Non metastatic castrate-resistant prostate cancer (M0 CRPC)

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Disclosure

Participation to advisory boards/honorarium for: Amgen, Astellas, Astrazeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, MSD, Orion, Sanofi
CRPC M0: Definition

• A man with prostate cancer:
  – Who often had a previous local treatment
  – PSA relapse and then received ADT (or ADT together with primary local Tx)
  – Who is now progressing by PSA while on ADT

• No detectable metastases on conventional imaging (bone scan, CT scan)

• Testosterone at castrated levels
High-risk nmCRPC patients, at risk of metastases or death, can be readily identified.

Time to bone metastases or death by PSA doubling time (PSADT)

Time to bone metastases or death by PSA level

High-risk nmCRPC is a deadly cancer

All patients had PSA ≥ 8 and/or PSADT ≤ 10 months at baseline.

OS, overall survival

PSMA-Pet: detection of 17 lymph nodes with diameter below the morphological detection limit; Median 0.46mm; Max 0.66; Min 0.32

Little radioactivity in the bladder
Cleavage of the tracer in the kidneys
Renal storage of the chelator

Giesel et al., Clinical Genitourinary Cancer 2017
Previous Phase III trials in M0 CRPC

Atrasentan (n=941)

Zibotentan: Enthuse 15 trial (n=1421)

Denosumab (n=1432)

Nelson JB, Cancer 2008; 113:2 478-87
A 65-year old man with CRPC M0, PSA DT= 4 months. Assuming drugs are available, would you recommend:

1- Surveillance and start treatment for M1
2- Enzalutamide
3- Apalutamide
4- Darolutamide
5- Either apalutamide, darolutamide or enzalutamide
PROSPER/SPARTAN/ARAMIS Study Design: in High-Risk M0 CRPC

Similar trials with Enzalutamide (Prosper), Apalutamide (Spartan) and Darolutamide (Aramis)

Estimated Enrollment: 1,200-1,500
- M0 CRPC
- PSA doubling time of ≤10 months
- ECOG PS 0-1

Primary endpoints:
- Metastasis-free survival

Key secondary endpoints:
- OS
- Time to first SSE
- Time to initiation of first cytotoxic chemo
- Time to pain progression

K Fizazi, personal slide
## SPARTAN and PROSPER: patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>SPARTAN</th>
<th>PROSPER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APA (n = 806)</td>
<td>PBO (n = 401)</td>
</tr>
<tr>
<td><strong>Median age, years</strong></td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td><strong>Median PSADT, months</strong></td>
<td>4.4</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>PSADT, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td><strong>Bone-sparing agent use, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>Nodal status at study entry, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>N1</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td><strong>ECOG PS at study entry, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

SPARTAN and PROSPER: primary endpoint – MFS

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

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

SPARTAN secondary endpoint

Time to symptomatic progression: 55% risk reduction with APA

HR (95% CI): 0.45 (0.32–0.63)  
p < 0.0001

Patients without symptomatic progression (%)

AP, NR

PBO, NR

No. at risk

APA 806 769 732 601 478 344 226 127 49 19 4 0

PBO 401 373 344 270 206 152 96 45 17 7 0 0

NR, not reached.

SPARTAN and PROSPER: time to PSA progression

**SPARTAN**

- 94% risk reduction in PSA progression
- Median time to PSA progression: APA NR vs PBO 3.7 months

**PROSPER**

- Time to median PSA progression: ENZA 37.2 vs PBO 3.9 months

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SPARTAN and PROSPER secondary endpoint: OS

**SPARTAN**

- HR (95% CI): 0.70 (0.47–1.04)
- p = 0.07

**PROSPER**

- HR (95% CI): 0.80 (0.58–1.09)
- p = 0.1519

- 30% risk reduction of death (HR 0.70; p = 0.07)
- Median OS: APA NR vs PBO 39 months
- 20% risk reduction of death (HR 0.80; p = 0.15)
- Median OS: ENZA NR vs PBO NR

SPARTAN and PROSPER: effect of treatment on QoL prior to progression

**SPARTAN**
FACT-P

![](chart1.png)

**PROSPER**
FACT-P

![](chart2.png)

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FACT-P, Functional Assessment of Cancer Therapy–Prostate; QoL, quality of life; SD, standard deviation; W, week.

SPARTAN: QoL declines following progression

![Graph showing FACT-P total score changes over time for Apalutamide and Placebo groups.](image)

- **FACT-P total score**
- **Least squares mean change from baseline**
- **Number of patients in each cycle**
  - Apalutamide: 787, 769, 750, 732, 707, 689, 657, 631, 598, 486, 373, 274, 179
  - Placebo: 390, 382, 376, 358, 339, 289, 276, 255, 208, 181, 99, 62, 44

Background: next-generation androgen receptor inhibitors

- Darolutamide is structurally distinct from apalutamide and enzalutamide
- Low blood–brain barrier penetration\(^1,2\)
- This could result in less CNS toxicity and improved tolerability


ARAMIS: Metastases-Free Survival

Median Metastasis-free Survival (95% CI) (mo)

- Darolutamide: 40.4 (34.3–NR)
- Placebo: 18.4 (15.5–22.3)

Hazard ratio, 0.41 (95% CI, 0.34–0.50) P<0.001

ARAMIS: PSA-PFS

Median Survival without PSA Progression (95% CI)

- Darolutamid: 33.2 (25.9–NR)
- Placebo: 7.3 (3.9–7.4)

Hazard ratio: 0.13 (95% CI: 0.11–0.16), P<0.001

ARAMIS: OS

Median Survival (95% CI)

- Darolutamide: mo
- Placebo: NR (44.5–NR)

Hazard ratio, 0.71 (95% CI, 0.50–0.99)
P=0.045

<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>
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<tbody>
<tr>
<td>Probability of Survival</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0</td>
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</table>

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>955</th>
<th>932</th>
<th>880</th>
<th>737</th>
<th>586</th>
<th>428</th>
<th>302</th>
<th>218</th>
<th>123</th>
<th>64</th>
<th>35</th>
<th>8</th>
<th>0</th>
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<tbody>
<tr>
<td>Darolutamide</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>554</td>
<td>529</td>
<td>467</td>
<td>394</td>
<td>307</td>
<td>214</td>
<td>154</td>
<td>110</td>
<td>56</td>
<td>34</td>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Secondary endpoint: Time to pain progression (BPI-SF)
35% risk reduction of increase in pain

HR 0.65 (95% CI 0.53–0.79)  P<0.0001

Darolutamide: 40.3 months (median)
Placebo: 25.4 months (median)

BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; HR, hazard ratio.
**Exploratory endpoint: Time to deterioration of FACT-P PCS**

*Time to deterioration (unconfirmed)* was longer for darolutamide than placebo

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**Graph:**
- **Darolutamide:** Median time to deterioration = 11.1 months
- **Placebo:** Median time to deterioration = 7.9 months

**HR Calculation:**
- HR = 0.80
- 95% CI: 0.70–0.91
- *P*-value = 0.0005

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*Time to deterioration was defined as time from randomization to date of ≥3 point decline in FACT-P PCS score from baseline. *P*-value calculation was for descriptive purposes only.


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**Presented by:** Karim Fizazi
**Post-hoc analysis: Time to deterioration of EORTC QLQ-PR25 subscales**

<table>
<thead>
<tr>
<th>EORTC QLQ-PR25 symptom subscale</th>
<th>Median time to deterioration (95% CI)</th>
<th>Favors darolutamide</th>
<th>Favors placebo</th>
<th>Log-rank test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bowel symptoms</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hormone treatment-related</td>
<td>18.4 (14.8–18.5)</td>
<td>0.78 (0.66–0.92)</td>
<td>11.5 (11.1–14.8)</td>
<td>&lt;0.01</td>
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<tr>
<td>symptoms</td>
<td>(N=955)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Incontinence aid</td>
<td>36.6 (15.1–NE)</td>
<td></td>
<td>听课未提供数据</td>
<td></td>
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<tr>
<td>(10.1–NE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual activity</td>
<td>33.2 (33.0–NE)</td>
<td></td>
<td>听课未提供数据</td>
<td></td>
</tr>
<tr>
<td>(15.8–NE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Urinary symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stools/bloating</td>
<td>22.1 (14.8–NE)</td>
<td></td>
<td>听课未提供数据</td>
<td></td>
</tr>
<tr>
<td>(10.1–NE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood in stools</td>
<td>30.1 (14.8–NE)</td>
<td></td>
<td>听课未提供数据</td>
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<tr>
<td>(14.8–NE)</td>
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<tr>
<td>Interference with daily activities</td>
<td></td>
<td></td>
<td>听课未提供数据</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urge</td>
<td>25.8 (22.0–33.1)</td>
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<td>听课未提供数据</td>
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<tr>
<td>(11.2–15.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Interference with daily activities</td>
<td></td>
<td></td>
<td>听课未提供数据</td>
<td></td>
</tr>
</tbody>
</table>

- Darolutamide showed clinically significant delays in time to deterioration compared with placebo for urinary and bowel symptoms.
- Time to deterioration for the other subscales were not statistically different between groups.
Summary of the 3 trials

<table>
<thead>
<tr>
<th>Key Baseline Key Results</th>
<th>PROSPER</th>
<th>SPARTAN</th>
<th>ARAMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enza (N=930)</td>
<td>Placebo (N=465)</td>
<td>Apa (N=803)</td>
</tr>
<tr>
<td>median PSA DT</td>
<td>3.8</td>
<td>3.6</td>
<td>4.4</td>
</tr>
<tr>
<td>PSA DT &lt;6mo</td>
<td>77</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>PSA DT &gt;6mo</td>
<td>23</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>HR MFS</td>
<td>0.29 (0.24-0.35)</td>
<td>0.28 (0.23-0.35)</td>
<td>0.41 (0.34-0.50)</td>
</tr>
<tr>
<td>Median MFS</td>
<td>36.6</td>
<td>14.7</td>
<td>40.5</td>
</tr>
<tr>
<td>HR time to PSA prog</td>
<td>0.07 (0.05-0.08)</td>
<td>0.06 (0.05-0.08)</td>
<td>0.13 (0.11-0.16)</td>
</tr>
<tr>
<td>Median time to PSA prog</td>
<td>37.2</td>
<td>3.9</td>
<td>NR</td>
</tr>
<tr>
<td>HR OS</td>
<td>0.80 (0.06-1.09)</td>
<td>0.70 (0.47-1.04)</td>
<td>0.71 (0.50-0.99)</td>
</tr>
<tr>
<td>median OS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Preferred Terms</td>
<td>PROSPER (N=930)</td>
<td>SPARTAN (N=803)</td>
<td>ARAMIS (N=954)</td>
</tr>
<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Placebo</td>
<td>Darolutamide</td>
</tr>
<tr>
<td></td>
<td>(N=465)</td>
<td>(N=398)</td>
<td>(N=554)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.6 (3-4)</td>
<td>30.4 (3-4)</td>
<td>12.1 (3-4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11.9 (3-4)</td>
<td>24.8 (3-4)</td>
<td>6.6 (3-4)</td>
</tr>
<tr>
<td>Rash</td>
<td>2.3 (0.0)</td>
<td>23.8 (3-4)</td>
<td>2.9 (0.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.8 (0.3)</td>
<td>20.3 (1.0)</td>
<td>6.9 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.4 (0.3)</td>
<td>18.1 (0.0)</td>
<td>5.0 (0.2)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>5.9 (0.2)</td>
<td>16.1 (1.1)</td>
<td>3.6 (0.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8.4 (0.1)</td>
<td>15.9 (0.0)</td>
<td>8.1 (0.3)</td>
</tr>
<tr>
<td>Fall</td>
<td>11.4 (1.3)</td>
<td>15.6 (1.7)</td>
<td>4.2 (0.8)</td>
</tr>
<tr>
<td>Fracture</td>
<td>11.2 (2.4)</td>
<td>11.7 (2.7)</td>
<td>4.2 (0.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.8 (0.4)</td>
<td>9.3 (0.6)</td>
<td>4.5 (0.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.6 (0.0)</td>
<td>8.1 (0.0)</td>
<td>0.2 (0.0)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.3 (0.2)</td>
<td>0.2 (0.0)</td>
<td>0.2 (0.0)</td>
</tr>
<tr>
<td>Mental impairm dis</td>
<td>5.0 (0.5)</td>
<td>5.1 (0.0)</td>
<td>0.4 (0.0)</td>
</tr>
<tr>
<td>SAE</td>
<td>24.0 (0.0)</td>
<td>24.8 (0.0)</td>
<td>24.8 (15.8)</td>
</tr>
<tr>
<td>AE discontinuation</td>
<td>9.0 (0.0)</td>
<td>10.6 (0.0)</td>
<td>8.9 (3.4)</td>
</tr>
</tbody>
</table>
Conclusion: M0 CRPC

• Quite rare situation, unmet need
• Even rarer if next generation imaging is used
• 3 agents (Darolutamide, Enzalutamide, Apalutamide):
  – Clear and meaningful improvement of MFS
  – Remarkable safety profile with Darolutamide
  – Clear suggestion that clinical endpoints are improved (Pain progression, OS)
  – Cost-effectiveness?