefit

**ARAMIS**
- Darolutamide
- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

**Secondary Endpoint: Overall Survival**

**SPARTAN\(^1\)**
- Apalutamide
- 22% reduction in risk of death
- Median follow-up of 52.0 months
- Median OS was significantly longer for APA
  - 73.9 vs 59.9 mo
  - HR = 0.73 (95% CI 0.61-0.89); \(P = 0.0011\)

**PROSPER\(^2\)**
- Enzalutamide
- 27% reduction in risk of death
- Median follow-up of 48 months
- Median OS was significantly longer for ENZA
  - 67.0 mo vs 56.3 mo
  - HR = 0.78 (95% CI 0.64-0.96); \(P = 0.0161\)

**ARAMIS\(^3\)**
- Darolutamide
- 31% reduction in risk of death
- Median follow-up of 29.1 months
- Median OS was significantly longer for DARO
  - HR = 0.69 [95% CI, 0.53-0.88]; \(P = .003\)

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PSMA-PET Results in Patients With High-Risk nmCRPC (Negative Conventional Imaging, PSADT <10 mo)\textsuperscript{1}

<table>
<thead>
<tr>
<th>Category Based on mITNM Stage, n (%)</th>
<th>All patients (N = 200)</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>91 (46)</td>
</tr>
<tr>
<td>T0N0M0 (no PC lesion)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>T0N1M0</td>
<td>13 (7)</td>
</tr>
<tr>
<td>TrN0M0</td>
<td>48 (24)</td>
</tr>
<tr>
<td>T0N1M0</td>
<td>26 (13)</td>
</tr>
<tr>
<td>TrN1M0</td>
<td></td>
</tr>
<tr>
<td>Any M1</td>
<td>109 (55)</td>
</tr>
<tr>
<td>T0N0M1</td>
<td>31 (16)</td>
</tr>
<tr>
<td>T0N1M1</td>
<td>42 (21)</td>
</tr>
<tr>
<td>TrN0M1</td>
<td>9 (5)</td>
</tr>
<tr>
<td>TrN1M1</td>
<td>27 (14)</td>
</tr>
<tr>
<td>N/M disease extent</td>
<td></td>
</tr>
<tr>
<td>Unifocal (1 lesion)</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Oligometastatic (2-3 lesions)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Multiple/disseminated (≥ 4 lesions)</td>
<td>91 (46)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1).

Conclusions: nmCRPC

- Apalutamide, Enzalutamide and Darolutamide delay MFS in men with nmCRPC by ~2 years
- SPARTAN, PROSPER, and ARAMIS established favorable benefit–risk ratio for patients with nmCRPC and PSADT <10 months (median PSADT: ≈4 months)
- Updates at ASCO 2020 show all 3 drugs have significant OS benefit
- These studies provide the best evidence for early treatment of patients with CRPC and no metastases on conventional imaging
Unanswered Questions: nmCRPC

• How will next generation PET imaging (PSMA) change the disease state of nmCRPC? Will nmCRPC even exist in a few years?
• How does a clinician decide on one of these agents?
• How does the sequencing of therapies influence the choice of therapy in a patient’s longitudinal history?
• How often should patients with nmCRPC be imaged? Should you rely on PSA alone?
Clinical States of Prostate Cancer

- Clinically localized
- "Rising PSA" state
- Non-metastatic, castration-sensitive
- Metastatic, castration-sensitive
- Non-metastatic CRPC
- Metastatic CRPC

Death from prostate cancer

Death from other causes
Castration Resistant Prostate Cancer
# Positive Trials in mCRPC: OS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Prior Docetaxel</th>
<th>Comparator</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>Mostly No</td>
<td>Placebo</td>
<td>0.775</td>
<td>0.032</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>No</td>
<td>Mitoxantrone</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Yes</td>
<td>Mitoxantrone</td>
<td>0.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abiraterone/ Prednisone</td>
<td>No</td>
<td>Prednisone</td>
<td>0.81</td>
<td>0.0033</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Prednisone</td>
<td>0.646</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>No</td>
<td>Placebo</td>
<td>0.706</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Placebo</td>
<td>0.631</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radium-223</td>
<td>Mostly Yes</td>
<td>Placebo</td>
<td>0.70</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Is There A Difference In AR-Targeted Therapies For mCRPC?
AR-Targeted Therapies Improve Survival in mCPRC

Abiraterone

Enzalutamide
PSA Responses Diminish With Second-Line AR Therapy

<table>
<thead>
<tr>
<th></th>
<th>First Line</th>
<th>Second Line</th>
<th>First Line</th>
<th>Second Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% PSA Decline</td>
<td>55-60%</td>
<td>4-8%</td>
<td>38-46%</td>
<td>13-29%</td>
</tr>
</tbody>
</table>
Randomized Phase II: Abi vs Enza

**Graph C:**
- **Abiraterone + prednisone** vs **Enzalutamide**
- Best PSA decline from baseline (in %)
- P = 0.046 (Fisher exact test)

**Graph B:**
- Progression-free survival
- Abiraterone vs Enzalutamide
- At risk:
  - Abiraterone: 101, 72, 48, 31, 21, 13, 10, 5, 3, 2, 0
  - Enzalutamide: 101, 75, 56, 36, 28, 16, 9, 6, 4, 2, 0
- HR (95% CI) for Enzalutamide arm: 0.82 (0.58 - 1.16) | P = 0.27
Targeting Androgen Signaling

- AR targeted therapies improve survival
- Abiraterone and enzalutamide both work
  - Enza has a slightly higher PSA response rate
  - PFS is equivalent and still too short (7.4 mo)
- Certain patients progress more rapidly
  - Liver and lung mets
Radium-223: Overall Survival

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

Placebo, n = 307
Median OS: 11.3 months

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

Osteoporotic Fractures are More Frequent with AR Targeted Therapies in mCRPC

Fractures are commonly reported in the investigational arm of phase III studies with new AR pathways inhibitors.

USPI. U.S. prescribing information.
## Bone Protecting Agents Protect Against Osteoporotic Fractures

Bone fractures and cumulative incidence safety population

<table>
<thead>
<tr>
<th>Time point</th>
<th>Treatment and use of bone protecting agents</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With exposure to BPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enza+Rad (N=39)</td>
<td>Enza (N=49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cum Incidence (95% CI)*</td>
<td>Cum Incidence (95% CI)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>6 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>5.6 (1.0-16.3)</td>
</tr>
<tr>
<td>9 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>22.3 (10.0-37.5)</td>
</tr>
<tr>
<td>12 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>37.4 (21.8-53.1)</td>
</tr>
<tr>
<td>15 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>43.6 (26.8-59.3)</td>
</tr>
<tr>
<td>18 months</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td>43.6 (26.8-59.3)</td>
</tr>
</tbody>
</table>

* the one fracture in this group occurred at month 27
Radium-223

- Radium-223 improves OS in mCRPC patients with symptomatic bone metastases
- PSA does not usually decline, though alk phos may
- If you use ART with radium, make sure the patient is also on a BPA (eg denosumab)
What About Chemotherapy for mCRPC?
Docetaxel: 1st Drug in mCRPC to Improve Survival!

Petrylak  N Engl J Med. 2004
Tannock N Engl J Med. 2004

HR: 0.83, \( P=0.03 \)
But Docetaxel Combos Have Failed

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Investigational agent</th>
<th>Overall survival (docetaxel plus investigational agent vs docetaxel)</th>
<th>Hazard ratio for survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAL-2</td>
<td>2009</td>
<td>GVAX</td>
<td>12.2 months vs 14.1 months</td>
<td>1.70</td>
<td>0.008</td>
</tr>
<tr>
<td>ASCENT</td>
<td>2011</td>
<td>Calcitriol</td>
<td>17.8 months vs 20.2 months</td>
<td>1.33</td>
<td>0.019</td>
</tr>
<tr>
<td>CALGB 90401</td>
<td>2012</td>
<td>Bevacizumab</td>
<td>22.6 months vs 21.5 months</td>
<td>0.91</td>
<td>NS</td>
</tr>
<tr>
<td>VENICE</td>
<td>2013</td>
<td>Aflibercept</td>
<td>22.1 months vs 21.2 months</td>
<td>0.94</td>
<td>NS</td>
</tr>
<tr>
<td>SWOG 0421</td>
<td>2013</td>
<td>Atrasentan</td>
<td>17.8 months vs 17.6 months</td>
<td>1.04</td>
<td>NS</td>
</tr>
<tr>
<td>ENTHUSE</td>
<td>2013</td>
<td>Zibotentan</td>
<td>20.0 months vs 19.2 months</td>
<td>1.00</td>
<td>NS</td>
</tr>
<tr>
<td>READY</td>
<td>2013</td>
<td>Dasatinib</td>
<td>21.5 months vs 21.2 months</td>
<td>0.99</td>
<td>NS</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>2014</td>
<td>Custirsen</td>
<td>23.4 months vs 22.2 months</td>
<td>0.93</td>
<td>NS</td>
</tr>
<tr>
<td>MAINSAIL</td>
<td>2015</td>
<td>Lenalidomide</td>
<td>17.7 months vs NR</td>
<td>1.53</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; NS, not significant.

Liaw and Oh, Nat Clin Rev Oncol 2015
Cabazitaxel Improves OS In 2nd Line Setting

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>377</td>
<td>378</td>
</tr>
<tr>
<td>6 months</td>
<td>300</td>
<td>321</td>
</tr>
<tr>
<td>12 months</td>
<td>188</td>
<td>231</td>
</tr>
<tr>
<td>18 months</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>24 months</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>30 months</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Proportion of OS (%)

0 months 6 months 12 months 18 months 24 months 30 months

| Hazard Ratio | 0.70 |
| 95% CI       | 0.59–0.83 |
| P-value      | <.0001 |

Median OS (mo)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
</tbody>
</table>
mCRPC: Impact of Recent Evidence and Approvals

**Key Eligibility Criteria**
- 2L+ mCRPC
- +/- DDR mutations

**CARD**
cabazitaxel vs abiraterone or enzalutamide

**PROfound**
olaparib vs physician’s choice

**TRITON2**
rucaparib monotherapy

CARD: STUDY DESIGN

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTA (before or after docetaxel)
N = 255

RANDOMIZE

1:1

Cabazitaxel (25 mg/m² Q3W) + prednisone + G-CSF
n = 129

Abiraterone (1000 mg QD) + prednisone
OR
Enzalutamide (160 mg QD)
n = 126

Endpoints
Primary: rPFS
Key secondary: OS, PFS, PSA response, tumor response
Other secondary: Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

Stratification factors:
- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs > 6–12 months)
- Timing of ARTA (before vs after docetaxel)

ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QD, once daily; Q3W, every 3 weeks; rPFS, radiographic progression-free survival.
CARD Trial: Overall Survival

Kaplan-Meier Estimate

Patients, n  Median OS, mo (95% CI)
Cabazitaxel  129  13.6 (11.5-17.5)
ABI or ENZA  126  11.0 (9.2-12.9)

HR = 0.64 (95% CI, 0.46-0.89)
P = .0078

No. at Risk
<table>
<thead>
<tr>
<th></th>
<th>Cabazitaxel</th>
<th>ABI or ENZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 mo</td>
<td>129</td>
<td>126</td>
</tr>
<tr>
<td>3-6 mo</td>
<td>122</td>
<td>116</td>
</tr>
<tr>
<td>6-9 mo</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>9-12 mo</td>
<td>77</td>
<td>64</td>
</tr>
<tr>
<td>12-15 mo</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>15-18 mo</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>18-21 mo</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>21-24 mo</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Chemotherapy in mCRPC

• Docetaxel and cabazitaxel remain important therapeutic options in mCRPC

• Need to consider prior therapies in sequencing chemotherapy

• CARD: sequential AR-targeted therapies have less value than 3rd line cabazitaxel chemotherapy in mCRPC
Advancing Prostate Cancer Therapy: New Targets...Novel Approaches

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer\(^1,2\)

- **23%** of mCRPCs harbor DNA repair alterations (DDR)
- The frequency of DDR mutations increases with disease progression
- **About half of these (~12%)** have germline alterations in DDR genes
- Age and family history do not affect mutation frequency

PROfound: Olaparib in DDR Mutant mCRPC

Key Eligibility Criteria
- mCRPC with disease progression on prior NHA (eg, abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification Factors
- Previous taxane
- Measureable disease

Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)

Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

PROfound Primary Endpoint: rPFS (Cohort A)\(^1,2\)

rPFS by BICR in Patients With Alterations in *BRCA1*, *BRCA2*, or *ARM* (Cohort A)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n = 162)</th>
<th>Physician’s Choice (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, %</td>
<td>106 (65.4)</td>
<td>68 (81.9)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>7.39</td>
<td>3.55</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.34 (0.25-0.47)</td>
<td>(P &lt; .001)</td>
</tr>
</tbody>
</table>

NCT02987543
Prespecified sensitivity analysis based on investigator assessment:
HR = 0.24 (95% CI, 0.17-0.34); \(P < .0001\)

Despite a 67% crossover rate in the placebo arm, men receiving olaparib with BRCA1/2 or ATM mutations had a significant improvement in OS (HR 0.69 but adjusting for crossover, HR 0.42)
In May 2020, based on data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic homologous recombination repair\textsuperscript{a} gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone\textsuperscript{1,b}.
TRITON2: Phase 2 Study of Rucaparib in mCRPC with HRR Aberrations — Study Design

**Screening**
- Identification of a deleterious somatic or germline alteration in HRR gene\(^a\)

**HRR Genes**
- BRCA1, BARD1, FANCA, RAD51B, BRCA2, BRIP1, NBN, RAD51C, ATM, CDK12, PALB2, RAD51D, CHEK2, RAD51, RAD54L

**Key Eligibility Criteria**
- mCRPC
- Deleterious somatic or germline alteration in HRR gene
- Progression on AR-directed therapy (e.g., abiraterone, enzalutamide, or apalutamide) and 1 prior taxane-based chemotherapy for CRPC
- ECOG PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

**Primary endpoints**: Confirmed ORR per modified RECIST/PCWG3 by central assessment (patients with measurable disease at baseline), confirmed PSA response (≥50% decrease) rate (patients with no measurable disease at baseline)

**Treatment (28-d Cycles)**
- Rucaparib 600 mg BID
- Tumor assessments Q8W for 24 wk, then Q12W
- PSA assessments Q4W
- Treatment until radiographic progression or discontinuation for other reason

\(^a\) Alterations detected by local testing or central testing of blood or tumor samples. Deleterious alterations were defined as protein-truncating mutations, large protein-truncating rearrangements, splice site mutations, deleterious missense mutations, and homozygous deletions.

## TRITON2: Phase 2 Study of Rucaparib in mCRPC With HRR Aberrations—ORR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRCA1/2 (n = 57)</th>
<th>ATM (n = 21)</th>
<th>CDK12 (n = 9)</th>
<th>CHEK2 (n = 5)</th>
<th>Other (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (43.9)</td>
<td>2 (9.5)</td>
<td>0</td>
<td>0</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>3 (5.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7.7)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>22 (38.6)</td>
<td>2 (9.5)</td>
<td>0</td>
<td>0</td>
<td>4 (30.8)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>26 (45.6)</td>
<td>10 (47.6)</td>
<td>5 (55.6)</td>
<td>3 (60.0)</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>5 (8.8)</td>
<td>8 (38.1)</td>
<td>3 (33.3)</td>
<td>2 (40.0)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>1 (1.8)</td>
<td>1 (4.8)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Confirmed PSA response rate (all evaluable patients)</td>
<td>51/98 (52%)</td>
<td>2/57 (3.5%)</td>
<td>1/14 (7.1)</td>
<td>1/7 (14.3)</td>
<td>5/14 (35.7%)</td>
</tr>
</tbody>
</table>

- 43.9% confirmed objective responses were reported in 57 patients with BRCA1/2 mutation
- 52.0% confirmed PSA response in 98 PSA-evaluable patients with BRCA1/2 mutation

---

<sup>a</sup> Per modified RECIST/PCWG3 criteria.  
<sup>b</sup> 1 patient had FANCA alteration.  
<sup>c</sup> 2 patients had a PALB2 alteration; 1 patient each had a BRIP1 or RAD51B alteration.  
In May 2020, based on data from the TRITON2 study, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious BRCA1/2 (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy\(^1\)

The TRITON3 study is underway and recruiting patients with mCRPC and homologous recombination gene deficiency\(^2\)

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Advancing Prostate Cancer Therapy: New Targets...Novel Approaches

Sipuleucel-T Survival Benefit

- Sipuleucel-T was approved based on HR 0.775 (~4 month OS benefit)
- Survival curves separate after 6 months
- Treatment is done in 5 weeks
  - Few side effects
KEYNOTE-199: Study Design

- mCRPC
- ≥1 prior targeted endocrine therapy
- 1-2 prior chemotherapy regimens, including docetaxel
- Measurable disease per RECIST 1.1

Cohort 1: PD-L1+

Cohort 2: PD-L1-

Cohort 3: Any PD-L1; bone

Cohort 4: RECIST-measurable disease

Cohort 5: Bone-only/predominant, RECIST-nonmeasurable disease

- Treatment in all cohorts: Pembrolizumab 200 mg every 3 weeks for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

Pembrolizumab in mCRPC

Change From Baseline in Sum of Target Lesions, Cohorts 1+2

<table>
<thead>
<tr>
<th>Change From Baseline</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1% to −100%</td>
<td>36%</td>
</tr>
<tr>
<td>−30% to −100%</td>
<td>10%</td>
</tr>
<tr>
<td>0% to +100%</td>
<td>64%</td>
</tr>
<tr>
<td>0% to +19%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Change From Baseline, %

10% RR

Change From Baseline in PSA, Cohorts 1+2+3

<table>
<thead>
<tr>
<th>Change From Baseline</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1% to −100%</td>
<td>19%</td>
</tr>
<tr>
<td>−50% to −100%</td>
<td>11%</td>
</tr>
<tr>
<td>−90% to −100%</td>
<td>5%</td>
</tr>
<tr>
<td>0% to +100%</td>
<td>81%</td>
</tr>
<tr>
<td>0% to +24%</td>
<td>11%</td>
</tr>
</tbody>
</table>

11% PSA declines

### KEYNOTE-199: Update Cohorts 4 and 5

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Cohort 4 (n = 81)</th>
<th>Cohort 5 (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>10 (12)</td>
<td>NA</td>
</tr>
<tr>
<td>CR</td>
<td>2 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>PR</td>
<td>8 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>SD of any duration</td>
<td>31 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-CR/non-PD of any duration</td>
<td>0 (0)</td>
<td>23 (51)</td>
</tr>
<tr>
<td><strong>DCR (CR + PR + SD or non-CR/non-PD)</strong></td>
<td><strong>41 (51)</strong></td>
<td><strong>23 (51)</strong></td>
</tr>
<tr>
<td>PD</td>
<td>31 (38)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>NE(^a)</td>
<td>2 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>No assessment(^b)</td>
<td>7 (9)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

---

Combination Approaches: COSMIC-021

- Radiographic progression after prior enzalutamide and/or prior abiraterone
- ECOG PS 0-1
- Prior chemotherapy not permitted except docetaxel for mCSPC

Cohort 6: CRPC expansion

cabozantinib 40 mg PO orally + atezolizumab 1,200 mg IV q3w

<table>
<thead>
<tr>
<th></th>
<th>CRPC Cohort (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, (80% CI), %</strong></td>
<td>32 (23-42)</td>
</tr>
<tr>
<td><strong>CR, n (%)</strong></td>
<td>3 (6.8)</td>
</tr>
<tr>
<td><strong>PR, n (%)</strong></td>
<td>11 (25)</td>
</tr>
<tr>
<td><strong>SD, n (%)</strong></td>
<td>21 (48)</td>
</tr>
<tr>
<td><strong>PD, n (%)</strong></td>
<td>8 (18)(^a)</td>
</tr>
<tr>
<td><strong>Missing, n (%)</strong></td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>DCR (CR + PC + SD), n (%)</strong></td>
<td>35 (80)</td>
</tr>
<tr>
<td><strong>DOR, median (range), mo</strong></td>
<td>8.3 (2.8-12.5+)</td>
</tr>
<tr>
<td><strong>Time to OR, median (range), mo</strong></td>
<td>1.6 (1-7)</td>
</tr>
</tbody>
</table>

\(^a\) One patient with PD had a subsequent immune-related PR per irRECIST.

Phase 2 TheraP: $^{177}$Lu-PSMA-617 vs Cabazitaxel in mCRPC

Eligibility Criteria
- Progressive PSMA-positive mCRPC
- Prior treatment with docetaxel for mCRPC
- No prior second-generation antihormonal agents

$^{177}$Lu-PSMA-617 (6-8 GBq IV Q6W for maximum of 6 cycles)

Cabazitaxel (20 mg/m$^2$ IV Q3W for maximum of 10 cycles)

- Primary endpoint:
  PSA ≥ 50% response rate (PSA50-RR)

PSA50-RR:
- Cabazitaxel: 37% (95% CI 27% - 46%)
- Lu-PSMA: 66% (95% CI 56% - 75%)

Lu-PSMA: 29% absolute (95% CI, 16-42; $P < .0001$) greater PSA50-RR compared with cabazitaxel

New Therapies in mCRPC

- PARP inhibitors have significant clinical activity in mCRPC with recent FDA approvals expected to benefit patients with DDR mutations
- Novel immunotherapy combinations and biomarker analyses may lead to broader use of immunotherapy
- Theranostics targeted towards PSMA are promising with results of randomized trials expected soon
Local Therapy
Androgen Deprivation
Therapies After LHRH Agonists and Antiandrogens
Surgery / Radiation
Standard Androgen Deprivation Therapy
Denosumab, Zoledronic Acid
Darolutamide
Apalutamide
Enzalutamide
Abiraterone
Radium-223
Death
Docetaxel
Sipuleucel-T
Docetaxel
Cabazitaxel
Docetaxel