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, Janssen, Orion, Sanofi
CRPC M0: Definition

• A man with prostate cancer:
  – Who often previously received a local treatment
  – Who experienced a PSA relapse and then received Androgen Deprivation Therapy (or together with 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
Impact of PSA Doubling Time on Disease Progression

- Men (N=201) with non-metastatic prostate cancer and rising PSA despite ADT were followed for 48 months to assess development of metastatic disease and survival.

**Time to bone metastases or death by PSA level**

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

Imaging: How Should Patients be Monitored?

Current imaging techniques

- **$^{99m}$Tc bone scan**
  - Does not allow tumor measurement
  - Underestimates prevalence of bone metastases

Emerging imaging strategies

- PET
- MRI

No clear recommendations for frequency of follow-up scans$^2$

Data are lacking to support recommendations$^2$

New imaging techniques may detect metastases at a much lower burden and may create a group of early oligo-metastatic (M+) CRPC$^3$

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)

Denosumab (n=1432)

Zibotentan: Enthuse 15 trial (n=1421)

Nelson JB, Cancer 2008; 113:2 478-87
Next-generation AR targeted agents in M0 CRPC

<table>
<thead>
<tr>
<th>Study name</th>
<th>N patients</th>
<th>Treatments</th>
<th>Primary end-point</th>
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</thead>
<tbody>
<tr>
<td>SPARTAN (NCT 01946204)</td>
<td>1200</td>
<td>Apalutamide 240mg once daily or Pbo</td>
<td>Metastasis-free survival</td>
</tr>
<tr>
<td>PROSPER (NCT02003924)</td>
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<td>Enzalutamide 160mg once daily or Pbo</td>
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<td>ARAMIS (NCT02200614)</td>
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<td>Darolutamide 600mg twice daily or Pbo</td>
<td>Metastasis-free survival</td>
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</tbody>
</table>
PROSPER Study

**Primary endpoint**
- MFS (defined as time from randomization to radiographic progression or time to death without radiographic progression from randomization to 112 days of discontinuation of trial regimen)

**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

**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)

**Enzalutamide 160 mg/day + ADT**
- N=1401
- First patient enrolled: Nov 2013
- MFS primary completion date: Jun 2017
- OS (secondary endpoint)

**Placebo + ADT**
- R 2:1
- Placebo + ADT

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.
SPARTAN — Overall Study Design
Phase 3 Placebo-Controlled, Randomized International Study

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

**On-Study Requirement**
- Continuous ADT

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

- **Randomization**
- Metastasis-free survival (primary end point)
- 2nd progression-free survival (PFS2)

2:1 (N = 1207)

- Apalutamide (APA) 240 mg QD + ADT (n = 806)
- Placebo (PBO) + ADT (n = 401)

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

NCT01946204

ABI/PRED, abiraterone acetate plus prednisone; nmCRPC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.
PROSPER: Metastases-Free Survival

Median (CI₉₅), moi
HR (IC₉₅)
p
36.6 (33.1-NR)
14.7 (14.2-15.0)
0.29 (0.24-0.35)
< 0.0001

ENZA + ADT (n = 933)
PBO + ADT (n = 468)
SPARTAN: Metastases-Free Survival

HR=0.28 (95% CI, 0.23-0.35)  
*P* < 0.0001

APA, 40.5 mo (median)
PBO, 16.2 mo (median)

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<tr>
<th>Months</th>
<th>No. at risk APA</th>
<th>No. at risk PBO</th>
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<td>401</td>
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<td>16</td>
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<td>20</td>
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<td>24</td>
<td>180</td>
<td>34</td>
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<td>28</td>
<td>96</td>
<td>13</td>
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<td>3</td>
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<td>44</td>
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SPARTAN: Time to Symptomatic Progression

HR=0.45 (95% CI, 0.32-0.63)  
P < 0.0001

No. at risk

<table>
<thead>
<tr>
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<th>APA</th>
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<td>732</td>
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<td>344</td>
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Secondary endpoint: time to PSA progression

- Time to PSA progression was 37.2 months with enzalutamide vs. 3.9 months with placebo (p<0.001).
- Enzalutamide treatment resulted in a 93% lower risk of PSA progression (HR: 0.07; 95% CI: 0.05, 0.08; p<0.001)

SPARTAN: Time to PSA Progression

Time to PSA Progression
94% risk reduction in PSA progression

HR, 0.06 (95% CI, 0.05-0.08)
P < 0.0001

No. at risk
APA  806  695  597  435  306
PBO  401  139  50  14  8

Months
215  128  69  29  11  2  0

Patients Without PSA Progression (%)

PBO, 3.7 mo (median)
APA, not reached
*Only patients with ≥ 1 postbaseline PSA assessment were included in the analysis.

SPARTAN: PSA response

PSA End Points

PSA ≥ 50% decline
APA: 90%
PBO: 2%

APA (n = 753)
PBO (n = 372)
• At the first interim OS analysis, 103 of 933 patients (11%) receiving enzalutamide and 62 of 468 patients (13%) receiving placebo had died; median OS was NR in either group

• The first pre-planned interim analyses indicated a statistically non-significant 20% lower risk of death with enzalutamide vs. placebo (HR: 0.80; 95% CI: 0.58, 1.09)

Secondary End Point: Overall Survival
30% risk reduction of death

HR, 0.70 (95% CI, 0.47-1.04)
P = 0.07

APA, not reached
PBO, 39.0 mo (median)

104 events/427 target events = 24%

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>APA</td>
<td>806</td>
</tr>
<tr>
<td>PBO</td>
<td>401</td>
</tr>
</tbody>
</table>

Presented by: Eric Small, MD, FASCO
### PROSPER: Adverse events of special interest*

<table>
<thead>
<tr>
<th></th>
<th><strong>Enzalutamide Group</strong></th>
<th></th>
<th><strong>Placebo Group</strong></th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>(n = 930)</td>
<td><strong>All Grades</strong></td>
<td><strong>Grade ≥3</strong></td>
<td><strong>All Grades</strong></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>114 (12)</td>
<td>43 (5)</td>
<td>25 (5)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Major adverse</td>
<td>48 (5)</td>
<td>34 (4)</td>
<td>13 (3)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>cardiovascular event‡</td>
<td>48 (5)</td>
<td>1 (&lt;1)</td>
<td>9 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>48 (5)</td>
<td>1 (&lt;1)</td>
<td>9 (2)</td>
<td>0</td>
</tr>
<tr>
<td>disorders§</td>
<td>11 (1)</td>
<td>5 (1)</td>
<td>9 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>9 (1)</td>
<td>5 (1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Convulsion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Posterior reversible</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>encephalopathy</td>
<td></td>
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</tr>
</tbody>
</table>

- A higher percentage of patients receiving enzalutamide reported falls and nonpathologic fractures than did those receiving placebo (17% vs. 8%).
- *Adverse events were collected up to 30 days after the last dose of study drug.
- †Includes increased blood pressure.
- ‡Includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure.
- §Includes memory impairment, disturbance in attention, cognitive disorders, amnesia, dementia Alzheimer’s type, senile dementia, mental impairment, and vascular dementia.

Adverse events were collected up to 30 days after the last dose of study drug.

### Results: Treatment Associated Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>APA (n = 803)</th>
<th></th>
<th>PBO (n = 398)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Gr 3/4</td>
<td>All</td>
<td>Gr 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30.4%</td>
<td>0.9%</td>
<td>21.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>23.8%</td>
<td>5.2%</td>
<td>5.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>16.1%</td>
<td>1.1%</td>
<td>6.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15.9%</td>
<td>0</td>
<td>7.5%</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>15.6%</td>
<td>1.7%</td>
<td>9.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Fracture</td>
<td>11.7%</td>
<td>2.7%</td>
<td>6.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.1%</td>
<td>0</td>
<td>2.0%</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.2%</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Presented By Eric Small at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care
Most patients reported no change or an improvement in HRQoL (FACT-P total)

ENZA=enzalutamide; FACT-P=Functional Assessment of Cancer Therapy – Prostate; HRQoL=health-related quality of life; PBO=placebo
PRO End Points: FACT-P and EQ-5D VAS

HRQoL was maintained with the addition of APA to ADT

**FACT-P**

**EQ-5D VAS**

PRO, patient-reported outcome; VAS, visual analog scale; HRQoL, health-related quality of life.

Presented by: Eric Small, MD, FASCO

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Conclusion: M0 CRPC

• Quite rare situation, unmet need
• Even rarer if next generation imaging is used
• Two agents (Enzalutamide, Apalutamide)
  – Clear and meaningful improvement of MFS
  – Acceptable toxicity, some issues though (CV, fractures, etc)
  – No (yet?) demonstration of hard endpoint improvement (OS, etc)
  – Cost
• Darolutamide data to come soon