Management of de novo metastatic prostate cancer

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Disclosures

• Speaking honorarium – Pfizer

• I will discuss indications for pharmaceutical products which do not have Health Canada approval.
Objectives

• Review systemic therapy options for de novo metastatic prostate cancer
• Discuss emerging data for combination systemic therapy and local therapy mCSPC
• Raise awareness for ongoing clinical trials in mCSPC
Wine List

• ADT + docetaxel
• ADT + abiraterone
• ADT + NSAA
• How to choose?
• Is more better?
• Summary
### Cases

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>73M presents with fatigue, low back pain</td>
<td>73M presents after annual PSA with GP was 36. Some mild fatigue and low back pain.</td>
<td>73M admitted for NSTEMI. Poor mobility, socially isolated. In hospital imaging shows numerous bone mets.</td>
</tr>
<tr>
<td>CT scan shows bone, LN, and liver mets</td>
<td>Bone scan shows 5 bone mets in lumber spine and pelvis. No other mets.</td>
<td>PSA 54.</td>
</tr>
<tr>
<td>PSA 289</td>
<td></td>
<td></td>
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<tr>
<td>Biopsy shows adeno with neuroendocrine differentiation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADT vs ADT + docetaxel

• 3 phase 3 trials: CHAARTED, STAMPEDE, GETUG-AFU 15

• Trial populations were slightly different in terms of de novo vs recurrent, high vs low volume

• Compared ADT to ADT + docetaxel x 6-9 cycles
**Median OS (months)**

- ADT plus docetaxel: 57.6
- ADT alone: 47.2

**HR, 0.72 (95% CI, 0.59 to 0.89); P = .0018**

**Survival (proportion)**

**Time (months)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>ADT plus docetaxel</th>
<th>ADT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>36</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>48</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>60</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>72</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>84</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>96</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>108</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**No. at risk:**

- ADT plus docetaxel: 397 366 314 245 155 67 28 7 2 0
- ADT alone: 393 352 278 198 126 45 21 2 0 0
**CHAARTED**

**HIGH VOLUME DE NOVO METASTATIC**

- **ADT plus docetaxel**: Median OS = 48.0 months
- **ADT alone**: Median OS = 33.1 months

HR: 0.63 (95% CI: 0.49 to 0.81); *P* < .001

**LOW VOLUME DE NOVO METASTATIC**

- **ADT plus docetaxel**: Median OS = 58.3 months
- **ADT alone**: Median OS = 59.8 months

HR: 0.86 (95% CI: 0.52 to 1.42); *P* = .55

<table>
<thead>
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<th>Time (months)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>12</td>
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<td>24</td>
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<td>48</td>
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<td>84</td>
<td>11</td>
<td>9</td>
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<tr>
<td>96</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>108</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at risk:

- **ADT plus docetaxel**: 75 73 63 52 31 13 7 2 0 0
- **ADT alone**: 79 75 63 48 32 11 7 0 0 0
ADT vs ADT + docetaxel

• CHAARTED and STAMPEDE both showed a significant OS advantage to ADT + docetaxel compared to ADT alone

• GETUG-AFU 15 did not show a significant difference in OS

• Subgroup analysis from all three trials showed a greater benefit for high-volume disease compared to low-volume disease

• No significant difference between recurrent or de novo metastatic disease
Docetaxel toxicity

• Expected docetaxel toxicity profile
  • 6-15% febrile neutropenia
  • <1% treatment-related death
ADT vs ADT + docetaxel

- Docetaxel improves overall survival for patients with metastatic castrate sensitive prostate cancer

- Greatest benefit for patients with high-volume disease

- Survival advantage for both de novo and recurrent metastatic disease
ADT vs ADT + abiraterone

• Two phase 3 trials: LATITUDE and STAMPEDE

• Studies used a different patient populations
  • LATITUDE = M1 high-risk
  • STAMPEDE = M0 high-risk, N+ and M1

• No prior docetaxel

• Compared ADT to ADT + abiraterone 1000mg daily + prednisone
LATITUDE

Median OS:
ADT + placebo = 36.5mo
ADT + abiraterone+prednisone = 53.3mo

Figure 2: Kaplan-Meier curve of overall survival in the intention-to-treat population
ADT = androgen deprivation therapy.
ADT vs ADT + abiraterone

- Both trials showed significant improvement in overall survival

- Significant benefit seen in subgroup of de novo metastatic disease (recurrent population quite small)

- Unclear of the interaction with disease volume
Abiraterone HR-QOL

• Addition of abiraterone improved time to skeletal related events

• Addition of abiraterone improved proportion living without pain
Abiraterone toxicity

• Expected side-effect profile as seen in CRPC setting

• Grade 3-4:
  • hypertension = 20%
  • Hypokalemia = 11%
  • Transaminitis = 4-7%
ADT vs ADT + abiraterone

• Abiraterone + prednisone improves overall survival for patients with metastatic castrate sensitive prostate cancer

• Abiraterone + prednisone reduces proportion living with pain and time to skeletal-related events
ADT vs ADT + NSAA

** neither apalutamide nor enzalutamide have Health Canada indications for castrate-sensitive prostate cancer **

• Three phase 3 trials: TITAN (apalutamide vs placebo), ARCHES (enzalutamide vs placebo), ENZAMET (enzalutamide vs 1st Gen NSAA)

• All M1 CSPC

• 10-25% of patients received prior docetaxel
2y OS:
   ADT + placebo = 73.5%
   ADT + apalutamide = 82.4%
HR 0.67, 95% CI 0.51-0.89
ENZAMET

3y OS:
- ADT + placebo = 72%
- ADT + enzalutamide = 80%
ADT vs ADT + NSAA

• TITAN and ENZAMET have shown improvement in OS for addition of NSAA

• Both trials showed improvement in OS for low and high-volume disease

• Improvement in OS for both de novo and recurrent metastatic disease
NSAA HR-QOL

- Addition of NSAA reduced time to symptomatic skeletal event and time to clinical progression

- Most QOL data is not mature
NSAA Toxicity

• Apalutamide:
  • Rash 27% (Grade 3-4 = 6%)
  • Hypothyroid 6% (Grade 3-4 = 0%)

• Enzalutamide
  • As seen with CRPC
  • Seizure 2% (Grade 3-4 = <1%)
  • Fatigue (Grade 3-4 = 6%)
  • Hypertension (Grade 3-4 = 8%)
ADT vs ADT + NSAA

• Addition of NSAA to ADT improves OS for de novo metastatic prostate cancer

• Improvement in OS for both de novo and recurrent mCSPC

• Improvement in OS for both low and high-volume disease

• QOL data is early but some improvement in time to symptomatic skeletal events and time to clinical progression
How to choose?

• STAMPEDE direct comparison of docetaxel and abiraterone arms did not show any significant difference in survival
  • Worst toxicity profile was similar between two arms but different

• Network meta-analysis (GETUG, CHAARTED, STAMPEDE, LATITUDE) showed no significant difference in survival, suggests slightly better QOL data for abiraterone

• No comparison trials between docetaxel and NSAA or abiraterone and NSAA

Sydes Ann Oncol 2018, Feyerabend Eur J Oncol 2019
Why choose - add more?
Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting
ADT vs ADT + docetaxel + NSAA

• Subgroup analysis of TITAN and ENZAMET did show significant difference in OS for NSAA in patients with prior docetaxel but there was an improvement in PFS

• Ongoing studies:
  • ARASENS – mCSPC treated with ADT+docetaxel +/- darolutamide
  • PEACE-1 trial – mCSPC ADT+docetaxel +/- abiraterone +/- radiotherapy
Treatment of the primary

• STAMPEDE population randomized to radiotherapy or no radiotherapy to the primary tumour
  • Prior docetaxel (18%) but no abiraterone

• Whole population:
  • Improvement in failure free survival but not overall survival (HR 0.92, 95% CI 0.80-1.06)

• Low-volume disease
  • Improvement in 3yr OS (81% vs 73%, HR 0.68, 95% CI 0.52 to 0.90)
### Cases

#### Case 1
- 73M presents with fatigue, low back pain
- CT scan shows bone, LN, and liver mets
- PSA 289
- Biopsy shows adeno with neuroendocrine differentiation

#### Case 2
- 73M presents after annual PSA with GP was 36. Some mild fatigue and low back pain.
- Bone scan shows 5 bone mets in lumber spine and pelvis. No other mets.

#### Case 3
- 73M admitted for NSTEMI. Poor mobility, socially isolated. In hospital imaging shows numerous bone mets.
- PSA 54.
Summary

• ADT-alone, docetaxel and abiraterone are treatment options for selected patients with de novo metastatic prostate cancer

• Recent trial data show promising results for addition of NSAA to ADT in this patient population.

• Further data is needed understand role of abiraterone or NSAA for patients who received docetaxel.
Thank you

Go Bianca!
CHAARTED

- Newly diagnosed metastatic (M1) CSPC
  - Median age 64
  - De novo metastatic 72.8%

- Arm A: ADT
- Arm B: ADT + docetaxel x 6 cycles
CHARTED

**HIGH VOLUME DE NOVO METASTATIC**

- ADT plus docetaxel: Median OS 48.0 months
- ADT alone: Median OS 33.1 months
- HR, 0.63 (95% CI, 0.49 to 0.81); \( P < .001 \)

**LOW VOLUME DE NOVO METASTATIC**

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**Survival (proportion)**

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<td>1</td>
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<tr>
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**No. at risk:**

<table>
<thead>
<tr>
<th>ADT plus docetaxel</th>
<th>ADT alone</th>
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<tr>
<td>75</td>
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STAMPEDE

- Advanced prostate cancer
  - Recurrent (3%)
  - M1 (59%) and/or
  - N+ (15%) and/or
  - high-risk locally advanced (22%) defined as 2 of 3: (i) T3-4, (ii) Gleason 8-10, (iii) PSA ≥ 40
  - Median age 65

- Arm A: Standard of care
- Arm B: Standard of care + docetaxel + prednisone x 6 cycles

Median OS:
SOC = 71mo
SOC+Doc = 81mo
HR 0.78, 95% CI 0.66-0.93
## STAMPEDE

### SOC vs SOC + Doc

<table>
<thead>
<tr>
<th>Variable</th>
<th>SOC (n)</th>
<th>SOC + Doc (n)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastasis status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>65/460</td>
<td>31/230</td>
<td>0.95 (0.62-1.47)</td>
</tr>
<tr>
<td>M1</td>
<td>350/724</td>
<td>144/262</td>
<td>0.76 (0.62-0.92)</td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>139/522</td>
<td>45/260</td>
<td>0.58 (0.41-0.81)</td>
</tr>
<tr>
<td>N+</td>
<td>241/594</td>
<td>111/298</td>
<td>0.85 (0.68-1.07)</td>
</tr>
<tr>
<td>NX</td>
<td>35/68</td>
<td>19/34</td>
<td>1.02 (0.57-1.83)</td>
</tr>
<tr>
<td><strong>Gleason sum score</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤7</td>
<td>76/282</td>
<td>22/110</td>
<td>0.67 (0.41-1.07)</td>
</tr>
<tr>
<td>8-10</td>
<td>286/810</td>
<td>126/436</td>
<td>0.76 (0.62-0.94)</td>
</tr>
<tr>
<td>Unknown</td>
<td>53/92</td>
<td>27/46</td>
<td>1.08 (0.66-1.77)</td>
</tr>
<tr>
<td><strong>Age at randomisation</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Under 70 years</td>
<td>311/833</td>
<td>121/419</td>
<td>0.73 (0.59-0.90)</td>
</tr>
<tr>
<td>70 years or older</td>
<td>104/351</td>
<td>54/173</td>
<td>0.90 (0.64-1.26)</td>
</tr>
<tr>
<td><strong>WHO performance status</strong></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>283/922</td>
<td>119/461</td>
<td>0.77 (0.62-0.96)</td>
</tr>
<tr>
<td>1+</td>
<td>132/262</td>
<td>56/131</td>
<td>0.79 (0.57-1.09)</td>
</tr>
<tr>
<td><strong>NSAID or aspirin use</strong></td>
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</tr>
<tr>
<td>No use</td>
<td>300/891</td>
<td>125/444</td>
<td>0.77 (0.63-0.95)</td>
</tr>
<tr>
<td>Uses either</td>
<td>115/293</td>
<td>50/148</td>
<td>0.81 (0.58-1.14)</td>
</tr>
<tr>
<td><strong>Is radiotherapy planned?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not planned</td>
<td>371/844</td>
<td>151/424</td>
<td>0.75 (0.62-0.91)</td>
</tr>
<tr>
<td>Planned</td>
<td>843/1889</td>
<td>244/669</td>
<td>1.19 (0.73-1.95)</td>
</tr>
<tr>
<td><strong>Recurrent disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>402/1117</td>
<td>170/564</td>
<td>0.78 (0.65-0.94)</td>
</tr>
<tr>
<td>Yes</td>
<td>13/67</td>
<td>5/28</td>
<td>0.80 (0.26-2.48)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>0.78 (0.60-0.93)</td>
</tr>
</tbody>
</table>
GETUG-AFU 15

- Newly diagnosed metastatic (M1) CSPC
  - Median age 64
  - De novo metastatic 72.0%

- Arm A: ADT
- Arm B: ADT + docetaxel x 9 cycles

**Fig. 1** – Overall survival in the overall population.
ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.
GETUG-AFU 15

• Similar HR to CHAARTED and STAMPEDE but not statistically significant

**HIGH VOLUME DISEASE POPULATION**

**Fig. 2 – Overall survival for patients with high-volume disease.**

ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.
LATITUDE

- Newly diagnosed high-risk M1 prostate cancer
  - 2 of 3:
    - Gleason $\geq 8$
    - $\geq 3$ bone mets
    - $\geq 1$ visceral mets
  - Prior docetaxel = none
  - Median age 67
  - De novo NR%

- Arm A: ADT + placebo
- Arm B: ADT + abiraterone + prednisone

Median OS:
- ADT + placebo = 36.5mo
- ADT + abiraterone + prednisone = 53.3mo

Figure 2: Kaplan-Meier curve of overall survival in the intention-to-treat population
ADT = androgen deprivation therapy.
STAMPEDE

- Advanced prostate cancer
  - Recurrent (4%)
  - M1 (49%) and/or
  - N+ (20%) and/or
  - high-risk locally advanced (27%) defined as 2 of 3: (i) T3-4, (ii) Gleason 8-10, (iii) PSA ≥ 40
  - Prior docetaxel = none
  - Median age 67

- Arm A: Standard of care
- Arm B: Standard of care + abiraterone + prednisone

Median OS (not reported):  
SOC = ~42 mo  
SOC + abiraterone+prednisone = NR

HR 0.61